Thrombocytopenia in the parturient

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Summary
Thrombocytopenia in pregnant women can be associated with substantial maternal and neonatal morbidity. It may result from a range of conditions and early implementation of some specific treatment may improve both maternal and neonatal outcome. In this review we discuss the clinical features of the more common causes of thrombocytopenia associated with pregnancy, and provide an overview of the anaesthetic considerations.

Keywords
Pregnancy, Thrombocytopenia; gestational thrombocytopenia, pre-eclampsia, HELLP, thrombotic thrombocytopenic purpura, immune thrombocytopenic purpura.

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Thrombocytopenia occurs in approximately 10% of pregnant women and may be caused by a variety of obstetric conditions (Table 1) [1]. Although some of these diseases are not associated with adverse effects or outcomes of pregnancy, others can be associated with serious maternal as well as fetal/neonatal morbidity and mortality. A multidisciplinary team approach involving obstetrician, haematologists, paediatricians and anaesthetists is essential for the optimal management of pregnant women with thrombocytopenia. Thrombocytopenia in the obstetric patient may be the result of a range of conditions, from benign disorders such as incidental gestational thrombocytopenia to life-threatening syndromes such as the ‘haemolysis, elevated liver enzymes, low platelets’ syndrome (HELLP) [2]. The diagnosis of specific disorders is often difficult because the time of onset of these disorders during pregnancy and their clinical manifestations often overlap.

The aim of this article is to review the differential diagnosis of thrombocytopenia in pregnancy and highlight the clinical features and management of the various diseases that cause thrombocytopenia, and to summarise the anaesthetic considerations in the management of thrombocytopenia in the parturient.

Method
Sources for this review include Medline 1980–2003 searched under the following Medical Subject Headings: thrombocytopenia, pregnancy, platelets, pre-eclampsia, HELLP, and thrombotic thrombocytopenic purpura (TTP). The bibliographies of the included studies were scanned for additional references (reference dredging). The National Library of Medicine Pub Medical internet site was also used.

Haemostatic changes in normal pregnancy
During normal pregnancy, major changes in haemostasis include increasing concentrations of most clotting factors, decreasing concentrations of some natural anticoagulants and diminishing fibrinolytic activity [3]. These changes create a state of hypercoagulability that is most marked around term and the immediate postpartum period, thereby decreasing bleeding complications that may be associated with delivery. The most important initial factors for haemostasis at delivery, however, are uterine muscle contractions and constriction of the spiral arteries that interrupt blood flow.
Table 1 Causes of thrombocytopenia in pregnancy.

<table>
<thead>
<tr>
<th>Causes</th>
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<tbody>
<tr>
<td>Normal</td>
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<tr>
<td>Incidental or gestational thrombocytopenia</td>
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<tr>
<td>Pseudothrombocytopenia (laboratory artefact with EDTA</td>
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<tr>
<td>anticoagulant)</td>
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<tr>
<td>Disorders with increased platelet consumption</td>
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<td>Immune thrombocytopenic purpura</td>
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<td>Pregnancy induced hypertension/HELLP syndrome</td>
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<td>Thrombotic thrombocytopenic purpura</td>
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<tr>
<td>Haemolytic uraemic syndrome</td>
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<tr>
<td>Infection-associated (HIV, malaria)</td>
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<tr>
<td>Drug-induced (heparin, sulphonamides, penicillin, rifampicin,</td>
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<tr>
<td>quinine)</td>
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<tr>
<td>Systemic lupus erythematous</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
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<tr>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td>Amniotic embolism</td>
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<tr>
<td>Disorders with reduced platelet production</td>
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<tr>
<td>Congenital thrombocytopenia</td>
</tr>
<tr>
<td>Aplastic anaemia</td>
</tr>
<tr>
<td>Leukaemia</td>
</tr>
<tr>
<td>Drug-induced thrombocytopenia</td>
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<tr>
<td>Myelodysplasia</td>
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All blood coagulation factors except XI and XIII increase during normal pregnancy [4, 5]. The plasma fibrinogen concentration increases from non-pregnant levels of 2.5–4 g.l\(^{-1}\) to 6 g.l\(^{-1}\) in late pregnancy and labour. The increase in the concentration of the two components of the factor VIII complex, Factor VIII and von Willebrand factor (VWF) antigen, occur in parallel in the first half of pregnancy, but then diverge because of a two-fold increase in von Willebrand factor antigen. Factor XI concentrations decrease to approximately 60% of the non-pregnant values. Factor XIII concentrations fall to about 50% of the normal non-pregnant value at term. The increase in factors VII and X is highest in mid-pregnancy and remains high in the third trimester.

Most blood coagulation inhibitors are unchanged. Antithrombin and protein C levels are normal during pregnancy. However, the plasma concentration of free protein S decreases markedly during pregnancy and may contribute to the hypercoagulable state [6, 7]. The level of tissue factor pathway inhibitor increases in pregnancy.

Plasma fibrinolytic activity is reduced during pregnancy and labour, and returns to normal within 1 h after placental delivery. The diminished fibrinolysis is caused by increased concentrations of plasminogen activator-1 derived from endothelial cells and plasminogen activator inhibitor-2 derived from the placenta.

The normal platelet count range in non-pregnant women is 150–400 × 10\(^{9}\).l\(^{-1}\). In uncomplicated pregnancies, recent studies have reported that the platelet count decreases by an average of 10% during the third trimester as a result of haemodilution or accelerated destruction leading to younger and larger platelets [8]. Incidental thrombocytopenia in pregnancy is usually benign. The mean platelet volume increases, suggesting that a compensated state of progressive platelet destruction occurs during the third trimester [9, 10]. The concentration of plasma β-thromboglobulin (a specific protein in the α-granules that is secreted during platelet activation) increases in the second and third trimesters of pregnancy [11].

Platelet activation, coagulation and fibrinolytic activity are enhanced during delivery [7]. Significant increases in fibrinogen degradation products occur in 21% of parturients during labour, with 32% showing the similar increases in the immediate postpartum period. At 24–72 h after delivery, fibrinogen degradation remains elevated in only 10% of women. Platelet count returns to normal 24–72 h postpartum [12, 13], and fibrinolytic activity decreases rapidly [7]. During placental separation, the clotting mechanism is activated and factor VIII activity transiently increases after delivery, shortening coagulation times [14].

In the pregnant women, thrombocytopenia is defined as a platelet count of less than 150 × 10\(^{9}\).l\(^{-1}\); counts of 100–150 × 10\(^{9}\).l\(^{-1}\) are defined as mild thrombocytopenia, counts of 50–100 × 10\(^{9}\).l\(^{-1}\) as moderate thrombocytopenia, and counts of less than 50 × 10\(^{9}\).l\(^{-1}\) as severe thrombocytopenia. Thrombocytopenia is caused either by increased platelet destruction or decreased platelet production. In pregnancy, increased platelet destruction may be mediated by immunological mechanisms, abnormal platelet activation, or platelet consumption [15]. Increased destruction or utilisation of platelets during pregnancy occurs in microangiopathies (exposure to abnormal blood vessels) such as thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, haemolysis, elevated liver enzymes, low platelet (HELLP) syndrome, and pre-eclampsia.

**Gestational or incidental thrombocytopenia**

Gestational or incidental thrombocytopenia, the most common cause of thrombocytopenia during pregnancy, occurs in 5–8% of all pregnant women and accounts for 75% of pregnancy-associated thrombocytopenia. The decreased platelet count may be related to haemodilution and/or accelerated platelet turnover with increased platelet production in the bone marrow, and increased trapping or destruction at the placenta [16]. The quantitative decrease in platelet count is balanced by enhanced platelet reactivity [17]. Some authors, however, have described decreased platelet activation mediated by a plasma factor that selectively inhibits prostaglandin-dependent activation during pregnancy [18].

The features of gestational thrombocytopenia include a platelet count usually below 70 × 10\(^{9}\).l\(^{-1}\) which returns to
a normal level following delivery within 12 weeks. The women are asymptomatic with no history of bleeding and thrombocytopenia is usually detected as part of antenatal screening. The women have no history of thrombocytopenia prior to pregnancy but may have thrombocytopenia in previous pregnancies. Gestational thrombocytopenia is a diagnosis of exclusion. However, when a platelet count is below $70 \times 10^9 \text{L}^{-1}$, a pathological cause of thrombocytopenia becomes substantially more likely. Gestational thrombocytopenia usually occurs in the late second or third trimester. There is an extremely low risk of fetal or neonatal thrombocytopenia [19]. In non-hypertensive pregnant women, investigations are only required when thrombocytopenia occurs early in pregnancy or progressively decreases during the pregnancy or when the platelet count is less than $70 \times 10^9 \text{L}^{-1}$. Further investigations must be undertaken in pregnant women who are symptomatic or who do not regain a normal postpartum platelet count. If a thrombocytopenic but otherwise healthy pregnant woman has a platelet count $>70 \times 10^9 \text{L}^{-1}$ and no history of previous thrombocytopenia, a meticulous physical examination, careful blood pressure assessment and monitoring and a peripheral blood film examination should be undertaken. The confirmation of normal platelet count prior to pregnancy decreases the probability of an underlying immune thrombocytopenic purpura [20]. Antiplatelet antibody tests do not differentiate gestational thrombocytopenia from idiopathic thrombocytopenia. In a study of 250 pregnant women with thrombocytopenia (90 with idiopathic thrombocytopenia, 160 with presumed gestational thrombocytopenia) that evaluated eight different platelet antibodies, platelet-associated IgG was elevated in 69.5% of women with gestational thrombocytopenia and in 64.6% of women with idiopathic thrombocytopenia ($p = 0.24$). Although 85.9% of women with idiopathic thrombocytopenia had indirect IgG compared with 60.3% women with gestational thrombocytopenia ($p < 0.001$), significant overlap existed and limited its clinical value [21]. It appears that there are no specific diagnostic tests that can distinguish gestational thrombocytopenia from mild idiopathic thrombocytopenia. Therefore, the only means of differentiation is to monitor platelet counts closely, to detect levels that decrease below the range of $50–70 \times 10^9 \text{L}^{-1}$, and to document a normal neonatal platelet count and a restoration of a normal maternal platelet count after delivery. Women with gestational thrombocytopenia are not at risk of either maternal haemorrhage or fetal haemorrhage.

**Immune thrombocytopenic purpura (ITP)**

ITP is characterised by immunologically mediated platelet destruction and an increase in circulating megathrombocytes. The patient produces IgG antiplatelet antibodies that recognise platelet membrane glycoproteins. The antibody-coated platelets are then destroyed by the reticuloendothelial system (primarily the spleen) at a rate that exceeds the capacity of the bone marrow to produce new platelets. However, antiplatelet antibodies are present in only 80% of cases.

ITP occurs in approximately one case of thrombocytopenia per 1000 pregnancies and accounts for 5% of cases of pregnancy-associated thrombocytopenia [22]. It is the most common cause of significant thrombocytopenia in the first trimester. ITP is a diagnosis of exclusion because there are no pathognomonic signs, symptoms or laboratory tests. The four consistent features that are associated with the condition are persistent thrombocytopenia (platelet count $<100 \times 10^9 \text{L}^{-1}$) with or without peripheral megathrombocytes; normal or increased number of megakaryocytes detected by bone marrow aspiration; absence of splenomegaly; and exclusion of systemic diseases or drugs that are known to cause thrombocytopenia.

Most women with ITP have a history of bruising easily, petechiae, epistaxis, and gingival bleeding preceding pregnancy, although some may be asymptomatic. Symptoms of haemorrhage are rare unless the platelet count is $<20 \times 10^9 \text{L}^{-1}$. A history of prior thrombocytopenia, underlying autoimmune disease or a platelet count $<50 \times 10^9 \text{L}^{-1}$ makes the diagnosis of ITP more likely. In patients with mildly decreased platelet count and with no prior history of thrombocytopenia, it can be difficult to distinguish ITP from gestational thrombocytopenia, because platelet-associated IgG may be elevated in both diseases [21]. An immunological test that measures antibodies that react with specific platelet glycoproteins (monoclonal antibody immobilisation of platelets) cannot differentiate these two syndromes consistently [23]. From a clinical view, in the absence of a platelet count prior to pregnancy, a platelet count $<100 \times 10^9 \text{L}^{-1}$ in the first trimester that declines progressively as the pregnancy progresses is consistent with ITP. In contrast, mild thrombocytopenia occurring in the second or third trimester and not associated with proteinuria or hypertension indicates incidental or gestational thrombocytopenia [24]. ITP is an insidious disease with initial symptoms such as easy bruising and petechiae. Pregnancy does not alter the clinical course of ITP. However, there are anecdotal reports of deterioration of symptoms during pregnancy and improvement postpartum [2].

Patients with platelet counts $>30 \times 10^9 \text{L}^{-1}$ and no bleeding do not usually require immediate treatment. Platelet transfusion is indicated if bleeding occurs or if the platelet count is $<30 \times 10^9 \text{L}^{-1}$ [9, 23]. More aggressive measures may be required to increase the platelet count to
a level to allow epidural analgesia for labour and adequate haemostasis during delivery. A platelet count >50 × 10^9.L⁻¹ is usually adequate in this regard, although some authors recommend a platelet count >100 × 10^9.L⁻¹ [25]. Drug therapy usually commences with oral prednisone (1–2 mg.kg⁻¹.day⁻¹), with reduction of doses until the platelet count stabilises at 75–100 × 10^9.L⁻¹. However, steroid therapy increases the incidence of gestational diabetes, pregnancy-induced hypertension and premature rupture of placental membranes. Patients with low platelet counts should receive steroids at around 37 weeks of gestation in order to increase maternal and foetal platelet counts. Betamethasone or dexamethasone is preferred because placental enzymes inactivate a major portion of the prednisone dose that is presented to the fetus [26]. They are not at higher risk for postpartum uterine bleeding because myometrial contractions produce mechanical haemostasis without a significant contribution from platelets. Platelet numbers should be maintained above 50 × 10^9.L⁻¹ for delivery. Platelet counts below 20 × 10^9.L⁻¹ should be augmented using platelet transfusions.

The neonate of a mother with ITP may develop ITP as a result of the transplacental transfer of maternal antiplatelet IgG [24]. At delivery, 10–20% of these neonates have platelet counts below 50 × 10^9.L⁻¹ and, in 5%, platelet counts may be <20 × 10^9.L⁻¹ [27]. The major fetal risk is intracranial haemorrhage causing neurological sequelae or death, but this is rare [28]. There is no consistent and reliable correlation between the fetal platelet numbers at delivery and the severity of maternal thrombocytopenia or the concentration of maternal antiplatelet IgG [21, 27]. The most reliable predictor of fetal thrombocytopenia is the presence of thrombocytopenia at delivery of a prior sibling [29]. Determination of fetal platelet count can only be achieved by fetal scalp sampling during labour or percutaneous umbilical blood sampling, although the latter is associated with bleeding and fetal bradycardia (~1%) [30].

In 1977, a case report of intracranial haemorrhage after a vaginal delivery of a thrombocytopenic infant to a mother with ITP led to the recommendation that women with ITP should be delivered by Caesarean section. However, this approach has not been subjected to randomised controlled studies and has been recently been questioned [31, 32]. Cook and colleagues reviewed literature that included 474 pregnant women with ITP and reported that the incidence of intracranial haemorrhage among neonates with severe thrombocytopenia (<50 × 10^9.L⁻¹) was 4% after Caesarean delivery and 5% after vaginal delivery [31]. A literature review of 18 studies on maternal ITP that involved 601 neonates showed that 12% of neonates had severe thrombocytopenia, but that intracranial haemorrhage only occurred in 1% (6/601) of neonates and was not related to the mode of delivery [33]. It is currently recommended that fetal platelet count using percutaneous umbilical blood samples should be measured first, and delivery by Caesarean section undertaken if the fetal platelet count is <50 × 10^9.L⁻¹ [34].

Umbilical cord platelet counts should be measured from umbilical blood obtained at delivery regardless of the method of delivery. Daily monitoring of platelet numbers in the neonate is necessary because neonatal platelet count can decrease for 4–5 days post delivery. The neonate’s platelet count is usually normal by 1 month of age.

**Pre-eclampsia and HELLP syndrome**

Pre-eclampsia is characterised by hypertension and proteinuria (>300 mg.24 h⁻¹) developing after 20 weeks of gestation, and occurs in 6% of all pregnancies [35]. The pathological lesions of pre-eclampsia involve deficient remodelling of the maternal uterine vasculature by the placental trophoblast early in pregnancy [36]. Abnormal expression of cell adhesion molecules, and vascular endothelial cell growth factor and its receptor by trophoblasts in pre-eclampsia have been reported [37, 38]. This causes uteroplacental vascular insufficiency leading to abnormal release and metabolism of nitric oxide, prostaglandins and endothelin by placental tissues. These changes lead to platelet activation, generalised endothelial dysfunction and hypertension [39]. Circulating platelets adhere to damaged or activated endothelium, causing enhanced platelet clearance. Although increased levels of platelet-associated IgG are detected in patients with pregnancy-induced hypertension (PIH), this finding is not specific and does not provide an immunological basis for the thrombocytopenia [40]. Clearance of
IgG-coated platelets may be further increased by the reticulo-endothelial system and platelet activation due to thrombin generation [2]. Platelet function may also be impaired in women with pre-eclampsia even if their platelet count is normal.

Pre-eclampsia is present in 21% of cases of maternal thrombocytopenia [28]. Thrombocytopenia occurs in 50% of pre-eclamptic patients and occasionally precedes other manifestations of the disease. The thrombocytopenia is usually moderate and clinical haemorrhage is uncommon unless the patient develops disseminated intravascular coagulopathy. A decreasing maternal platelet count is considered as an early sign of worsening of pre-eclampsia and may occur even before other clinical manifestations of the disease are apparent. The pathogenesis of thrombocytopenia in women with severe pre-eclampsia is unknown, although vascular endothelial damage, impaired prostacyclin production and increased deposition of fibrin within the vascular bed have been suggested. Accelerated platelet destruction, platelet activation, increased platelet volume and increased megakaryocyte production have been observed [2]. An increased response of platelet calcium to arginine vasopressin preceding thrombocytopenia as early as in the first trimester has been reported and has been proposed as a possible predictor of the development of the disease [41]. Activation of the coagulation cascade occurs in most pre-eclamptic patients, but routine tests such as activated partial thromboplastin time, prothrombin time and fibrinogen concentrations are normal. However, fibrinogen D-dimers and thrombin-antithrombin complexes are elevated in most cases.

Only neonates born prematurely are at risk of neonatal thrombocytopenia, and especially those with intrauterine growth retardation [15]. The platelet count in neonatal thrombocytopenia associated with pre-eclampsia is rarely below $20 \times 10^9 \text{L}^{-1}$ and does not cause fetal bleeding complications [28]. Term infants of mothers with PIH are no more likely to be thrombocytopenic than those of normal mothers.

The HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome, a variant of pre-eclampsia, is characterised by microangiopathic anaemia, SGOT > 70 units.\text{L}^{-1}, and thrombocytopenia (<100 \times 10^9 \text{L}^{-1}) and is associated with a maternal mortality of about 3.3%. Severe epigastric or right upper quadrant abdominal pain, which need not be associated by proteinuria and hypertension, are common symptoms. It is more common in multiparae, occurs in a slightly younger age group (19 years vs 25 years), and can manifest in approximately 30% of cases postpartum [42, 43]. It has been suggested that the underlying primary pathological lesion in the HELLP syndrome might be endothelial dysfunction and damage, which leads to platelet aggregation, consumption and eventually thrombocytopenia. Microthrombi deposited in the liver sinusoids cause obstruction to hepatic blood flow, consequently leading to liver distension and elevations of liver enzymes [42]. Although platelet activation has been suggested in the pathogenesis of pre-eclampsia or HELLP syndrome, prophylactic treatment of high-risk pregnant women with low-dose aspirin does not significantly decrease the incidence of pre-eclampsia [44].

The HELLP syndrome is associated with disseminated intravascular coagulation, placental abruption, acute renal failure, adult respiratory distress syndrome and intravascular coagulopathy. A decreasing maternal platelet count is considered as an early sign of worsening of pre-eclampsia and may occur even before other clinical manifestations of the disease are apparent. The pathogenesis of thrombocytopenia in women with severe pre-eclampsia is unknown, although vascular endothelial damage, impaired prostacyclin production and increased deposition of fibrin within the vascular bed have been suggested. Accelerated platelet destruction, platelet activation, increased platelet volume and increased megakaryocyte production have been observed [2]. An increased response of platelet calcium to arginine vasopressin preceding thrombocytopenia as early as in the first trimester has been reported and has been proposed as a possible predictor of the development of the disease [41]. Activation of the coagulation cascade occurs in most pre-eclamptic patients, but routine tests such as activated partial thromboplastin time, prothrombin time and fibrinogen concentrations are normal. However, fibrinogen D-dimers and thrombin-antithrombin complexes are elevated in most cases.

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Acute fatty liver of pregnancy

Mild microangiopathic haemolysis and thrombocytopenia are observed in acute fatty liver of pregnancy (AFLP) [50]. AFLP is most common in primiparae and affects one of 5000–10 000 pregnancies. These women present with malaise, nausea, epigastric and right upper quadrant pain, dyspnoea, cholestatic liver abnormalities, hypoglycaemia and decreased levels of fibrinogen and antithrombin. In 75% of these patients, there is laboratory evidence of disseminated intravascular coagulation caused by decreased hepatic synthesis of antithrombin. Management of patients with AFLP is supportive with emphasis of correction of hypoglycaemia, coagulopathy and electrolyte imbalances.

Other causes of thrombocytopenia in pregnancy

Disseminated intravascular coagulation can be associated with obstetric disorders such as placental abruption, amniotic fluid embolism, uterine rupture and intrauterine fetal death and may cause thrombocytopenia. In systemic lupus erythematosus (SLE) about 14–25% of patients develop thrombocytopenia caused by antiplatelet autoantibodies or circulating immune complexes [51]. Maternal autoantibodies can cross the placenta and cause fetal thrombocytopenia, especially in the presence of Ro- and La-antibodies [52].

Pregnant women suffering from antiphospholipid syndrome may have thrombocytopenia secondary to thrombosis, fetal loss or associated pre-eclampsia [53]. Approximately 28–42% of SLE patients have antiphospholipid and/or lupus anticoagulant, and have an increased risk of thromboembolism compared with those who lack these antibodies. The high fetal loss associated with the antiphospholipid syndrome is caused by recurrent thrombosis of the placental and decidual blood vessels.

Drug-induced thrombocytopenia occurs in pregnant as well as non-pregnant women. Quinidine and sulphonamides are among the most common drugs associated with acute thrombocytopenia [54].

Pregnant women with Type IIb von Willebrand disease may develop thrombocytopenia, which is caused by the enhanced clearance of platelets that bind to abnormal von Willebrand Factor molecule. HIV infection should be considered in any thrombocytopenic patient with risk factor [55].

Anaesthetic considerations

The choice of anaesthetic technique in the pregnant women with thrombocytopenia largely depends on the proposed method of delivery, gestational age of the fetus, coagulation status, associated obstetric complications, history of recent or current bleeding and other significant medical history. The risk of epidural haematoma in the general population is estimated to be 1 in 150 000 after epidural analgesia [56]. There are eight reports of spinal haematomas following obstetric epidural analgesia/anaesthesia in the literature but some of these are questionable [9, 57]. The incidence of epidural haematoma is 0.2–3.7 in 100 000 obstetric epidural blocks [59].

Circulating platelet numbers and their function determine the safety of regional anaesthesia. A lower limit of 100 × 10^9.l^-1 for platelet count is suggested as ‘safe’ for performing an epidural blockade, although there are no supporting data [60]. Several studies have attempted to address the issue of the risk of epidural haematoma when the platelet count is between 50 and 100 × 10^9.l^-1. Two

### Table 2 Clinical and laboratory features of HELLP, TTP, HUS.

<table>
<thead>
<tr>
<th>Feature</th>
<th>HELLP</th>
<th>TTP</th>
<th>HUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of presentation</td>
<td>&gt;37 weeks</td>
<td>mid-trimester</td>
<td>postpartum</td>
</tr>
<tr>
<td>CNS signs</td>
<td>variable</td>
<td>mild</td>
<td>severe</td>
</tr>
<tr>
<td>Renal failure</td>
<td>nil</td>
<td>present</td>
<td>nil usually</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>nil</td>
<td>severe</td>
<td>moderate</td>
</tr>
<tr>
<td>Fever</td>
<td>nil</td>
<td>present</td>
<td>nil</td>
</tr>
<tr>
<td>Purpura</td>
<td>nil</td>
<td>severe</td>
<td>nil usually</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>mild–moderate</td>
<td>mild</td>
<td>large</td>
</tr>
<tr>
<td>Creatinine increase</td>
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<td>no change</td>
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<tr>
<td>AST/ALT increase</td>
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<tr>
<td>Hyaline thrombocytes</td>
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<tr>
<td>Post-partum improvement</td>
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</tbody>
</table>

HELP = ‘Haemolysis, Elevated Liver enzymes, Low Platelets’. TTP = thrombotic thrombocytopenic purpura. HUS = haemolytic uraemic syndrome. AST = aspartate aminotransferase. ALT = alanine aminotransferase.
recorded in the 24 women who had a platelet count <100 × 10⁹ L⁻¹ [2, 61]. In a study of 2929 parturients, no complications associated with regional anaesthesia were recorded in the 24 women who had a platelet count <100 × 10⁹ L⁻¹ [62]. Beilin and colleagues reported that, over a 3-year period, 30 parturients who had platelet counts ranging from 69 to 98 × 10⁹ L⁻¹ safely received epidural anaesthesia [63]. A survey of American anaesthetists reported that 66% in academic practice and 55% of those in private practice would place an epidural anaesthetic when the platelet count is over 3-year period, 30 parturients who had platelet counts ranging from 69 to 98 × 10⁹ L⁻¹ safely received epidural anaesthesia [63]. A survey of American anaesthetists reported that 66% in academic practice and 55% of those in private practice would place an epidural anaesthetic when the platelet count is between 80 × 10⁹ L⁻¹ and 100 × 10⁹ L⁻¹ [64]. Most haematologists suggest that a platelet count >50 × 10⁹ L⁻¹ is safe for surgery and neuraxial blockade, provided platelet function is normal [5, 24].

Before carrying out further investigations to determine the cause of thrombocytopenia, factitious platelet counts due to laboratory artefacts must be ruled out by reviewing the peripheral blood film using a citrated blood sample. This artefact, termed as pseudo-thrombocytopenia, is caused by in vitro platelet clumping when EDTA is used as the anticoagulant, and is due to adhesion of platelets to the periphery of neutrophils in the presence of platelet agglutinins (IgG or IgM) [65].

The bleeding time test, a simple bedside test that evaluates the quality and quantity of platelets, is not considered to be reliable to determine the safety of epidural catheter placement because of wide observer variation. It is affected by technical (length and size of cut, occlusion pressure) and patient (ethnicity, diabetes, hypercholesterolaemia, etc.) factors [66]. Coagulation tests performed several weeks before delivery are not reliable in predicting coagulation abnormalities during labour [67]. In a study of 797 women, prothrombin time and the activated partial thromboplastin time were normal in all patients including those with low platelets and plasma fibrinogen concentrations (<2.9 gL⁻¹) and it was concluded that these tests are unnecessary in clinically normal parturients. The authors also reported that the percentage of women with platelet count values <100 × 10⁹ L⁻¹ increased from 0.5% (3/797) to 1.4% (11/797) between blood sampled during the 9th month of pregnancy and that obtained in labour.

The thromboelastogram (TEG) measures whole blood clotting, and the interactions between the coagulation cascade, fibrinogen, and platelets. However, TEG does not measure initial platelet adhesion to exposed collagen in the damaged vessel wall. Orlikowski measured platelet count, TEG variables and bleeding time in 49 parturients with pre-eclampsia. The thromboelastography variables, k time and maximal amplitude (MA) have a strong correlation with platelet count (k time – platelet count <100 × 10⁹ L⁻¹, r = –0.84, p = 0.02; MA – platelet count <100 × 10⁹ L⁻¹, r = –0.78, p = 0.04). An MA of 53 mm correlated with a platelet count of 54 × 10⁹ L⁻¹ (95% confidence limits, 40–75 × 10⁹ L⁻¹) and was associated with adequate clot formation produced by thromboelastography. The authors suggested that patients with platelet counts greater than 75 × 10⁹ L⁻¹ should not be denied regional anaesthesia [68]. In another study of TEG in normal pregnant women and in women with pre-eclampsia, all patients with a platelet count >75 × 10⁹ L⁻¹ had a normal MA, which indicated a normal clot [69]. It is difficult to draw firm conclusions about the reliability of TEG to predict which patients might develop epidural haematoma from these studies because few patients with platelet counts <75 × 10⁹ L⁻¹ received epidural anaesthesia.

Aggregometry (measures platelet aggregation in response to specific agonist such as ADP and epinephrine) and flow cytometry (measures platelet activation and aggregation) are not practical clinical tests because they are time-consuming and require technical expertise. The Platelet Function Analyser (PFA-100) may offer a rapid, simple point of care assessment of platelet aggregation. The PFA-100 platelet function analyser evaluates primary coagulation under high shear stress by measuring the time required for whole blood to occlude an aperture in a membrane coated with collagen and the platelet agonists, epinephrine (PFA-EPI), or adenosine diphosphate (PFA-ADP), called ‘closure time’. A 800-μl sample of citrated blood, maintained at 37 °C, is aspirated into stainless steel capillaries, through which a central aperture is cut into the membrane covered with collagen and epinephrine or collagen-ADP. Platelet activation and aggregation occurs on the membrane, resulting in the occlusion of the aperture and interruption of blood flow [70]. The test takes approximately 7 min. In a study of platelet function during pregnancy using the PFA-100 in patients with thrombocytopenia associated with pre-eclampsia, there was a correlation between platelet numbers and PFA-ADP closure time (normal range 71–118 s) particularly when the platelet count was less than 50 × 10⁹ L⁻¹ [71]. The PFA-ADP closure times were normal in healthy patients. However, the PFA-EPI closure times increased in six otherwise healthy patients, suggesting that PFA-EPI may give false positive values. Further evaluation of the PFA-100 in pregnant women with platelet counts of less than 50 × 10⁹ L⁻¹ is required [71]. Haemostasis is initiated by platelet adhesion to damaged vessel wall and the main disadvantage of all laboratory platelet function tests is that they do not measure the interaction between platelet and the vascular endothelium.
Large prospective studies with an estimated sample size of >200 000 patients are required to definitively determine whether it is safe to place an epidural or spinal anaesthetic in patients with a platelet count <100 x 10^9/L [63]. The entire clinical presentation of the patient must be considered when deciding on the appropriate choice of anaesthesia. It is important to ensure that there is no clinical evidence of bleeding and that the platelet count is not decreasing when epidural catheter placement is contemplated. A decreasing platelet count is considered a contraindication to neuraxial blockade, especially in dynamic conditions such as pre-eclampsia and ITP [63]. Pseudo-thrombocytopenia may be excluded. A manual platelet count is more accurate in patients with recent thrombocytopenia because automated counters are not reliable at low platelet counts. Specific questions about medications that might interfere with platelet numbers and function should be asked. A physical examination of the patient should include looking for evidence of bruising and bleeding at venepuncture sites or petechiae at the blood pressure cuff site. Consumptive coagulopathy associated with placental abruption and other conditions must be ruled out. When considering regional anaesthesia in patients with thrombocytopenia, spinal anaesthesia may be safer. A soft flexible catheter that is less likely to puncture blood vessels is preferred if an epidural anaesthetic is undertaken [66]. Careful monitoring of the patient in the postpartum period to detect early signs and symptoms of an epidural haematoma should be undertaken. General anaesthesia for urgent Caesarean section becomes necessary if coagulation is abnormal or there is bleeding.

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Anesthetic Considerations for the HIV-Infected Pregnant Patient

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It has been reported that women of childbearing age constitute a large percentage of the new cases of HIV/AIDS infection. Consequently, it is not uncommon to find pregnant women who are HIV positive. Because of the increased prevalence of HIV infection in pregnant women, many anesthesiologists encounter these patients in their practices. Infection with HIV in pregnancy often raises questions about the safety of regional anesthesia in these patients. This controversy first began when it was suggested that the introduction of a spinal needle in an HIV-infected parturient would spread the disease into the CNS, leading to the development of neurological sequelae of this disease. Nevertheless, recent analysis of the problem has shown HIV infection should not contraindicate regional anesthesia.

Key Words: HIV infection, acquired immunodeficiency syndrome (AIDS), pregnancy, obstetric anesthesia, regional, general

INTRODUCTION

Infection with Human Immunodeficiency Virus (HIV) has been described as a "disease that knows no borders and respects no moral code". Because of the increased prevalence of infection with HIV in pregnant women, many obstetric anesthesiologists are seeing these patients in their practices and must grapple with the question: Can regional anesthesia be safely performed in the parturient that is HIV-positive? In order to answer this question, and to be more familiar with the obstetric and anesthetic management of these women, this review will update and familiarize the anesthesiologist with the effect that this disease, and the drugs used for its treatment have on both the mother and her developing fetus. Anesthetic options for these patients will be reviewed with a focus on the use of neuraxial techniques. In addition, HIV infection passing from patient to physician can occur, and therefore safety measures that can be taken when handling body fluids or blood will also be reviewed.

IDENTIFICATION OF PREGNANT PATIENTS WITH HIV-INFECTION

Identification of HIV in the pregnant patient is of significant importance to obstetricians, neonatologists and anesthesiologists. It is unfortunate that only about 20% of physicians inquire about substance abuse when interviewing their patients. It can be presumed that even fewer inquire about the possibility of HIV infection.

The diagnosis of HIV infection in pregnancy often raises questions about the safety of regional anesthesia and analgesia in these patients. This controversy began when the introduction of a spinal needle was suggested to increase patient's risk for the development of the neurological sequelae of this disease. Despite this fear, it has now been well established that HIV infection does not contraindicate the administration of neuraxial anesthesia. HIV is a neurotropic virus, and the central nervous system is infected early in the course of the disease process. These findings have been confirmed by the isolation of virions and antibodies in the cerebrospinal fluid (CSF). Neurotropic predisposition to an HIV virus is...
responsible for the clinical evidence of neurological dysfunction at the time of AIDS diagnosis in up to 30 to 40% of infected patients.7

Human Immunodeficiency Virus is a retrovirus that carries enzyme reverse transcriptase, which converts the single-stranded viral RNA into double-stranded DNA. The double-stranded DNA may be subsequently integrated into the DNA material of the infected human cells. AIDS has grown from negligible numbers in 1980 to a cumulative total of 8.4 million cases, as reported by the World Health Organization, as of 1997.8 As of December 2002, the World Health Organization reported that a total number of adults and children living with HIV/AIDS had reached 42 million individuals.5 It has been estimated that with the onset of the new millennium, 90% of new AIDS cases will be found in the Third World countries. Recreational drug abuse and homosexual orientation appear closely related to most, but not all European and American AIDS patients.9 In most parts of Africa, heterosexual intercourse still remains the dominant mode of HIV transmission. In the United States, women have been identified as the fastest growing group of new AIDS patients.10 For example, in the United States in 1996, HIV infection was reported to be the leading cause of death in black women, and the third leading cause of death for all women in the 25-to 44-year-old age group.11

HIV/AIDS should be viewed as a clinical spectrum that may affect any system of the human body, -it is a multi-system disease. The clinical manifestations of HIV/AIDS are reviewed in Table 1.1218 This disease usually begins with a primary infection, followed by a period of clinical latency of variable length, leading to profound immunodeficiency, opportunistic infection and death. In some countries (e.g., USA), the HIV-positive patient, irrespective of her clinical condition, meets, by definition, the criteria for AIDS when the CD4+ T cell count drops below 200 cells/microliter.19 Diagnostic confirmation of the disease relies on the detection of antibodies to HIV antigens. It may take up to 10 to 12 weeks from the initial infection before the antibodies in human serum reach those of needed to confirm an HIV infection, which remains one of the major problems facing our society today. This disease has crossed international, geographic, economic and social borders. Pregnant women, unfortunately, are not immune to this disease, and in fact, women of childbearing age constitute a large percentage of new cases at detectable levels (window period). Two well-established diagnostic tests for HIV are based on antibody detection, which in-

**Table 1. Clinical Manifestations of HIV/AIDS**

<table>
<thead>
<tr>
<th>System</th>
<th>Clinical manifestations</th>
</tr>
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<tbody>
<tr>
<td>Nervous system</td>
<td>Myelopathy, aseptic meningitis, HIV encephalopathy, dementia complex, peripheral neuropathy</td>
</tr>
<tr>
<td>Pulmonary system</td>
<td>Opportunistic infections (pneumocystis carinii, mycobacterium tuberculosis, mycobacterium avium complex)</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>Pericardial disease, dilated cardiomyopathy</td>
</tr>
<tr>
<td>Gastrointestinal system</td>
<td>Oropharyngeal candidiasis, aphthous ulcers, leukoplakia, esophagitis, hepatobiliary involvement, HIV enteropathy with chronic diarrhea</td>
</tr>
<tr>
<td>Renal system</td>
<td>Focal and segmental glomerulosclerosis, end-stage renal failure</td>
</tr>
<tr>
<td>Hematological system</td>
<td>Normocytic normochromic anemia, thrombocytopenia, neutropenia, coagulation abnormalities</td>
</tr>
<tr>
<td>Endocrine system</td>
<td>Adrenal insufficiency, hypothyroidism, SIADH</td>
</tr>
<tr>
<td>Immunological system</td>
<td>Depression of immune function</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>AIDS-related wasting syndrome</td>
</tr>
</tbody>
</table>

clude the enzyme-linked immunosorbent assay (ELISA) and the Western blot test. The ELISA test measures the binding of anti-HIV antibodies from a patient’s serum to a mixture of antigens obtained from HIV that have been grown either in human tissue culture (first-generation test) or through recombinant DNA techniques (second-generation test). To confirm the diagnosis after a positive ELISA result, a Western blot test is usually performed, as a false positive result with the Western blot test occur less frequently than with ELISA.\textsuperscript{20}

TREATMENT OF HIV-INFECTED PREGNANT PATIENTS

Most currently used drug regimens for the treatment of HIV infected patients include three-drug protocols, combining a protease, or non-nucleoside reverse transcriptase, inhibitor, with two nucleoside reverse transcriptase inhibitors. As more complex treatment modalities become available, the clinical picture of HIV-infected patients may become more challenging for health care providers. Pregnant women should, in general, receive the same therapy as they would if not pregnant, taking into account the metabolic differences, concerns regarding specific drugs and additional indications for therapy, to prevent perinatal transmission.\textsuperscript{21} The physiological changes during pregnancy that may impact the pharmacokinetics of antiretroviral drugs include; increased plasma volume, cardiac output, glomerular filtration rate, decreased plasma proteins for binding of drugs and changes in the metabolic enzyme levels. The commonly used drugs, and their anesthetic implications, are reviewed in Table 2.\textsuperscript{22-24}

PREVENTION OF PERIPARTUM TRANSMISSION OF HIV-INFECTION

A high maternal viral load increases the likelihood of perinatal transmission of HIV\textsuperscript{25,26} and evidence suggests that most perinatal HIV transmissions occur during labor and delivery.\textsuperscript{27,28} Mock et al.\textsuperscript{27} conducted a prospective cohort study of 218 formula-fed infants of untreated HIV-infected mothers with a known infection outcome and a birth HIV-1 positive DNA PCR. Of the 49 infected infants in their study, 12 (24.5\%) were presumed to have been infected in utero, and 37 (75.5\%) infected intrapartum. The estimated absolute overall transmission rate was 22.5\% (5.5\% in utero transmission rate and 18\% intrapartum transmission rate). Low birth weight was associated with in utero transmission, whereas low maternal natural killer cell and CD4+T-lympho-

<table>
<thead>
<tr>
<th>Table 2. Anesthetic Implications of Anti-retroviral Drug Therapy</th>
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<tbody>
<tr>
<td>Drug</td>
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<tr>
<td>Zidovudine</td>
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<tr>
<td>Ganciclovir</td>
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<tr>
<td>Trimethoprim Sulfamethoxazole/</td>
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<tr>
<td>Didanosine</td>
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<td>Stavudine</td>
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<td>Zalcitabine</td>
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<td>Lamivudine</td>
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<td>Protease inhibitors</td>
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<td>Isoniazid</td>
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<td>Rifampin</td>
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<td>Ethambutol</td>
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<td>Pentamidine</td>
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<td>Phenytoin</td>
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cyte percentages were associated with intrapar-
tum transmission. Kind et al.29 studied the effect of elective cesarean section and zidovudine pro-
phylaxis on vertical HIV transmission. In their
cohort study, 67 out of 414 newborns were found
to be infected, producing an overall transmission
rate of 16.2%. An elective cesarean section, with
intact membranes, but without previous labor,
was associated with the lower transmission rate of
6%. The transmission rate was intermediate after
a spontaneous delivery or nonelective cesarean
section (18%), but higher after obstetric interven-
tions (27%). In this study, the combined use of an
elective cesarean section and zidovudine resulted
in a 0% transmission rate (none out of 31), com-
pared with 8% (seven out of 86) after an elective
cesarean section without zidovudine, and 17%
(four out of 24) after zidovudine alone and 20%
(55 out of 271) after no intervention. The authors
concluded that an elective cesarean section and
zidovudine prophylaxis appear to have an addi-
tive effect in the prevention of vertical HIV trans-
mission. Because of these recent findings, many
HIV-positive women are being advised to under-
go an elective cesarean section, and anesthesi-
ologists will be expected to take a more active role
in their management.

ANESTHETIC CONSIDERATIONS FOR
HIV-INFECTED PREGNANT PATIENTS

HIV is a neurotropic virus, and CNS invasion
occurs in the early stages of primary infection.
Therefore, neuraxial anesthetic techniques may be
safely used in many HIV-infected patients for
analgia during labor, with a cesarean section not
accelerating the progression of HIV to the central
nervous system.30 Anesthetic management of an
abdominal delivery must be tailored to the indi-
vidual obstetric indications, the urgency of deliv-
ery and the presence of any coexisting disease.
HIV seropositivity alone, however, should not
determine the preferred method of anesthesia for
a cesarean section or analgesia for labor.30 The fact
that a parturient has been diagnosed as HIV-
positive should not cause a physician to deny
appropriate care, and the American Medical
Association has suggested that physicians have an
ethical duty to treat HIV-positive patients.

A significant number of HIV-infected patients
have a past medical/social history that has in
some way contributed to infection with HIV.
Substance abuse (intravenous drug abuse in par-
ticular) remains a significant risk factor, and may
have anesthetic implications. Sexually transmitted
diseases, such as hepatitis B and syphilis, may
also alter the anesthetic management. A careful
physical examination, and documentation of
neurological deficits, should therefore be under-
taken before the induction of regional anesthesia.
31,32 The presence of AIDS-related dementia may
preclude the patient consenting to either surgery
or anesthesia. Involvement of the respiratory
system with an oropharyngeal and esophageal
pathology may make these patients more prone to
regurgitation, difficult intubation and aspiration.
Opportunistic pulmonary infections may neces-
sitate prolonged postoperative mechanical ventila-
tion. A careful examination of the cardiovascular
(subclinical cardiomyopathy) and renal systems
(nephropathy), as well as hematological studies
(neutropenia, thrombocytopenia), are indicated as
part of the anesthetic preoperative assessment.
Although thrombocytopenia may occur in the
HIV-positive patient, it is rare for the platelet
count to be low enough as to impact on the choice
of anesthetic. If, however, the platelet count falls
below 50,000, the risks of bleeding and the
development of epidural hematoma increase, and
the use of alternative anesthetic techniques should
be considered on a case-by-case basis. There ap-
pears to be no evidence of increased infectious
complications in parturients that receive neuraxial
anesthesia or analgesia.

Treatment for the complications of neuraxial
anesthesia, including the management of a post-
dural puncture headache, should not differ from
the management of HIV-negative parturients.
Specifically, should a post-dural puncture head-
ache occur, an epidural blood patch, with autolo-
gous blood, is safe and effective in HIV seroposi-
tive patients.33 If general anesthesia is selected,
dose adjustments for a history of drug abuse,
compromised liver and kidney functions or gene-
ralized muscle wasting, may be necessary. In
addition, HIV-related lung pathology may require
the use of a higher fraction of intraoperative in-
spired oxygen. An increased sensitivity to opioids and benzodiazepines may occur, particularly in patients with HIV associated mental changes.

OCCUPATIONAL EXPOSURE

Necessary safety measures (universal/standard precautions) must be employed when handling blood, blood products, body fluids and tissues from all patients. Because there is a "window period" between the primary HIV infection and seroconversion, the diagnosis can be delayed. Additionally, the transmission of other blood borne pathogens, such as hepatitis B and C, must also be considered. The use of gloves prevents 98% of an anesthesiologist’s contact with a patient’s blood and body fluids. 34-36 Facemasks and eye-shields further reduce the risk of exposure, and should be routinely used. The risk of HIV transmission from a needle-stick injury, with HIV-infected blood, is approximately 0.32%. 37 All health workers with needle stick injuries should have immediate access to antiretroviral drug therapy. Drugs should be taken within the first hour following exposure, which can reduce the rate of seroconversion by 80%. 38 Factors determining the risk of exposure of health-care workers include: the quantity of blood involved, the type of procedure for which the needle was used, the depth of the needle-stick injury and the viral titer of the HIV-infected patient.

SUMMARY

Regional anesthesia has become a paramount technique for the relief of pain during labor and delivery, and a hallmark of modern obstetric anesthesia practice. Can every HIV-positive patient safely receive spinal or epidural anesthesia? Obviously not. The decision to administer neuraxial analgesia or anesthesia should be individualized, and made only after review of the history (including coexisting diseases), a physical examination and appropriate laboratory tests. However, as demonstrated in this review, the vast majority of parturients with HIV positivity and AIDS can safely receive neuraxial blocks. When considering the optimal anesthetic to administer to an HIV-positive patient, the anesthesiologist must consider not only the patient and her disease, but also the available alternatives. As with all pregnant patients, the consequences of administering a general anesthetic to a stable parturient with HIV may include failed intubation and aspiration.

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Human Immunodeficiency Virus: Anesthetic and Obstetric Considerations

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The pandemic of acquired immune deficiency syndrome (AIDS) is on the threshold of its third decade of existence. The World Health Organization-United Nations statistics show that human immunodeficiency virus (HIV)/AIDS pandemia is set to get much worse. Women of reproductive age are the fastest growing population with HIV. Common signs and symptoms have become more moderate or subclinical, and new clinical presentations have emerged. It is quite apparent that HIV-disease affects multiple organ systems. Advances have been made in elucidating the pathogenesis of HIV. In addition, the molecular technique of viral load determination and the CD + T-lymphocyte count enable evaluation of the disease, its prognosis, and its response to therapy. There is limited specific information concerning the overall risk of anesthesia and surgery of HIV/AIDS patients. However, as far as can be determined, surgical interventions do not increase the postoperative risk for complications or death and should therefore not be withheld. There is also little evidence to suggest that HIV or antiretroviral drugs increase the rate of pregnancy complications or that pregnancy may alter the course of HIV infection. General anesthesia is considered safe, but drug interactions and their impact on various organ systems should be considered preoperatively. Regional anesthesia is often the technique of choice. Yet, one must take into consideration the presence of neuropathies, local infection, or blood clotting abnormalities. It should be emphasized that all practicing anesthesiologists should be familiar with the disease and should use prenatal anesthesia consultations and a team approach to assure optimal treatment for HIV patients.

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Acquired immune deficiency syndrome (AIDS) was first recognized more than 20 years ago, and since then it has reached pandemic proportions. Within 2 decades, more than 50 million people have been infected with the human immunodeficiency virus (HIV) and 20 million have died. Worldwide, two-thirds of the 36 million known carriers of HIV are living in sub-Saharan Africa (1). In the United States (US), 950,000 people have HIV/AIDS. In the year 2001, 15,000 of those people died from the disease (1). New infections occur at approximately 40,000 per year (2). Young women are the fastest growing population with HIV in the US. Almost 30% of new HIV infections in the year 2000 were among women. Eighty-two percent of the new infections occurred in ethnic/racial minorities, predominantly among African Americans. The parturient transmits the HIV perinatally; thus the epidemic in children parallels the epidemic among women (2,3). The transmission of the disease in nonbreast-fed infants occurs 30% of the time in utero and 70% during labor and delivery (4).

The overall risk of anesthesia and surgery in HIV positive patient needs further study. Twenty to 25 percent of HIV-positive patients will require surgery during their illness (5). Anesthesiologists need to be aware of the disease when deciding on the course of anesthesia. This multiorgan disease may be complicated either by opportunistic infections, tumors, substance abuse, or antiretroviral therapeutic drugs, which all can have an impact on anesthesia.

HIV is a member of the lentivirus family, a subtype of human retroviruses. It is characterized by a cytopathic action, a long latency period, and persistent viremia. As a result of impaired cell-mediated immunity, the infected person is more susceptible to viral, bacterial, mycobacterial, and malignant disease (6). Of the untreated patients, 10% will develop symptomatic
AIDS in the first 2–3 yr of infection. The remainder will develop the disease over a 10-yr time period (7).

**Diagnosis of HIV Infection**

As the viral envelope is composed of different glycoproteins, antibodies to these proteins or to the p24 antigenic core can be detected. The diagnostic techniques include serologic tests, viral culture, genomic detection, and amplification of viral ribonucleic acid (RNA) or proviral deoxyribonucleic acid (DNA).

Specific HIV antibodies can be detected serologically 2–8 wk (usually within 3 wk) after infection. The first antibodies to appear are immunoglobulin (Ig) M to the viral envelope glycoprotein. After a few days the IgG to p24 core antigen and gypcoprotein-gp120 appear. Antibody detection tests are the enzyme-linked immunosorbent assay (ELISA) and the more specific Western blot test (8).

HIV diagnosis can be made by direct detection of HIV using the ELISA test for p24 core antigen or by amplification and detection of proviral DNA or HIV RNA using polymerase chain reaction. This can be important for the monitoring of HIV treatment for detection of HIV in neonates of infected mothers (9). Viral load determination is used for diagnostic quantification and monitoring of HIV treatment (10). These viral load levels usually correlate with CD4+ T cell lymphocyte count. A successful anti-HIV therapy means viral load suppression to an undetectable blood level.

**Clinical Manifestations of HIV Infection**

Over time, antiretroviral therapy has changed the epidemiologic, demographic and clinical characteristics of AIDS. The signs and symptoms can be caused by the HIV infection, opportunistic infections, neoplasm, or by the antiretroviral drugs. As the highly active antiretroviral therapy (HAART) became more effective, life expectancy and the clinical appearance has become moderated or subclinical.

**Central and Peripheral Nervous System.** Some 30% of adults and 50% of children suffering from AIDS will develop neurological disorders (11). In the early stage of infection, headaches, photophobia, meningoencephalitis, depression, irritability, Guillain-Barre-like syndromes, or cranial and peripheral neuropathy can be observed. The latent phase of the disease is associated with demyelinating neuropathy and cerebrospinal fluid pathology. The late period of HIV infection is associated with meningitis, focal or diffused encephalopathy, myelopathy, myopathy, and peripheral neuropathy.

As the central nervous system (CNS) is the first crucial organ to be affected by anesthetic drugs, early diagnosis of HIV deserves careful evaluation of cognitive and neurologic dysfunction. Patients with AIDS are more sensitive to opioids and benzodiazepines, which also reflects the extent of neurological involvement. The probable mechanism is based on increased interleukin-1 levels causing an increased γ aminobutyric acid-mediator production (12). HIV infection, intracranial masses, or opportunistic infections may cause cerebral edema, cerebral hemodynamic disturbances, and increased intracranial pressure (ICP). These deserve anesthetic consideration and measures for reducing ICP and generally preclude the use of neuraxial anesthesia in patients with increased ICP. Peripheral neuropathy is the most frequent neurological complication in HIV patients (13). It affects approximately 35% of patients with AIDS and manifests clinically as a polyneuropathy and myopathy.

An autonomic dysfunction in the HIV-infected person may appear with or without CNS abnormalities. AIDS patients may present with uncommon autonomic disturbances, such as orthostatic syncope, hypotension, and diarrhea (14).

**Pulmonary Abnormalities.** The pulmonary manifestations of patients infected with HIV are caused mainly by opportunistic infections. The most common of these, *Pneumocystis carinii* infection, has become rarer with the use of HAART and prophylactic drug therapy (15). An immunocompromised person with a CD4+ lymphocyte count of <200 cells/mm³ is at increased risk for developing *P. carinii* pneumonia. The disease may present as adult respiratory distress syndrome and may be complicated by pneumatoceles, pneumothorax, or respiratory failure (16). Computed tomography of the chest in the early stages of the disease may reveal bilateral haziness of both lungs, whereas chest radiograph appears normal (17).

Tuberculosis (TB) is another concern in AIDS patients. The incidence of HIV-associated TB has been increasing, especially among women of childbearing age (18). Patients with both infections may present with atypical manifestations of TB that causes difficulty in making a diagnosis. Other pathologies that may affect the lungs are Kaposi’s sarcoma, lymphomas, and cavitary lung disease caused either by fungal pathogens or Nocardia.

**Cardiac Manifestations.** Advances in the treatment of HIV infection have improved longevity of HIV patients, thereby they develop more cardiac involvement (Table 1) (19). In the advanced stage of the disease, myocarditis is more common and is caused by opportunistic infections or neoplasm-like lymphomas and Kaposi’s sarcoma (20).

There are reports of various abnormalities associated with a hypercoagulable state (21). These include pulmonary hypertension, accelerated coronary arteriosclerosis, a decrease in left ventricular contractility.
Table 1. Manifestations of Human Immunodeficiency Virus Infection

<table>
<thead>
<tr>
<th>Cardiovascular</th>
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<tbody>
<tr>
<td>Pericardial effusion</td>
</tr>
<tr>
<td>Myocarditis (opportunistic infections, neoplasms)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>Endocarditis</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Drug-related cardiotoxicity</td>
</tr>
<tr>
<td>Thromboembolic complications</td>
</tr>
<tr>
<td>Rheological impairment (increase of tumor necrosis factor and interleukin 1-alpha)</td>
</tr>
<tr>
<td>Decreased left ventricular contractility</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagitis, dysphagia, odynophagia</td>
</tr>
<tr>
<td>Diarrhea, gastrointestinal bleeding, abdominal pain</td>
</tr>
<tr>
<td>Hepatitis</td>
</tr>
<tr>
<td>Biliary disease (acalculous cholangitis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Leukopenia, lymphopenia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Bone marrow suppression (infections, drugs, neoplasms)</td>
</tr>
<tr>
<td>Hypercoagulability</td>
</tr>
<tr>
<td>Acquired immune deficiency syndrome-related lymphoma (Hodgkin’s disease)</td>
</tr>
</tbody>
</table>

and myocardial infarction in young HIV patients. Preoperative cardiac evaluation is therefore mandatory and appropriate perioperative cardiovascular monitoring of these patients is of crucial importance (22).

Gastrointestinal Abnormalities. Gastrointestinal abnormalities are commonly encountered in patients with AIDS (Table 1). Signs and symptoms may originate from the oropharynx, esophagus, stomach, and hepatobiliary system (23). The main cause of dysphagia is Candida albicans esophagitis. Other common pathogens are cytomegalovirus (CMV), herpes virus, Kaposi’s sarcoma, histoplasmosis, and squamous cell carcinoma. In advanced AIDS, esophageal reflux is common, which may increase the risk for pulmonary aspiration on induction of general anesthesia (24). Abnormal liver function tests are also common in advanced AIDS and reflect the decreased metabolic and secretory ability of the liver in addition to coagulation abnormalities. Finally, electrolyte abnormalities are caused by diarrhea and decreased oral intake resulting from dysphagia or nausea.

Hematological Abnormalities. A wide spectrum of hematologic abnormalities in HIV patients is very common and may appear at any stage of the disease (Table 1). Bone marrow involvement and coagulation abnormalities may result from HIV infection, anti-HIV drugs, nutritional factors, and bone marrow infiltration by opportunistic infection or neoplastic diseases (25).

The literature contains reports of thrombotic episodes and various predisposing abnormalities related to a hypercoagulable state that correlate with the severity of HIV disease (26). The coexistence of HIV-related illness, such as malignancies and autoimmune disease, as well as antiretroviral drug therapy itself, may also predispose these patients to thromboembolic events (26).

Another coagulation abnormality seen in the HIV patients is idiopathic thrombocytopenic purpura that is caused by platelet serum immunoglobulin, or direct adverse effects of HIV infection on the megakaryocytes (25). Some of the antiretroviral (zidovudine) or antiopportunistic drugs (ganciclovir) may contribute to these hematologic abnormalities as a result of bone marrow suppression (25).

Renal Abnormalities. HIV patients are at risk for developing various renal diseases caused by HIV infection, viral hepatitis, drug abuse, antiretroviral drugs, and dehydration (27). The HIV-associated nephropathy is a distinct clinico-pathological syndrome presenting as a nephrotic syndrome. The use of angiotensin-converting enzyme inhibitors, steroids, and antiretroviral treatment may slow down its progression to end-stage renal failure (28). The use of an antiretroviral drug, such as adefovir, may cause acute toxic tubular necrosis (29). Indinavir, which is also commonly used, is associated with a 3% incidence of nephrolithiasis (30).

Endocrinologic and Metabolic Abnormalities. The course of HIV infection or AIDS can be complicated by a variety of endocrine and metabolic abnormalities. This may be a direct effect of HIV on the respective glands, by opportunistic infections, neoplasm, or antiretroviral drugs. Primary or secondary adrenal insufficiency is still the most serious endocrine complication in HIV patients (31). Thyroid function tests in AIDS patients may be abnormal, although clinical hypothyroidism is rare.

Hypoglycemia is another metabolic abnormality that may be caused by islet cell damage resulting from pentamidine treatment. Hyperinsulinemic hypoglycemia may be associated with hypopituitarism in an AIDS patient or as a complication of protease inhibitor treatment (22).

HIV and Pregnancy

One-third of new HIV positive patients in 2000 were women (1). In the US, the nationwide seroprevalence of HIV during pregnancy has been reported as 1.7 per 1000 pregnancies (32). The majority of pediatric HIV infections resulted from vertical transmission of the virus from mother to infant. This occurred 4.4% of the time during pregnancy, 60% of the time during delivery, and 35.6% of the time during breastfeeding (33).

A meta-analysis of the International Perinatal HIV group included 15 prospective European and North American studies of 8500 parturients. A reduction of
vertical transmission by more than 50% was observed when elective cesarean delivery was performed (34). More recently, elective cesarean delivery combined with antiretroviral therapy has reduced vertical transmission to <5% (35). The American College of Obstetricians and Gynecologists (ACOG) committee opinion of May 2000 stated that when viral loads are more than 1000 copies per milliliter, the benefit from elective cesarean delivery is beyond that achieved by antiretroviral therapy alone (36). It has been further noted that the mode of delivery should be individually assessed and that the viral load testing has to be followed every 3 mo. Many practitioners do not recommend elective cesarean delivery for HIV-infected women who are compliant with antiretroviral therapy and have undetectable HIV viral loads (37). The revised ACOG Committee Opinion also considers routine delivery by cesarean section to be problematic and potentially dangerous, especially in rural hospitals in Africa where maternal mortality approximates 230 per 100,000 (36). The incidence of complications is significantly increased when the CD4+ count is <200 mm−3 (38,39). Routine HIV testing should be offered to every pregnant person at risk of HIV infection.

The percentage of women diagnosed before delivery in the US has improved from 51% in 1993 to 80% in 1996 (40). The European Collaborative study has shown that 14% of HIV-infected pregnant women are immunocompromised, and there is no evidence to suggest that pregnancy alters the course of HIV infection (41).

Intrauterine growth retardation and premature delivery were reported among infants of HIV-infected women regardless of their infectious condition (41).

**Table 2. Antiretroviral Drugs [Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs)] and Side Effects**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>FDA Pregnancy Category</th>
<th>Dose</th>
<th>Adverse Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (AZT)</td>
<td>Retrovir*</td>
<td>C</td>
<td>100</td>
<td>mg 6×/day</td>
</tr>
<tr>
<td>Didanosine (ddi)</td>
<td>Videx†</td>
<td>B</td>
<td>200</td>
<td>mg b.i.d.</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>Zerit‡</td>
<td>C</td>
<td>40</td>
<td>mg b.i.d.</td>
</tr>
<tr>
<td>Zalcitabine (ddC)</td>
<td>Hivid‡</td>
<td>C</td>
<td>0.75</td>
<td>mg t.i.d.</td>
</tr>
<tr>
<td>Abacavir</td>
<td>Ziagen*</td>
<td>C</td>
<td>300</td>
<td>mg t.i.d.</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Epivir*</td>
<td>C</td>
<td>300</td>
<td>mg b.i.d.</td>
</tr>
<tr>
<td>Zidovudine plus Lamivudine</td>
<td>Combivir*</td>
<td>C</td>
<td>300</td>
<td>mg b.i.d.</td>
</tr>
<tr>
<td>Adefovir</td>
<td>Hepsera§</td>
<td>C</td>
<td>120</td>
<td>mg/day</td>
</tr>
</tbody>
</table>

Food and Drug Administration (FDA) Pregnancy Category = “B” (animal reproduction studies failed to demonstrate a risk to the fetus); “C” (safety in human pregnancy has not been determined).

* Manufactured by GlaxoSmithKline, Research Triangle Park, NC; † manufactured by Bristol-Myers Squibb, New York, NY; ‡ manufactured by Roche Pharmaceuticals, Basel, Switzerland; § manufactured by Gilead Sciences, Foster City, CA.

Antiretroviral Drugs

Three classes of antiretroviral drugs have gained Food and Drug Administration approval and are currently used in the management of HIV disease (44) (Tables 2–4).

1. Nucleosides analog reverse transcriptase inhibitors. These drugs inhibit the completion of reverse transcription by binding to the viral DNA. Side effects commonly reported with zidovudine treatment include headache, insomnia, nausea, and vomiting. Prolonged therapy can lead to neuropathy, malaise, myalgia and myopathy with increased creatinine-phosphokinase, and pancytopenia. Peripheral neuropathy is the most common side effect of zalcitabine. It correlates with the severity of HIV infection and may affect
30% of patients treated (45). Lamivudine is the least neurotoxic of the currently used nucleoside analogues. It may exacerbate preexisting neuropathy (46). However, combined antiretroviral therapy was shown to improve HIV-related peripheral neuropathy (47). Peripheral neuropathy is generally reversible on cessation of therapy.

2. Non-nucleotide reverse transcriptase inhibitors (NNRTIs). These drugs inhibit the enzyme reverse transcriptase by direct binding. Because they bind only to the HIV-1, resistance to them develops rapidly when given as a single drug. The recommendations are to use NNRTIs in combination with three or more drugs to enhance their effectiveness (48). The NNRTIs most commonly used are nevirapine, delavirdine, and efavirenz (Table 3). Their major side effect is skin rash, including Stevens-Johnson’s syndrome. Nevirapine causes cytochrome P450 enzyme induction (CYP3 A3/4) and may decrease serum levels of some anesthetic or sedative drugs (i.e., midazolam, fentanyl) (49).

3. Protease inhibitors (PIs) (Table 4). These drugs inhibit the HIV protease by binding to the active cleavage site. The most commonly used PIs are saquinavir, ritonavir, indinavir, and nelfinavir. Side effects are gastrointestinal symptoms, hyperglycemia, peripheral neuropathy, obstructive uropathy (30), increased liver enzymes, and hypertriglyceridemia (50). Efavirenz is a potent teratogenic drug that should be avoided during the first trimester of pregnancy (45). Indinavir may be associated with mild hyperbilirubinemia, hematuria, and renal failure resulting from obstructive uropathy (30). The PIs are metabolized by the cytochrome P450 isoenzyme cytochrome P3A4 (CYP3 A4). They competitively inhibit the enzyme and may increase the effects of drugs metabolized by cytochrome P450. Therefore, these anesthetic drugs should be titrated carefully (49). Ritonavir is the most potent inhibitor of CYP3 A4 and CYP3 D6 and is a less potent inhibitor of CYP2 C9/10 (51). Fentanyl, a synthetic opioid analgesic, is metabolized mainly by CYP3 A4 (51) and to a lesser extent by other CYPs (52).

Anesthetic Management

Assessment of risk and coexisting diseases during preoperative evaluation should focus on the patient’s status, type of surgery, and anesthesia, which, combined
with the Centers for Disease Control stage of HIV infection, the immunologic status (CD$_4^+$ cell count), and the coexistence of opportunistic infections and malignancies, should allow a good prediction for the perioperative risk of the HIV-patient to be construed. Advanced HIV infection, when accompanied with opportunistic infections or malignancies, may complicate the perioperative course and management. The CD$_4^+$ count/mortality relationship is useful in risk assessment. Regardless of surgical procedure, there is a 13.3% mortality rate 6 mo postoperatively when the CD$_4^+$ count is <50 mm$^{-3}$ and a 0.8% mortality rate when the CD$_4^+$ count is more than 200 mm$^{-3}$ (53).

Preoperative assessment consists of the history, physical examination, and laboratory studies. The history should include evaluation of opportunistic infections and malignancy and concurrent treatments with antiretroviral or antiopportunistic drugs. The laboratory work-up should include complete blood count, clotting functions, and glucose, liver, and renal function tests. Verification of the immunological status, i.e., the CD$_4^+$ lymphocyte cell count and viral load during the previous 3 mo, is important. Chest radiograph and electrocardiogram should be performed in all patients. Patients with a history or signs of cardiac or pulmonary dysfunction should undergo a more thorough evaluation (blood gases, pulmonary function tests, echocardiography, cardiac effort test, and radioactive cardiac scanning or even cardiac catheterization). One must remember that these patients have often been subjected to cardiotoxic antiretroviral drugs, may be in a hypercoagulable state, may have accelerated coronary arteriosclerosis, and often have decreased left ventricular contractility (19–22). They will require appropriate preoperative work-up and therapy before any anesthetic or surgical procedure.

**Anesthetic Techniques**

Factors that need to be considered when administering general anesthesia include the possible effects of anesthesia and opioids on the immune system, the pulmonary and neurologic status of the HIV patient, and possible interactions with anti-HIV medications. Laboratory data suggest a detrimental effect of opioids on immune function (54). However, the clinical significance of short-term opioid administration during general anesthesia is unclear and there are not enough clinical data available to justify its avoidance. The presence of neurologic manifestations, such as overt dementia, may impair the ability of the patient to provide preoperative consent (55) and may increase brain sensitivity to sedative or psychoactive drugs (opioids, benzodiazepines, and neuroleptics). Opportunistic infections may be associated with increased ICP, predominantly with toxoplasmosis. Because these infections respond rapidly to medical therapy, surgery should be postponed whenever possible when they are present. Increased ICP and CNS infections (meningitis, encephalopathy, or myelopathy) are contraindications to neuraxial anesthesia (56).

The diagnostic approach to patients with HIV infection and neuropathy, myopathy, or other neurological deficit consists of taking a comprehensive neurological history and physical examination. Blood studies are needed to exclude diabetes mellitus, vitamin deficiencies, alcoholism, hereditary diseases, and infectious diseases such as CMV or Lyme disease. Cerebrospinal fluid analysis and nerve or muscle biopsy may be required. Radiological studies of the spinal cord should be performed as part of the neurological evaluation to exclude compressive lesions in symptomatic patients. This is particularly important in a patient scheduled for a surgical procedure under regional anesthesia (57).

The complications associated with the use of succinylcholine, such as hyperkalemia or hyperpyrexia, are only a potential risk to be considered in the HIV patient with progressive neuropathy, myopathy, and muscle wasting. No such complication in HIV patients has been reported in the literature; hence, the use of succinylcholine is not absolutely contraindicated (58).

Pulmonary complications can occur as a consequence of opportunistic infections. This may lead to respiratory distress and hypoxemia, aggravated by a decrease in functional residual capacity seen during pregnancy. Regional anesthesia may be a preferable technique in these patients. However, a high motor block with intercostal muscle paralysis may not be tolerated. Regional anesthesia was shown to be associated with reduced morbidity and mortality in a wide range of patients, including treated HIV parturients having cesarean delivery under spinal anesthesia (59).

**Toxic Side Effects and Drug Interaction with Anesthesia**

Before administration of any anesthetics, the anesthesiologist should be aware of the possible toxic side effects or to the possible interaction of antiretroviral drugs with the anesthetics. For example, neuropathy or myopathy may dictate change of anesthetic techniques. Anemia and thrombocytopenia are major toxic side effects of zidovudine. PIs can affect glucose metabolism. Foscarnet can also alter calcium and magnesium balance. Other side effects include increased liver enzymes (trimethoprim-sulfamethoxazole), bronchospasm (aerosolized pentamidine), and ventricular arrhythmias (IV pentamidine).

Pis, such as ritonavir, are inhibitors of CYP450 which impair the metabolism of multiple anesthetics and analgesics, such as midazolam and fentanyl, and cardiac drugs, such as amiodarone and quinidine (51).
Nevirapine is an inducer of CYP<sub>450</sub> and therefore increasing doses of anesthetic drugs may be required in patients receiving the drug (60). Etomidate, atracurium, remifentanil and desflurane are not dependent on CYP<sub>450</sub> hepatic metabolism, and therefore, are preferable drugs.

When considering the type of anesthesia, regional anesthesia has the advantage of not interfering with the immune system or with antiretroviral drugs. Contraindications to regional anesthesia in these patients are sepsis and platelet abnormalities. The presence of neuropathy may reduce the appeal of regional anesthesia but there are no data to contradict its use. In a review of 96 HIV positive parturients, of whom 36 delivered under regional anesthesia, the advantages of regional anesthesia were confirmed (61). In a recent article (59), the effect of spinal anesthesia was studied in 45 HIV-treated parturients who underwent cesarean delivery. There were no perioperative complications or changes in immune function or viral load. The American Medical Association addressed the issue of providing care for patients with HIV and stated that physicians have an ethical duty to provide any treatment needed to HIV patients and avoid discrimination against such patients (62).

Postdural puncture headache may occur after regional anesthesia and may necessitate epidural blood patch. Tom et al. (63) found no increase in neurologic abnormalities in 6 HIV patients receiving an epidural blood patch during a follow-up period of 2 yr. There is no evidence to contraindicate the use of blood patch in HIV-positive patients. However, the small numbers reported may justify a conservative management as a first choice (64).

Magnetic resonance imaging (MRI) studies of the spinal cord in 55 symptomatic HIV patients showed neurologic involvement of the spinal cord in 49 patients, mostly of infectious origin (57). Currently, MRI is not often done in the preoperative HIV patient presenting with neurologic involvement, but is considered in a comprehensive neurological work-up or for neurosurgical indications to verify soft tissue pathology. There are increasing numbers of compromised HIV patients who are drug abusers, diabetics, postorgan transplantation recipients, and on long-term steroid treatment developing spinal infections. They are often diagnosed too late, mostly presenting with back pain or other neurologic signs or symptoms (65). Prolonged epidural catheterization in such severely compromised patients may be contraindicated (66). However, a series of 350 cancer patients who had prolonged epidural catheterization and were monitored closely for possible infection and promptly treated had no adverse sequelae (67).

Conclusions
The pandemic of AIDS is on the threshold of its third decade of existence. The World Health Organization and United Nations statistics indicate that HIV/AIDS pandemic will get much worse. Women of reproductive age are the fastest growing population with HIV. Common signs and symptoms have become more moderate or subclinical, and new clinical presentations have emerged. It is quite apparent that HIV disease affects multiple organ systems. Advances have been made in elucidating the pathogenesis of HIV. In addition, the molecular technique of viral load determination and the CD<sub>4</sub> T-lymphocyte count enable the evaluation of the disease, its prognosis, and its response to therapy. There is limited specific information concerning the overall risk of anesthesia and surgery on HIV/AIDS patients. However, as far as can be determined, surgical interventions do not increase the postoperative risk for complications or death and should therefore not be withheld. There is also little evidence to suggest that HIV or antiretroviral drugs increase the rate of pregnancy complications or that pregnancy may alter the course of HIV infection. General anesthesia is considered safe, but drug interactions and their impact on various organ systems should be considered preoperatively. Regional anesthesia is often the technique of choice. Yet, one must consider the presence of neuropathies, local infection or blood clotting abnormalities.

Anesthesiologists must be familiar with this disease, and prenatal anesthesia consultations and a team approach will optimize treatment for the pregnant woman with HIV.

References


Management of human immunodeficiency virus infection in pregnancy

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The HIV global epidemic is having a devastating effect on women of reproductive age; women aged 15–24 years are 2.5 times more likely to be infected than young men in the same age group. Further, mother-to-child transmission (MTCT) accounts for almost two-thirds of the new infections that occur in children worldwide, annually. MTCT of HIV-1 varies widely and is dependent on obstetric practices, mode of delivery, breastfeeding, and the level of the viral load in the mother.

Antiretroviral therapy (ART) in pregnancy is prescribed for two main reasons: (i) women who need ART medication for their own health; (ii) women who do not need treatment, or do not have access to treatment are offered prophylaxis to prevent MTCT, using one of a number of ART regimens known to be effective. HIV infection is also associated with significant maternal morbidity and mortality. Clinicians caring for HIV-infected women need to update their knowledge continuously to provide optimal care.

Key words: pregnancy; HIV; mother-to-child transmission; antiretroviral management.

An estimated 40 million people are living with HIV worldwide. Every day in 2003, an estimated 14 000 people were newly infected with HIV. More than 95% of these live in low- or middle-income countries, where women and children are most vulnerable. The epidemic is devastating for women, particularly in sub-Saharan Africa, where women are more likely to be infected with HIV than men. Among young people, this discrepancy is particularly high; women aged 15–24 years are up to 2.5 times more likely to be infected than young men in the same age group. It is therefore not surprising...
that of the 630 000 children infected with HIV annually worldwide, the great majority are infected by mother-to-child transmission (MTCT).¹

In the absence of an intervention, the risk of MTCT of HIV varies between 15 and 20% in non-breastfeeding women in Europe, and between 25 and 40% in breastfeeding African populations.² The principal risks of transmission are related to maternal plasma viral load, obstetric factors and infant feeding. MTCT is therefore largely preventable where antenatal HIV screening is available, feeding exclusively by artificial formula is feasible, and where there is provision for antiretroviral (ARV) therapy and delivery by caesarean section (C/S).

HIV infection in pregnancy is associated with significant maternal morbidity and mortality.³ Maternal deaths due to HIV and AIDS are now the leading cause of maternal mortality in South Africa, accounting for 23% of all maternal deaths. ³ Clinicians who care for HIV-infected women of reproductive age therefore need to keep abreast of the literature to provide optimal care, including counselling, to allow women to balance the risks and benefits while deciding on therapeutic or prophylactic options for themselves, and their children, respectively. Moreover, clinicians should be strong advocates for preventing new infections (HIV and other sexually transmitted infections), by providing appropriate counselling on safe sexual practices.

INTERACTIONS BETWEEN HIV AND PREGNANCY

Effect of pregnancy on HIV-disease progression

Studies in the USA and Europe have not shown pregnancy to have any effect on the progression of HIV disease.⁴⁵ Reports from resource-poor countries, however, suggest that progression accelerates with pregnancy, but it is difficult to interpret such reports because the sample sizes are small and the studies are subject to selection bias related to the indications for testing.⁶

Effect of HIV on pregnancy outcomes

Controversies about the outcomes of pregnancy in HIV-infected women still exist. In rich countries, reports do not suggest an increase in the frequency of preterm birth, low birth weight babies, intrauterine growth retardation and stillbirths in comparison with similar groups of HIV non-infected women.⁶ Higher rates of perinatal mortality, however, are reported in HIV-infected women from poor countries, with advanced HIV infections being associated with the highest neonatal death rates.⁶ The theory that there is a syndrome of malformation-related HIV infection has not been proven. Similarly, no studies have indicated that there is an increase in the frequency of birth defects related to HIV infection.⁶⁻⁸

ANTENATAL CARE IN THE HIV-INFEC TED

HIV testing

Among pregnant women, knowing one’s HIV status is the key to the prevention of MTCT. In countries where voluntary counselling and testing (VCT) for HIV and prevention of MTCT programmes are not an integral part of existing health services, it is common for women not to know their HIV status prior to pregnancy.
Therefore, it is the responsibility of all health care workers providing care for pregnant women to make sure that they are offered voluntary counselling and HIV testing options as early in pregnancy as possible. Counselling and options for testing for HIV should also accompany family planning and gynaecological consultations.

Concerns about the ethical issues of testing for HIV are discussed in Chapter 7. In brief, in the USA, the HIV test is offered with patient notification and the right to refuse. This approach is simple and practical but maintains the patient's autonomy. It recommends HIV testing and offers more consideration than that applied to the battery of routine antenatal tests for which the 'general care' consent suffices. Furthermore, the process is not so onerous as to dissuade clinicians from offering it, or the patient to perceive that she is at special risk. Mandatory testing without the right of refusal and VCT are other methods used for establishing the HIV status of the woman. The former is regarded as time-consuming and impractical by clinicians, while the latter impinges on the patient's rights.

Despite the practical approach recommended for HIV testing in the USA, there are a number of women, particularly in poor countries, who do not initiate antenatal care until late pregnancy, or even early labour. This is a particularly vulnerable group, and it has been reported that the prevalence of HIV infection in this group is much greater than in women who begin antenatal care early in pregnancy. There are, however, robust data indicating that initiating ARV therapy in late pregnancy and/or intrapartum, and neonatal prophylaxis, can reduce the risk of MTCT. Efforts should therefore be made to give counselling and use rapid tests, with informed consent, in late pregnancy or early labour, to discern the serostatus of such women.

All algorithms for testing for HIV do include individual post-test counselling by an appropriately trained health professional. Women diagnosed with HIV in pregnancy should be informed that interventions (such as ARVs, C/S, and avoidance of breastfeeding) can reduce the risk of MTCT from 30 to less than 2%. In addition, there should also be a clear referral pathway for women who are HIV infected and they should be managed by a team comprising a counsellor, HIV physician, an obstetrician, a midwife, a paediatrician and support groups.

Specific considerations during antenatal care

Other sexually transmitted infections

All pregnant women should be screened for genital infections, in view of the fact that increased HIV genital tract replication may occur due to other local infections. Viral load in cervical vaginal secretions has been shown to correlate with MTCT. Usually, genital tract viral load mirrors the plasma load but discordance may occur, notably in the presence of genital infections or ulceration. This therefore warrants testing for Chlamydia trachomatis, Neisseria gonorrhoea and bacterial vaginosis. Furthermore, screening for hepatitis B and C should also be performed.

PRESCRIBING ANTIRETROVIRAL THERAPY IN PREGNANCY

Effect of antiretroviral therapy on pregnancy outcome

It has been suggested that ARV therapy may increase the adverse outcomes of pregnancy. The rate of preterm labour has been reported to be increased with the use of highly active antiretroviral therapy (HAART). Data from the USA have not shown an increase in the rate of preterm birth with the use of dual nucleoside and
a protease-inhibitor regimen\textsuperscript{10}, but data from a European cohort study have shown higher rates of preterm birth as the number of ARV agents used has increased.\textsuperscript{8}

The effect of first trimester exposure to ARVs and folate antagonists used for prophylaxis against \textit{Pneumocystis carinii} pneumonia (PCP) should alert clinicians to the need to offer detailed fetal anomaly ultrasound scans, although there is no robust evidence that most ARVs are teratogenic or that preconceptual folic acid reduces neural tube defects in those HIV-infected women taking folate antagonists such as co-trimoxazole for the prevention of PCP.

There is preliminary evidence that pre-eclampsia is more common amongst those treated with ARV, compared with controls.\textsuperscript{17} The toxic effects of ARVs, however, overlap the clinical signs of severe pre-eclampsia, e.g. lactic acidosis is a recognised complication of certain ARVs and may mimic signs of pre-eclampsia. The ARV drugs stavudine and didanosine have been suspected of causing this problem, and pregnant women are stated to be particularly susceptible to lactic acidosis.\textsuperscript{18} Thus, if this complication is suspected, liver function tests and blood lactate should be monitored. The presenting symptoms of lactic acidosis are often non-specific but may include gastrointestinal disturbance, fatigue, fever and breathlessness.\textsuperscript{17,18}

HAART has been shown to be very effective in keeping viral loads at low levels and in dramatically improving the health of HIV-infected people, in spite of serious side effects. Pregnancy should not be regarded as a barrier to their use. ARV therapy is provided for two main reasons during pregnancy: first, for prevention of MTCT (therapy usually discontinued at, or soon after, delivery), and second, for treatment of maternal health (treatment continued indefinitely).

**Prevention of MTCT**

Perinatal transmission is the most common cause of HIV infection in infants and children worldwide.\textsuperscript{1} In the absence of interventions, the frequency of MTCT varies widely, with rates ranging from 15 to 40%. The wide range of these rates is possibly due to differences in patterns of breastfeeding, maternal viral load and obstetric practices. Most transmissions occur during the last 2 weeks of pregnancy, in labour, and during delivery. Although the actual mechanisms of vertical transmission have not been identified, possible reasons include microtransfusions during Braxton Hicks contractions, labour contractions, ascent of the virus through the vagina and cervix once membranes have ruptured, and absorption of the virus through the infant’s digestive tract during parturition. These possible mechanisms of transmission are supported by studies demonstrating reduced transmission following elective C/S, and increased infection with prolonged duration of ruptured membranes.\textsuperscript{19,20} Although there is very little evidence of the risks of antenatal procedures such as amniocentesis, cordocentesis and chorionic villus sampling, most clinicians advise that prophylactic ARV therapy may be necessary if these procedures are going to be performed.

For women who are HIV-infected but not taking HAART during pregnancy, and for women with a detectable viral load, scheduled planned caesarean delivery is of benefit in reducing MTCT.\textsuperscript{6} A meta-analysis of 15 prospective cohort studies, which included 8533 mother–child pairs, found a 50% reduction in transmission rates in women who underwent a scheduled C/S before the onset of labour or rupture of membranes.\textsuperscript{20} In women with a viral load undetectable by current laboratory techniques, the benefit of C/S is uncertain.\textsuperscript{21,22} Delivery by C/S is associated with anaesthetic, intraoperative and post-operative complications. Reports on morbidity and mortality related to C/S in
HIV-infected women are not consistent. Some studies indicate that sepsis rates are increased in HIV-infected women in comparison with those who are uninfected, and the complication rates are related to the level of immunocompromise.\cite{23,12} In poorly resourced countries the picture may be worse. The Saving Mothers Report\cite{3} shows that the commonest cause of maternal deaths in South Africa between 1999 and 2001 was non-pregnancy-related sepsis; the great majority of the women were HIV-infected and a considerable proportion of them had a C/S. However, other studies have found no differences in post-C/S complications between HIV-infected and non-infected women.\cite{12}

Women who opt for vaginal delivery should accept obstetric practices minimising MTCT. These practices include avoiding fetal scalp electrodes, fetal blood sampling, the use of the ventouse in the second stage of labour, episiotomies, and most importantly, keeping the fetal membranes intact for as long as possible in the first stage of labour.

**Maternal markers of MTCT (Table 1)**

The factor which best predicts the likelihood of infection in the neonate is maternal viral load.\cite{21,22} It is well established that, in the majority of women, a high plasma viral load and an associated low antenatal CD4 T-lymphocyte count mean an increased risk of MTCT.\cite{21} Two large studies demonstrated that perinatal transmission was significantly associated with maternal viral load.\cite{21,22} These studies also showed that no transmission occurred where plasma load was <1000\cite{11} and <500 copies/ml.\cite{22} Current plasma viral load assays have lower limits of detection than those used in the above studies\cite{21,22}, and a meta-analysis of seven prospective studies demonstrated 44 cases of perinatal transmission among 1202 women with viral loads <1000 copies/ml at, or near the time of, delivery.\cite{22} Thus, the highest rate of transmission is found in those women with HIV plasma viral loads >100 000 copies/ml. Conversely, transmission rates are low when viral loads are undetectable, but there is insufficient evidence for a viral load threshold below which transmission never occurs. However, the more effective a drug regimen, the greater the likelihood it will prevent transmission (Table 1).

**Antiretroviral regimens to prevent MTCT (Table 2)**

There is now good evidence, substantiated by the AIDS Clinical Trials Groups (ACTG) protocol 076, that zidovudine given as monotherapy, administered 5 times a day and initiated between 14 and 34 weeks of pregnancy, intravenously during delivery, and to infants for 6 weeks, reduces the risk of vertical transmission of HIV in non-breastfeeding populations by two-thirds, from 25 to 7.6\%.\cite{19} These findings have been supported by a number of observational studies, and zidovudine monotherapy is one option currently used to prevent perinatal transmission in HIV-infected women who are not on ARV therapy for their own health. Maximum benefit in respect to this option is gained by recommending elective C/S as the mode of delivery and exclusively formula feeding.\cite{19} Viral resistance, like any other course of monotherapy, can occur with zidovudine if this antiretroviral does not suppress viral loads to undetectable levels, may allow the emergence of a resistant virus compromising the use of ARV therapy in the future (Table 2).

An alternative option is a short-term antiretroviral therapy (START) regimen, where highly active antiretroviral drugs are taken for the duration of the pregnancy and
discontinued shortly after delivery, provided the maternal viral load is undetectable.\textsuperscript{23} It is recommended that zidovudine be included in any combination ARV because of its demonstrated efficacy in preventing MTCT and its relative safety. In addition, zidovudine’s passage through the placenta is excellent, while that of other ARVs is variable. The passage through the placenta allows inhibitory levels of the drug in the fetus, ensuring pre-exposure prophylaxis.

The majority of HIV occurs in resource-poor countries, thus complex and prolonged regimens are costly and logistically difficult to implement. Several studies have therefore reported on short-course regimens in order to determine if affordable regimens could be utilised. The first report of such a successful course, from Thailand, showed that the rate of perinatal transmission of the participants in the study, given a twice-daily dose of zidovudine beginning at 36 weeks, and during labour, was reduced by 50%.\textsuperscript{24} Slightly lower efficacy rates were observed in breastfeeding populations in two randomised trials, one in Cote d’Ivoire (37% reduction in transmission at 12 weeks’ neonatal age) and the other in Cote d’Ivoire/Burkina Faso (38% reduction by 6 months of age).\textsuperscript{25,26} Supporting evidence of the efficacy of abbreviated regimens of ARVs for prevention of HIV-1 from Wade et al\textsuperscript{10} indicates that rates of transmission varied depending on when zidovudine prophylaxis began. Respective rates of transmission for the prenatal and intrapartum periods and the first 48 hours of neonatal life were 6, 10 and 9.3%. In the absence of zidovudine prophylaxis, the transmission rates were 26%.

Nevirapine has also been used as a short-course therapy. Its low price, rapid onset of action, and the rapid fall in viral load that occurs after its use, make it attractive for

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|}
\hline
HIV-disease stage (CD4 count) & < 200 & 200–500 & > 500 \\
\hline\hline
Predicted viral load & High & Moderate to low & Low \\
\hline
Risk of maternal AIDS/death & High & Low & Low \\
\hline
Risk of MTCT & High & Moderate & Low \\
\hline
Recommended PMTCT interventions for non-breastfeeding populations & HAART & HAART/short-course MTCT prophylaxis dual or triple ARV regimen & Short-course MTCT prophylaxis dual or triple ARV regimen \\
\hline
Recommended PMTCT ART for breastfeeding populations & HAART & HAART/short-course MTCT prophylaxis dual or triple ARV regimen & Short-course MTCT prophylaxis dual or triple ARV regimen and counselling on safe infant feeding practices \\
\hline
\end{tabular}
\end{table}

\textsuperscript{174} J. Moodley and D. Moodley

AIDS, autoimmune deficiency syndrome; MTCT, mother to child transmission; ARV, antiretroviral; PMTCT, prevention of mother to child transmission; HAART, highly active antiretroviral therapy
### Table 2. ART options for prevention of mother-to-child transmission of HIV.

<table>
<thead>
<tr>
<th>Antepartum</th>
<th>Intrapartum</th>
<th>Post-partum mother</th>
<th>Post-partum infant</th>
<th>Perinatal transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US (PACTG 076)(^1)</strong></td>
<td><strong>ZDV only</strong></td>
<td><strong>Starting at 14–34 weeks</strong></td>
<td><strong>ZDV intravenous infusion</strong></td>
<td><strong>No ARV</strong></td>
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<td></td>
<td></td>
<td><strong>ZDV 100 mg 5×/day</strong></td>
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<tr>
<td><strong>Thailand (CDC)(^3)</strong></td>
<td><strong>ZDV only</strong></td>
<td><strong>Starting at 36 weeks</strong></td>
<td><strong>ZDV 300 mg q 3 hours</strong></td>
<td><strong>No ARV</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>ZDV 300 mg bid</strong></td>
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</tr>
<tr>
<td><strong>Ivory Coast (CDC)(^6)</strong></td>
<td><strong>ZDV only</strong></td>
<td><strong>Starting at 36 weeks</strong></td>
<td><strong>ZDV 300 mg q 3 hours</strong></td>
<td><strong>No ARV</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>ZDV 300 mg bid</strong></td>
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<tr>
<td><strong>South Africa, Uganda, Tanzania (PETRA)(^7)</strong></td>
<td><strong>ZDV/3TC</strong></td>
<td><strong>Starting at 36 weeks</strong></td>
<td><strong>ZDV 300 mg q 3 hours plus 3TC 150 mg q 12 hours</strong></td>
<td><strong>No ARV</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>ZDV 300 mg bid plus 3TC 150 mg bid</strong></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><strong>ZDV 300 mg bid plus 3TC 150 mg bid×7 days</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Uganda (HIVNET 012)(^8)</strong></td>
<td><strong>NVP vs ZDV</strong></td>
<td><strong>Non ARV</strong></td>
<td><strong>NVP 200 mg×1</strong></td>
<td><strong>Breast feeding</strong></td>
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<td></td>
<td><strong>ZDV 300 mg q 3 hours</strong></td>
<td><strong>Breast feeding</strong></td>
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<tr>
<td><strong>US/Europe/Brazil/Bahamas (PACTG 316)(^9)</strong></td>
<td><strong>NVP vs placebo</strong></td>
<td><strong>Non-study ARV</strong></td>
<td><strong>Standard intravenous ZDV NVP 200 mg×1</strong></td>
<td><strong>Non-study ARV</strong></td>
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Table 2 (continued)

<table>
<thead>
<tr>
<th>Antepartum</th>
<th>Intrapartum</th>
<th>Post-partum mother</th>
<th>Post-partum infant</th>
<th>Perinatal transmission</th>
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</thead>
<tbody>
<tr>
<td>Women and infants on standard ARV</td>
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<tr>
<td>South Africa (SAINT)</td>
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<tr>
<td>NVP vs ZDV/3TC</td>
<td>No ARV</td>
<td>NVP 200 mg×1 l</td>
<td>NVP 200 mg×1 l at 24–48 hours</td>
<td>Breast feeding (42%)</td>
</tr>
</tbody>
</table>

| South Africa (SAINT) | No ARV | ZDV 600 mg then 300 mg q 3 hours plus 3TC 150 mg q 12 hours | ZDV 300 mg bid plus 3TC 150 mg bid×7 days | ZDV 12 mg bid plus 3TC 6 mg bid×7 days (>2 kg) | 8 weeks 9.3% |

| Thailand/PHPT (Harvard) | Starting at 28 weeks | ZDV 300 mg q 3 hours | No ARV | Formula feeding | 6 weeks |

| Thailand/PHPT (Harvard) | ZDV 300 mg bid | ZDV 300 mg q 3 hours plus NVP 200 mg×1 l | No ARV | ZDV 2 mg/kg qid×7 days | 6.3% |

| Thailand/PHPT (Harvard) | ZDV 300 mg bid | ZDV 300 mg q 3 hours plus NVP 200 mg×1 l | No ARV | ZDV 2 mg/kg qid×7 days plus NVP 6 mg×1 l at 48–72 hours | 2% |

US, United States; PACTG, pediatric AIDS clinical trials group; ZDV, zidovudine; NVP, nevirapine; HIVNET 012, HIVNET 012 trial; ARV, antiretroviral; PETRA, The Perinatal Transmission Study.
prophylaxis, particularly in poor countries. Two studies from Africa, HIVNET 012, and the South African Intrapartum Nevirapine Trial (SAINT) have reported significant reductions with the use of short doses of nevirapine to mother and baby.\textsuperscript{27,28} In addition, the Perinatal Transmission Trial (PETRA) reported on a short course of zidovudine and lamivudine in a predominantly breastfeeding population. This trial enrolled 1823 women into four arms: (1) zidovudine–lamivudine given at 36 weeks and continued through labour and for 1 week after delivery; (2) zidovudine–lamivudine given intrapartum and 1 week post-delivery; (3) zidovudine–lamivudine given intrapartum only; and (4) placebo. There were significant reductions for HIV-1 transmission when compared to placebo for arms 1 and 2 but not 3.\textsuperscript{29}

More recently, an observational study from Thailand showed that zidovudine, from the 28th week of pregnancy, plus ‘a booster dose’ of nevirapine given to the mother in labour and to the baby as soon as possible after birth, was much more effective than a short course of zidovudine alone started at 28 weeks. The authors conclude that a single dose of nevirapine given to the mother at delivery and a dose to the baby as soon as possible after birth, added to oral zidovudine initiated at 28 weeks’ gestation, results in very low transmission rates (1.1%), with minimal medical and financial burdens. These low rates of transmission are very similar to those achieved with very complex, expensive and potentially toxic multi-drug maternal regimens.\textsuperscript{30} It is therefore not surprising that, in recently updated guidelines, the World Health Organization (WHO) recommends this regimen for the prevention of MTCT of HIV-1 for pregnant women who do not require ARVs for their own health.\textsuperscript{31}

\textit{Monotherapy and viral resistance}

There are concerns regarding the use of monotherapy, and of the combination of drugs for prevention of MTCT only. Fewer transmissions are likely to occur with combinations, and viral resistance may be lower, but these factors must be balanced against the exposure of the mother and fetus to a number of potentially toxic drugs. There have also been recent concerns regarding the development of viral resistance with the use of single-dose nevirapine (NVP) in resource-poor countries. Whilst single-dose NVP has been successful in limiting transmission rates of HIV, as proven by the HIV-NET 012 study\textsuperscript{27}, the emergence of resistant mutations after a single dose of NVP, owing to its long half-life, is worrying. In a sub-study from HIV-NET 012, it was reported that in a subset of 140 women with subtypes A and D, the rate of NVP resistance increased from 7 days to 8 weeks. The mutations 7181C and K103N were found, and the study confirmed that there is a correlation between subtype and the selection and decay of NVP-related resistance.\textsuperscript{32}

In a study by Jourdain et al\textsuperscript{33}, resistance mutations to nucleoside reverse transcriptase inhibitors were detected 10 days after delivery in 5% of mothers, and among the women who received intrapartum nevirapine, 32% had at least one mutation that conferred resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs). This group of researchers also addressed the question whether ARVs given to prevent MTCT might compromise the efficacy of ARV drugs subsequently administered for HIV-1 treatment in the mother. Their findings suggest that those who receive single-dose nevirapine alone, or combination regimens for the prevention of MTCT, and in whom mutant variants develop, may be less likely than women who do not receive intrapartum nevirapine, or have resistance mutations, to have maximal viral suppression when NNRTI-based treatment is initiated soon after delivery.\textsuperscript{33} The actual significance of these data still requires clarification, as ARVs were initiated within 6 months of delivery,
and it has been reported that HIV viral mutant strains fade with time.\textsuperscript{32} Delay in initiating treatment, therefore, may not result in similar findings. Given that access to treatment remains scarce in resource-poor settings, these studies do not so much caution against the use of NVP treatment, as stress the urgent need to explore more viable options that prevent transmission but do not compromise treatment during subsequent pregnancies, or treatment for children.

**WOMEN TREATED WITH ARV THERAPY FOR THEIR OWN HEALTH**

These women are likely to have advanced disease with high viral loads (> 10,000–20,000 copies/ml, and/or decreasing, or low CD4 counts < 350 × 10^6/l). Treatment with ARV therapy should be avoided in the first trimester, but treatment which suppresses plasma viraemia is targeted, to improve both maternal morbidity and mortality and to prevent perinatal transmission.

Studies have found that membranes ruptured for more than 4 hours were associated with double the risk of HIV transmission.\textsuperscript{34,35} The relevance of these studies for women with undetectable viral loads is uncertain.

**Preventing progression of HIV disease in pregnancy in resource-limited countries**

Preventing the progression of HIV-1 disease using low-cost immunomodulating interventions in poorly resourced countries has been proposed. Recently, multivitamin supplements (vitamins A, B, C and E) have been shown to delay the progression of HIV disease, in a randomised trial which enrolled 1078 pregnant women with HIV in a double-blind, placebo-controlled trial in Dar Es Salaam, Tanzania.\textsuperscript{36} The authors indicate that multivitamin supplements provide an effective, low-cost method of delaying the progression of HIV disease and thereby delaying the initiation of ARV therapy in HIV-infected women.\textsuperscript{36}

**Post-partum management**

It is estimated that breastfeeding increases the overall MTCT rate by 14% for women infected with HIV before birth and by 30% in mothers infected post-natally.\textsuperscript{37} Breastfeeding in industrialised countries is therefore avoided. In resource-poor settings, it may be difficult to balance the need for babies to receive breast milk with the need to avoid breast milk transmission of HIV. Advice may need to change as new information and options become available. In poor countries, therefore, advice regarding breastfeeding should remain that breast milk will always be the best, cheapest, and only food and drink needed by most young babies.

**Management of the neonate**

Early diagnosis of positive infants, preferably at 6 weeks after they are born, and 4 weeks after any breastfeeding ends, is important for the families, so that clinical resources can be used where they are most needed.

Maternal antibodies crossing the placenta are detectable in most neonates of mothers who are HIV positive. For this reason, polymerase chain reaction is used for
the diagnosis of infant infections at birth, 3 weeks, 6 weeks and 6 months. The definitive test is the HIV antibody test—a negative result at 18 months of age confirms that the child is uninfected.

SOME ASPECTS OF THE USE OF ANTIRETROVIRAL DRUGS IN PREGNANCY

Monitoring virological and immunological status

The cornerstones of monitoring are viral loads and CD4 counts. Treatment in the non-pregnant is generally indicated when the CD4 counts falls to \(<200\) \(\text{mm}^3\) or when plasma ribonucleic acid (RNA) levels are \(>55,000\) copies/ml. Controversy exists whether the treatment should be initiated at CD4 counts \(<350\) \(\text{mm}^3\). These guidelines are also recommended for pregnant women. Implementation of these recommendations should be individualised and is dependent on factors such as the woman's willingness and readiness to commit to take lifelong therapy; the benefits and risks in asymptomatic individuals; and of adherence to the treatment. Adherence to therapy is the sine qua non of successful therapy. Haphazard or intermittent therapy compliance leads to drug resistance.

Once therapy is initiated, success is based on monitoring viral loads. This should occur on a regular basis. The speed at which viral loads fall varies with the baseline level, but a fall in levels should be seen within a month and undetectable levels are reached by 6 months with a highly active antiviral drug regimen. If this goal is not achieved, or there is a re-emergence of detectable levels of virus, then failure of the drug therapy, or resistance to the virus has occurred. A decision as to a new therapy regimen must be considered following resistance testing.

Drug therapy

There are a number of HAART regimens used, and they are classified into nucleoside reverse transcriptase inhibitors, protease inhibitors and NNRTIs. A large number of choices exist within these categories. In general terms, dual nucleoside reverse transcriptase inhibitors and a protease inhibitor or a NNRTI have been recommended. However, certain medications should not be used in combination; zidovudine and stavudine have overlapping toxicities; didanosine and stavudine have recently been linked to several cases of mitochondrial toxicity in pregnancy; and didanosine and zalcitabine in combination have diminished efficacy.

In the mother, clinical disorders associated with mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis and lactic acidosis. Although these disorders are rare, clinicians must be aware of these serious morbidities in pregnant HIV-infected women receiving nucleoside reverse transcriptase inhibitors, and investigate all new symptoms thoroughly. Alternatively, liver enzyme tests should be performed routinely in the last trimester of pregnancy.

Amongst the NNRTIs, efavirenz should not be used because of reported teratogenic effects in monkey models. Protease inhibitors have been linked to abnormal glucose metabolism, nephrolithiasis and hyperbilirubinaemia. Despite concerns about toxicity, pregnant women should be provided with ARV therapy, as the benefits to baby and mother outweigh any harm. Nonetheless, all pregnant women on ARVs should have
regular monitoring of liver function tests and blood counts to detect toxicity as early as possible.

CONCLUSION

The management of HIV-infected women in pregnancy should be undertaken by a multidisciplinary team consisting of an obstetrician, neonatologist, HIV expert and support staff. Women who need ARV treatment for their own health should receive it, to improve their health and decrease HIV transmission to their babies. Asymptomatic women, or those who do not require ARV therapy for their own health, should receive the most efficacious regimen to reduce MTCT to a minimum.

SUMMARY

The management of HIV in pregnancy focuses on caring for those already infected and preventing the transmission of HIV to the baby. A holistic approach to these goals should involve a multidisciplinary team consisting of an obstetrician, neonatologist, HIV physician and support team.

ARV therapeutic regimens are complex and potentially harmful and require strict adherence to therapy if the development of viral mutant strains is to be avoided. ARV regimens are given either to prevent MTCT or to improve maternal health. In the latter instance, indications for ARV therapy follow those for the non-pregnant adult.

Clinicians managing the HIV-infected pregnant woman must update their knowledge continuously and be aware of any drug toxicity associated with ARV regimens so that any new symptom may be investigated aggressively. Monitoring of response to drugs is done by performing regular estimations of viral loads, as the aim of the ARV regimen is to achieve a state in which the viral load is undetectable.

Prevention of MTCT includes not only the use of ARV as prophylaxis but also appropriate obstetric practices such as avoiding episiotomies, keeping the fetal membranes intact, avoiding the use of the ventouse and advising against breastfeeding, where feasible.

Practice points

- testing for HIV status should be offered to all pregnant women, utilising a practical protocol, without infringing human rights
- pregnant women should have access to all of the same therapies as non-pregnant women, except that (i) efavirenz, (ii) hydroxyurea, and (iii) a combination of stavudine and didanosine, should not be issued
- all pregnant women should receive ARV, either for their own health, or for the prevention of MTCT of HIV, using appropriate regimens
- C/S should be recommended to all women with viral loads > 1000 copies/ml
REFERENCES


REVIEW ARTICLE
Obesity and obstetric anaesthesia

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Summary
The prevalence of obesity continues to increase despite preventive strategies. Obese parturients are at increased risk of having either concurrent medical problems or superimposed antenatal diseases such as pre-eclampsia and gestational diabetes. Moreover, they have a tendency to labour abnormally contributing to increased instrumental delivery and Caesarean section. Obesity is a risk factor for anaesthesia related maternal mortality. Morbidly obese women must be considered as high-risk and deserve an anaesthetic consultation during their antenatal care. The significant difficulty in administering epidural analgesia should not preclude their use in labour. A more liberalised use of regional techniques may be a means to further reduce anaesthesia-related maternal mortality in the obese population. The mother’s life should not be jeopardised to save a compromised fetus. Prophylactic placement of an epidural catheter when not contraindicated in labouring morbidly obese women would potentially decrease anaesthetic and perinatal complications associated with attempts at emergency provision of regional or general anaesthesia. Early mobilisation, aggressive chest physiotherapy and adequate pain control are essential components of effective postoperative care.

Obesity is a global health problem whose prevalence is increasing. The World Health Organization (WHO) characterised obesity as a pandemic issue whose prevalence is higher in women than in men [1]. Consequently, the anaesthetist is increasingly confronted with the problems of anaesthetising obese patients, and even more so the obstetric anaesthetist. Adding to the spectrum of medical and surgical pathologies, obesity is also associated with an increased incidence of antenatal disorders. A thorough understanding of physiology, pathophysiology, associated conditions, their complications and the implications for analgesia and anaesthesia should place the anaesthetist in a better position to care for these patients.

Definition
Obesity is often defined simply as a condition of abnormal or excessive fat accumulation in adipose tissue to the extent that health may be impaired [2]. The underlying process is positive energy balance and weight gain. Obesity is often expressed with reference to body mass index (BMI).

Body mass index = \( \frac{\text{weight (in kg)}}{\text{height}^2 \text{(in m)}} \).

Though BMI is a useful measure of prevalence and associated health risks of obesity, it does not account for the wide variation in the distribution of fat and may not correspond to the same degree of fitness in different individuals. WHO classifies obesity primarily based on the association between BMI and mortality (Table 1) [1].

Epidemiology
The prevalence of obesity is increasing at an alarming rate in both developed and developing countries. In pregnant women in the United States at the end of the last century, the prevalence ranged from 18.5% to 38.3% according to the cohort studied and the cut-off point used to define overweight [3]. A Brazilian study at a similar time reported the prevalence of obesity in pregnancy to be 5.5% [4]. The Health Survey of England published in

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2002 gives us data about the prevalence of obesity in England. Females in the reproductive age group (16–44 years) have shown a dramatic increase in BMI (Fig. 1). The percentage of women with BMI above 30 increased from 12% in 1993 to 18.3% in 2002. Even more alarming is that the percentage of morbidly obese women has doubled in the last decade [5]. This illustrates the problem we are facing.

Physiological changes in obesity and pregnancy

Physiological changes associated with pregnancy are significant enough to have serious anaesthetic implications. When these are compounded by obesity, the anaesthetist may have to deal with a patient with seriously limited physiological reserve. Often, obesity has associated co-morbidities and pathological changes in different organ systems.

Respiratory system

All aspects of oxygenation and ventilation are affected in pregnancy. The physical, mechanical and hormonal changes influence the respiratory system. Table 2 summarises these changes in pregnancy, obesity and the combined effect of pregnancy with obesity [6–10]. Fortunately, not all changes associated with pregnancy in obese women are detrimental. In fact, there may be some improvement in respiratory function in an obese patient who becomes pregnant; especially the functional residual capacity, which usually improves [6]. Hormonal changes, through the relaxing effect of progesterone on smooth muscle, decreases airway resistance, thus reducing some of the negative effects of obesity on the respiratory system [8, 9]. Studies that have shown the respiratory effects of obesity in pregnancy to be minimal were carried out in the sitting position, whereas the supine position may alter the volume, flow and mechanical properties of breathing.

Obstructive sleep apnoea (OSA) is not uncommon in obese women who become pregnant. Pregnancy has some protective effects on sleep apnoea, despite the hyperaemia of nasal passages. Early in pregnancy, the increased sensitivity of the respiratory centre decreases apnoeic episodes and, in the later part of pregnancy, women tend to sleep on their side, thereby decreasing the likelihood of airway obstruction. Chronic hypoxia, hypercapnia and pulmonary hypertension increase

<table>
<thead>
<tr>
<th>Table 1 WHO classification of obesity.</th>
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<tr>
<td>Classification</td>
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<tr>
<td>Normal</td>
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<td>Overweight</td>
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<td>Obese class 2</td>
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<td>Obese class 3</td>
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WHO, World Health Organization; BMI, Body Mass Index.

<table>
<thead>
<tr>
<th>Table 2 Changes in the respiratory system (changes represent a general trend rather than absolute values).</th>
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<tbody>
<tr>
<td>Parameter</td>
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<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Progesterone level</td>
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<td>Sensitivity to CO₂</td>
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<td>Tidal volume</td>
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<td>Respiratory rate</td>
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<td>Minute volume</td>
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<td>PₐO₂</td>
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<td>PₐCO₂</td>
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↑ = increase; ↓ = decrease; ↔ = No change (multiple arrows represent the degree of intensity).

CO₂ = carbon dioxide; FEV₁ = forced expiratory volume in 1 s; VC = vital capacity; V/Q = ratio of ventilation to perfusion; DLco = diffusion capacity of lung for carbon monoxide; PₐO₂ = Partial pressure of oxygen; PₐCO₂ = partial pressure of carbon dioxide.

Figure 1 Prevalence of obesity among females aged 16–44 in England as measured by BMI (source: Health survey for England 2002).

2002 gives us data about the prevalence of obesity in England. Females in the reproductive age group (16–44 years) have shown a dramatic increase in BMI (Fig. 1). The percentage of women with BMI above 30 increased from 12% in 1993 to 18.3% in 2002. Even more alarming is that the percentage of morbidly obese women has doubled in the last decade [5]. This illustrates the problem we are facing.
maternal morbidity and mortality significantly [11, 12]. Caesarean section, despite being lower abdominal surgery, potentially leads to reduced lung volume and capacities compared to non-obese patients [13].

**Cardiovascular system**

Pregnancy is associated with wide-ranging cardiovascular changes in line with increased oxygen demand. Obesity induced pathological changes have profound effects on cardiac, endothelial and vascular function. Unlike the respiratory system, where pregnancy offers some favourable effects in obese patients, the cardiovascular system is further stressed. The endocrinological, inflammatory and microvascular changes associated with obesity remain and are further augmented in pregnancy [14–16]. Table 3 summarises the changes in normal pregnancy, obese patients and obese pregnant women [14–20].

The extent of cardiovascular pathological changes secondary to obesity is dependent on the duration of obesity and its severity [18]. Any extra amount of fat deposited in the body demands its share of cardiac output. Every 100 g of fat deposited increases the cardiac output by 30–50 ml.min⁻¹. This is also accompanied by an increase in blood volume. Volume load initially brings about left ventricular hypertrophy and then subsequently the myocardium starts to dilate against the increased pressure overload. The pressure overload is secondary to increased sympathetic activity due to the potentiating effects of hormones such as leptin, insulin and some inflammatory mediators. The heart rate increases in line with elevated cardiac output, thereby decreasing the diastolic interval and thus the time for myocardial perfusion. Impaired myocardial diastolic relaxation leads to diastolic dysfunction. If fat deposition occurs in myocardial tissue, then conduction and contractility can be seriously affected [18, 19]. Hence, it is not uncommon to see systolic, diastolic or both systolic and diastolic dysfunction of the left ventricle. Right ventricular failure can be present in patients with pulmonary hypertension and OSA. Congestive heart failure is a consequence in the presence of any additional stress [9, 10, 16, 18, 19].

Insulin resistance and dyslipidaemias affect the vascular tree and increased inflammatory mediators such as C-reactive protein, IL-6, and TNF-α affect endothelial function. This endothelial dysfunction in pregnant women may predispose to the development of pregnancy-induced hypertension [15, 16, 19, 21]. The well-known effect of an enlarged uterus compressing abdominal major vessels and causing supine hypotension syndrome (SHS) can also be seen in obese patients. This can be greatly exacerbated in obese parturients where a large panniculus adds to the uterine compression. The problem may extend postoperatively if the panniculus is large enough to cause compression of the vessels by itself. Tseuda et al. reported two cases of sudden death on assuming the supine position in morbidly obese patients, which they attributed to circulatory changes brought about by changes in their position [22]. Drenick & Fisler also reported cases of postoperative cardiac arrest in obese surgical patients. There was no pathology found at autopsy to explain the cardiac arrest [23].

**Gastrointestinal changes**

Both anatomical and hormonal changes increase the incidence and severity of gastric reflux in pregnant women. Hiatus hernia is more common in obese patients and obesity itself increases the risk of aspiration under anaesthesia. When pregnancy is associated with obesity, the likelihood of regurgitation and aspiration substantially increases. Roberts and Shirley studied obese and non-obese pregnant women in labour; the gastric volume in obese parturients was five times greater than in controls [24].

**Endocrine and reproduction**

Because obese girls reach critical mass earlier than normal weight girls, they tend to reach menarche earlier. An αb protein called leptin is implicated in the mechanism. Obesity-induced changes in the reproductive system mean there is a reduced likelihood that these women will become pregnant [25]. Despite the potential

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**Table 3** Changes in the cardiovascular system. Table shows the general trend. Extent of variability in each parameter depends on duration, degree of obesity and associated co-morbid states.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pregnancy</th>
<th>Obesity</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>↑ or ↔</td>
<td>↑↑</td>
<td>↔ or ↓</td>
</tr>
<tr>
<td>Cardiac Index</td>
<td>↓</td>
<td>↑</td>
<td>↑ or ↓</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Blood volume</td>
<td>↑↑</td>
<td>↑</td>
<td>↑ or ↓</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>↓</td>
<td>↑</td>
<td>↑ or ↓</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Supine hypertension</td>
<td>Present Hypertrophy</td>
<td>Present Hypertrophy and dilation</td>
<td>Hypertrophy and dilation</td>
</tr>
<tr>
<td>Left ventricular morphology</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Sympathetic activity</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Systolic function</td>
<td>↔</td>
<td>↔ or ↓</td>
<td>↔ or ↓</td>
</tr>
<tr>
<td>Diastolic function</td>
<td>↔</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Pulmonary wedge pressure</td>
<td>↔</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Absent</td>
<td>May be present</td>
<td>May be present</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>↔</td>
<td>n/a</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

↑ = increase, ↓ = decrease, ↔ = no change (multiple arrows represent the degree of intensity). n/a = not applicable.
anatomical difficulties of intercourse, pregnancy is by no means uncommon. Onset of menopause is earlier by an average of 4 years [25]. Obese parturients exhibit insulin resistance [21] and are more prone to develop gestational diabetes, which may persist even after pregnancy [26].

**Perinatal outcomes of obesity**

**Maternal morbidity**

The major maternal complications reported to be associated with obesity during pregnancy include hypertensive disease (chronic hypertension and pre-eclampsia), diabetes mellitus (pregestational and gestational), respiratory disorders (asthma and sleep apnoea), thromboembolic disease, Caesarean section and infections (primarily urinary tract infections, wound infections and endometritis) [27]. Association between obesity and hypertensive disorders of pregnancy, diabetes, delivery by Caesarean section (both primary and repeat) are well documented [28–30]. Although obese parturients are at significant risk of pre-eclampsia, they do not seem to be at increased risk of HELLP (Haemolysis, Elevated Liver enzymes, Low Platelets) syndrome [31]. As discussed before, dyslipidaemias, lipid peroxidation, endothelial damage, platelet aggregation and inflammatory mediators make direct and indirect contributions towards the pathophysiology of the hypertensive disorders of pregnancy [21]. Complications during labour such as intrapartum fetal distress, meconium aspiration, failure to progress, abnormal presentation, shoulder dystocia and an increased rate of instrumental delivery are more common [28, 32, 33]. Moreover, the success of vaginal birth after Caesarean section has been shown to decrease stepwise with increasing maternal BMI [32, 34]. Postoperative endometritis and wound infection are significantly higher in obese women [33–35] Obesity is an intrinsic risk factor for both increased operative blood loss and postpartum haemorrhage [36]. Carter et al. have demonstrated a significant association between BMI, eating attitudes and symptoms of anxiety and depression in the postpartum period that are not present during pregnancy [37]. Overall, the literature suggests that obese pregnant women have a 14–25% incidence of pre-eclampsia, a 6–14% incidence of gestational diabetes and a 30–47% likelihood of Caesarean delivery [27, 28].

**Fetal morbidity**

Maternal obesity is associated with fetal macrosomia, increased risk of birth defects and fetal deaths [38–40]. Various studies have revealed an increased risk of a variety of conditions such as neural tube defects, especially spina bifida, omphalocele and heart defects, in particular ventricular outflow tract defects or multiple anomalies [39]. Moreover, increasing maternal size represents a major risk factor for failure of ultrasound to diagnose fetal anomalies [41]. Chauhan et al. reported a higher incidence of umbilical arterial acidosis (pH < 7.10) among obese women regardless of whether they had a trial of labour or repeat Caesarean delivery [29]. The higher incidence of fetal compromise in morbidly obese women could be the result of an inability to assess the fetus adequately because of size, underlying medical complications such as chronic hypertension, pregestational diabetes or that traditional intrauterine resuscitative efforts are inadequate in overweight patients. Obese women face difficulties with both lactogenesis and initiation of breastfeeding because of a decreased prolactin response to suckling [42, 43]. Breast-feeding is protective of childhood obesity [44]. The worries about propagation of a vicious circle are being confirmed by the longitudinal study of British cohort from 1958 that concludes maternal weight rather than birth weight as an important risk factor for childhood obesity and adult BMI [45].

**Weight gain and changes**

Pregnancy is normally associated with weight gain that consists of the growing fetus and enlarging maternal-fluid and soft-tissue compartments including fat. On average, a 3.5 kg weight gain is mostly due to maternal storage of fat during pregnancy [46]. Ledermann et al. showed that women who are overweight or obese and gain weight as recommended during pregnancy appear to have a small or negligible increase in total body fat [17]. The main components of weight gain in these heavier women are fluid and non-fat soft tissues. Community based studies have also reported that maternal obesity is not associated with increased weight gain after pregnancy, though they are generally at risk of gaining more weight [47].

**Anaesthetic considerations**

Obesity has been identified as a significant risk factor for anaesthesia related maternal mortality [48, 49]. The increased incidence of operative procedures, both elective and emergency, and the concurrent medical and antenatal problems may contribute to the risk. Postoperative complications such as wound infection, deep vein thrombosis, atelectasis and chest infection are more prevalent [49–51]. In addition to the associated medical problems, the anaesthetist is challenged by these patients with technical difficulties of airway management and insertion of regional blocks. No anaesthetic technique is without special hazards in grossly obese patients.

**Airway**

The incidence of failed tracheal intubation is approximately 1 in 280 in the obstetric population compared to 1 in 2230 in the general surgical population [52–54]. This
contrasts with an incidence of difficult intubation in an obese population as high as 15.5% [55]. In his institutional experience, Dewan [7] reports the incidence as high as 33% in morbidly obese parturients. Interestingly, a 6-year review of failed intubations in obstetric patients in a UK region reported 36 cases of failed intubation and the average BMI of these women was found to be 33 [53]. So it is evident that difficult or failed tracheal intubation in obese parturients is very high and optimal assessment and management of the airway cannot be overemphasised in this population.

Though there are no bony differences between the pregnant and non-pregnant population, obese and non-obese patients, fat deposition in obese and soft tissue changes during pregnancy do influence the airway. Operational factors such as poor head positioning, cricoid pressure [56] and anxiety contribute to the difficulty on occasion. In addition, pregnancy induced hypertension, upper respiratory tract infection, stridor and voice changes may suggest the presence of airway oedema. Weight gain in excess of 15 kg during pregnancy has been shown to be associated with an increase in suboptimal laryngoscopic views [57].

Although not totally reliable, assessment of oropharyngeal structures using the Mallampatti classification has been shown to strongly correlate with the prediction of difficult intubation in obstetric anaesthesia [58, 59]. Other features shown to be significant include short neck, receding mandible and protruding maxillary incisors [58]. The combination of two tests (Mallampatti and thyromental distance), albeit in a small study of 80 obstetric patients receiving general anaesthesia, has been shown to be 100% sensitive with 70% positive predictor value [59]. These tests can be done in less than 1 min; hence they are also useful in an emergency scenario. A previous uneventful general anaesthetic for either obstetric or non-obstetric reasons may not be helpful because of weight gain. However, previous anaesthetic charts inform of laryngoscopic view. In cases of documented difficult intubation, further airway imaging (X-ray and computerised tomography) is questionable as the combined clinical and radiological measurements only improve predictability of a difficult airway by 0.04% compared to clinical assessments alone [60]. Anaesthesia for both emergency and elective scenarios should be planned in advance. It is appropriate to involve patients in the decision-making process for safe delivery of the fetus.

Respiratory system

The likelihood of OSA has been alluded to, but it is often under-diagnosed in women of childbearing age [11]. Normal women in late pregnancy have difficulty with sleep maintenance and spend less time in the supine position. It is possible that, inasmuch as complaints of difficulty in sleeping and daytime fatigue are common, women suffering from OSA are not identified. Careful history taking may help diagnose OSA. Prompt diagnosis by polysomnography and treatment with continuous positive airway pressure may be beneficial. Pulmonary hypertension and right heart failure need to be excluded in parturients with OSA [12, 61]. Measurement of oxygen saturation by pulse oximetry, both in sitting and supine positions, may provide evidence of airway closure during normal tidal volume ventilation, thereby identifying candidates for postoperative oxygen administration. Pre-operative arterial blood gas examination provides information regarding the current status of ventilation and oxygenation. Detailed pulmonary investigations including chest X-ray should be reserved for those with more severe respiratory disease. Pre-operative antibiotics and chest physiotherapy are ideally reserved for patients with concurrent chest infection.

Cardiovascular system

Cardiovascular co-morbidities such as hypertension, ischaemic heart disease and heart failure dominate the clinical picture in the obese population and these can co-exist in obese parturients. Nearly 40% of the obese population experience angina without demonstrable coronary artery disease [62]. Hence, routine electrocardiograph recording may be useful. Cardiologists should be involved early in the care of symptomatic morbidly obese parturients to investigate and optimise the disease status wherever appropriate.

Gastrointestinal and endocrine systems

Gastro-oesophageal reflux and diabetes mellitus are the most commonly seen disorders [28]. Any previous laboratory investigations such as fasting blood glucose concentration and liver function tests should be noted. If there is any abnormality of liver function, HELLP syndrome should be ruled out.

Though aggressive prophylaxis against acid aspiration is advocated for all obese mothers undergoing Caesarean section [24, 63], there is a lack of conclusive evidence for starvation policies and prophylaxis during labour. Current evidence suggests avoiding solids and semisolids once a woman is in active labour or requests analgesia [64]. Sodium citrate and ranitidine remain the most commonly used drugs for acid aspiration prophylaxis in the UK [65].

Practical considerations

Obese parturients share a battery of technical difficulties along with their non-pregnant counterparts. Blood pressure measurement will require an appropriate sized cuff; otherwise both systolic and diastolic readings will be
overestimated. There is a strong argument in favour of invasive blood pressure monitoring peri-operatively if there are difficulties in getting the appropriate size cuff and positioning of the arm, as commonly used regional blocks demand frequent monitoring of blood pressure [66]. Venous access can be difficult and extravasation may not be immediately apparent. Patients should be warned about the difficulties and the possible need for central venous access and arterial cannulation in the perioperative period. When regional anaesthesia is contemplated, examination of needle insertion sites and spinal bony landmarks might predict difficulty [67].

Many of the other vital accessories are related to the physical size of parturients and need to be considered well in advance of the delivery. The weight bearing capacity of delivery beds and operating tables should be adequate to accommodate super-morbidly obese parturients. Suitable equipment (trapezes, lifters and hoover matts) and sufficient numbers of personnel for safe transfer of women within the hospital must be available. Sufficiently large blood pressure cuffs should be made available wherever blood pressure readings might be taken, including clinics, wards and the delivery suite. Mechanical devices for thrombo-prophylaxis such as stockings of appropriate size and sequential compression devices are other requisites for these patients.

**Anaesthetic management**

**Analgesia for labour**

Analgesia during labour is of significant importance for the positive experience of childbirth for many mothers. Increased prepregnancy weight is associated with an increased incidence of fetal macrosomia and labour abnormalities such as shoulder dystocia. Each of these is a known risk factor for more painful contractions and complicated labour. Melzack et al. reported a positive correlation of BMI with the severity of labour pain [68]; however, this has been questioned by Ranta et al. [69]. Although there are various modalities of pain relief, analgesia using neuroaxial blockade has been shown to be the most effective [70]. The anticipated technical difficulties should not preclude the use of epidural analgesia in obese parturients. Effective pain relief during labour can improve maternal respiratory function and attenuate sympathetically mediated cardiovascular responses [71, 72]. Available evidence shows that the rate of Caesarean delivery does not increase with epidural analgesia during labour [70], though obesity increases the need for Caesarean section. Hence, placing a functional epidural catheter is advantageous should any operative intervention be required. In addition, epidural analgesia can be extended into the postoperative period where adequate pain relief can optimise care.

The challenges for the anaesthetist should not be underestimated. Technical difficulties include positioning the patient correctly, identification of the midline, identification of the epidural space, and dislodgement of catheters [51, 66, 73]. The initial failure rate for epidural catheter placement can be very high (42%) [51] and multiple attempts of catheter placement are common. Jordan et al. noted 74.4% of massively obese parturients needed more than a single attempt and 14% needed more than three attempts for successful epidural placement [50]. The knee–chest position required for siting epidurals in the lateral position is difficult to obtain in the obese. One study found that cardiac output decreased more in the lateral decubitus position with maximal lumbar flexion compared with the sitting position [74]. Moreover, in the lateral position, gravity can drag down the pad of fat obscuring the midline. Another study found the depth of the epidural space from skin to be greater in patients where the epidural was inserted in the lateral decubitus position [75]. Overall, the sitting position is preferable. Various techniques have been reported to identify the midline in difficult scenarios. They include using the prominence of the seventh cervical vertebrae and the gluteal cleft to identify the midline and using a 26-G 8.5 cm spinal needle to probe subcutaneous tissue and delineate the position of a posterior process above and below a lumbar interspace [76]. Where it is difficult to identify the space, parturients can assist verbally in directing needle to the midline [66] and tilting the table towards the anaesthetist can encourage opening of interspinous spaces by forcing the parturient to bend forwards. The difficulty in location of the midline increases the likelihood of lateral projection of the needle apparently increasing the depth of the space and malpositioning of the catheter [77]. The paramedian approach to identify the epidural space is sometimes popular in difficult cases. With the back pad of fat and pregnancy induced softening of the tissues, there is a higher incidence of false positives in identifying the epidural space. It has been argued that the loss of resistance technique is more reliable than the techniques that are dependent on subatmospheric pressure in the obese. The depth of epidural space at the L3–4 interface positively correlates with BMI [75, 78].

Some of the difficulties can be circumvented by using ultrasound to identify the epidural space and calculate its depth [79, 80]. Ultrasound studies have confirmed the significant changes in spinal anatomy in pregnancy and found the skin–epidural distance to be greater in pregnancy. They have also revealed that the safety zone between transfixation of the ligamentum flavum and
inadvertent dural puncture is smaller [81]. Although the epidural space may be deeper in overweight people, the majority of studies report that only a few have an epidural space deeper than 8 cm [75, 78]. Hence it seems appropriate to use a standard needle to identify the epidural space on the first attempt. A successfully placed catheter can easily be dislodged by the drag of the back pad of fat when parturients move around in bed. Wasson postulates that a 6 cm lateral movement of skin site relative to the spine would drag 2 cm of catheter out of the epidural space [82]. Moreover, the catheter is subjected to a drag when the flexed back is relaxed immediately after a successful placement. These should be taken into consideration when deciding the length of catheter to be left in the space for a successful working epidural. The other common reasons for a successfully placed catheter to fail include inadequate dose of local anaesthetic, poor drug spread, misplacement of the catheter, septae within the epidural space and fetal malpositioning leading to more stimulation. With increased operative intervention in obese parturients, it is prudent to make sure that the epidural is working well and, if not, to replace the catheter at the earliest possible opportunity. Hodgkinson et al. have shown that BMI and weight are the major determinants of cephalad spread of epidural anaesthesia and that in obese patients the sitting position reduced cephalad spread [83, 84]. However, Milligan et al. showed no difference in the spread of epidural analgesia between obese and non-obese patients requesting labour analgesia, either in the sitting or in the lateral position [85].

Entonox can be a useful adjunct. Other forms of inhalational analgesia involving isoflurane and desflurane provide better analgesia when compared to nitrous oxide alone but cause more sedation and amnesia. Whereas intramuscular opioid injections may be unreliable, patient controlled intravenous analgesia has been used successfully in obese patients. However, opioids in labour have been associated with maternal and fetal side-effects [86]. All these methods potentially cause maternal drowsiness and lead to airway obstruction, thus inherently carrying a risk to the obese parturients.

### Anaesthesia for Caesarean section

Obesity and Caesarean section have been identified as independent risk factors for maternal morbidity and mortality [28]. In Why Mothers Die 2000–02, 35% of all the women who died were obese, 50% more than in the general population [49]. Analysis of direct maternal deaths due to anaesthesia reported in the confidential enquiries from 1979 to 2002 reveals the dominance of deaths under general compared to regional anaesthesia (Table 4 [49, 87–93]). Hawkins, in her analysis of maternal deaths in the United States, also reported that the absolute number of deaths due to complications of general anaesthesia, although small, is not decreasing over time [94] (Fig. 2). Regional anaesthesia is a safer option than general anaesthesia for delivery of the fetus [49, 94]. The principles in the anaesthetic management of these patients include

- regional anaesthesia unless contraindicated;
- care provided by experienced medical personnel (both anaesthetist and obstetrician);
- anticipation of problems and effective preparation in terms of equipment, monitoring and personnel;
- general anaesthesia, if required should be delivered with tracheal intubation and controlled ventilation;
- postoperative care that includes close monitoring, early mobilisation, and physiotherapy; a high dependency setting may achieve this most appropriately;
- judicious use of neuraxial, oral and intravenous opioids for postoperative pain relief.

### Table 4 Direct maternal deaths due to anaesthesia by types of anaesthesia in United Kingdom 1979–2002. Derived from CEMD reports. Since 1979, maternal deaths are reported as direct and indirect.

<table>
<thead>
<tr>
<th>Year</th>
<th>Total (n)</th>
<th>GA (n)</th>
<th>RA (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000–02</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>1997–99</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1994–96</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1991–93</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>1988–90</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>1985–87</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>1982–84</td>
<td>18</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>1979–81</td>
<td>22</td>
<td>22</td>
<td>0</td>
</tr>
</tbody>
</table>

GA, general anaesthesia; RA, regional anaesthesia.
It is not surprising that obese parturients undergoing Caesarean section are at increased risk of bleeding [36, 50] and require longer operating time [50, 51]. Panniculus retraction is another issue in morbidly obese parturients. Cephalad retraction of the panniculus can cause severe cardiovascular compromise. There has been at least one report of fetal death attributed to severe hypotension following panniculus retraction [95]. The dense regional block up to the fourth thoracic dermatome required for Caesarean section can compound cardiovascular compromise. Paralysis of intercostal muscles along with the supine position and cephalad retraction of the panniculus has the potential to increase the work of breathing substantially and provoke respiratory failure in this susceptible population. Suspending the abdominal panniculus vertically may alleviate some of these problems [95].

Regional anaesthesia

Single shot spinal anaesthesia remains the most common type of anaesthesia employed for delivery of the fetus by Caesarean section. The advantage of using subarachnoid block includes a dense reliable block of rapid onset. However, relevant issues include technical difficulties, potential for high spinal block, profound dense thoracic motor blockade leading to cardiorespiratory compromise and inability to prolong the blockade. Technical difficulties are the same as those for locating the epidural space. However, it is often easier to identify the epidural space with a large gauge stiff epidural needle than with a smaller gauge flexible spinal needle. Many anaesthetists use an epidural needle as an introducer for a spinal needle in difficult cases. It is widely believed that local anaesthetic requirements are less in pregnant patients, more so in obese patients. Proposed mechanisms for the enhanced neural blockade in pregnancy include hormone-related changes in the action of spinal cord neurotransmitters, potentiation of the analgesic effect of endogenous analgesic systems, increased permeability of the neural sheath or other pharmacokinetic/dynamic differences [96]. Both pregnancy and obesity increase intra-abdominal pressure and cause compression of the inferior vena cava, which leads to engorgement of the epidural venous plexus and increased epidural space pressure. This in turn reduces the volume of cerebrospinal fluid in the subarachnoid space. Magnetic resonance imaging has confirmed the decreased cerebrospinal fluid volume in obese parturients [97]. Greene suggests that obesity per se does not decrease local anaesthetic requirements, rather the larger buttocks of obese patients place the vertebral column in the Trendelenburg position, exaggerating the spread of spinal anaesthesia [98]. There is little evidence in the literature to suggest an exaggerated spread in obese patients for a given amount of local anaesthetic agent [99–102]. Whatever the mechanism, the consequences of extensive blockade in the presence of a potentially difficult airway dictate the amount of local anaesthetic agent given intrathecally. Duration of surgery may extend beyond the duration of single-shot spinal anaesthesia and in such cases intra-operative induction of general anaesthesia is undesirable and potentially hazardous. Although continuous spinal anaesthesia represents an alternative [103], the merit of using it routinely for Caesarean section is yet to be proved. Hence, while choosing single-shot spinal anaesthesia, the consequences of extensive blockade and prolonged surgery must be borne in mind.

Compared with spinal anaesthesia, epidural anaesthesia offers several advantages, including an easily titratable local anaesthetic dose and level of anaesthesia, ability to extend the block for prolonged surgery, slower and more easily controllable haemodynamic changes, a decreased potential for excess motor blockade and its utilisation for postoperative analgesia. Hodgkinson and Hussain demonstrated that height of blockade for a given volume of local anaesthetic agent is proportional to BMI and weight but not height [83]. The decreased volume of the epidural space, for reasons discussed above, may contribute to excessive spread of local anaesthetic agents in obese parturients. However, incremental injection of local anaesthetic doses reduces the effect of obesity on the spread of epidural anaesthesia. Extending labour epidural analgesia for Caesarean section requires additional local anaesthetic agent at higher concentrations. An optimum dose for this remains undetermined.

A combined spinal-epidural technique represents an attractive alternative [104], combining the advantages of rapid onset and dense block with the ability to prolong the block and use postoperatively. Furthermore, use of less local anaesthetic agent intrathecally may circumvent the problems of sudden onset of hypotension. However, the technical challenge of correctly placing an epidural catheter remains.

General anaesthesia

In England, 5–19% of Caesarean sections are done under general anaesthesia in the majority of the units [105]. The anatomical and physiological changes caused by both obesity and pregnancy are less favourable to anaesthetists, resulting in an increased incidence of difficult intubation and rapid desaturation during the apnoeic phase. The potential for an unanticipated difficult airway, difficult mask ventilation and rapid desaturation emphasises the need for an additional pair of experienced hands when administering general anaesthesia. In known cases of difficulty, awake intubation by direct laryngoscopy, fiber optic bronchoscope or Bullard laryngoscope [106] is
an alternative method of securing the airway. Awake intubation poses its own problems. The nasal route is not recommended because of the characteristic engorgement of nasal mucosa during pregnancy. Hypertension and catecholamine release during the procedure could adversely affect uterine blood flow. Moreover, it is difficult to perform in urgent scenarios such as maternal haemorrhage or fetal distress [7]. In any of these circumstances, the mother’s life should not be endangered to save a compromised fetus.

In an otherwise normal airway, administration of general anaesthesia begins with effective denitrogenation of the lungs, as obese parturients desaturate rapidly compared to normal patients. Denitrogenation can be performed by either 3 min of tidal breathing with 100% oxygen or by four maximal breaths with 100% oxygen. There is little evidence to support one technique over the other [107, 108]. Hence, it is reasonable that urgency of Caesarean section dictates the technique of denitrogenation. The choice of intravenous induction agent is relatively unimportant if there are no co-existing medical problems. Dewan suggests that at least 4 mg.kg−1 of thiopental (up to a maximum dose of 500 mg) should be used if chosen, to avoid the risk of maternal awareness, hypertension and decreased uterine blood flow during light anaesthesia [7]. Administration of a larger dose may be associated with delayed arousal in the event of failed intubation. Succinylcholine remains the muscle relaxant of choice for intubation. Bentley et al. observed increased pseudo-cholinesterase activity in obese non-pregnant patients. They recommended that anaesthetists should administer succinylcholine on the basis of total rather than lean body weight in adult patients [109]. However, pregnancy reduces pseudo-cholinesterase activity. Hence the dose of succinylcholine 1.0–1.5 mg.kg−1 up to a maximum of 200 mg is reasonable [7]. Tracheal intubation should be confirmed by the repetitive and characteristic waveform of capnography in addition to auscultation. Endobronchial intubation should also be promptly recognised and corrected to avoid intra- and postoperative pulmonary complications. In the event of failure to intubate the trachea after rapid sequence induction, it is imperative to institute a failed intubation drill without delay. Repeated attempts and a second dose of succinylcholine are seldom beneficial and often detrimental. The primary objective in the management of failed intubation is to ensure adequate maternal oxygenation despite the concerns of fetal well-being or risk of regurgitation.

In morbidly obese patients, a relatively high-inspired oxygen concentration may be necessary compared to non-obese counterparts, necessitating use of high concentrations of volatile agents. Under general anaesthesia, functional residual capacity (FRC) decreases because of the supine position, use of volatile agents, muscle relaxants and cephalad retraction of a panniculus, leading to early closure of small airways, exaggerating hypoxaemia. Various techniques such as higher tidal volumes, high inspired oxygen and the use of positive end-expiratory pressure (PEEP) have been used to maintain adequate oxygenation. In high-risk cases, emptying of the stomach and administration of sodium citrate via an orogastric tube before extubation may be helpful. Extubation should be attempted only in awake patients with adequate reversal of neuromuscular blockade, as there have been incidences of failed extubation in obese parturients [50, 51]. A 30° head-up tilt is a more favourable position for extubation than supine in the obese population [110].

**Postoperative care**

Obese parturients are at increased risk of postoperative complications such as hypoxaemia, atelectasis and pneumonia, deep vein thrombosis and pulmonary embolism, pulmonary oedema, postpartum cardiomyopathy, postoperative endometritis and wound complications such as infection and dehiscence [50, 51]. Early mobilisation, thromboprophylaxis, aggressive chest physiotherapy and adequate pain control are the key to the success of effective postoperative care.

In the recovery room, critical respiratory events (desaturation, hypoventilation and airway obstruction) occur twice as commonly in the obese compared to non-obese [111]. Computerised tomography has demonstrated that obesity predisposes to the formation of pulmonary atelectasis per se and even more so under general anaesthesia, persisting into the postoperative period [112]. Moreover, even after spinal anaesthesia, there is a BMI dependent decrease in respiratory function [113]. Hence, these critical respiratory events may not be benign and can lead to postoperative pulmonary morbidity. Nursing in the reclined position and oxygen supplementation can potentially reduce critical respiratory events. Early mobilisation has been shown to improve the respiratory volumes in the immediate postoperative phase [113]. Interestingly, Hood and Dewan found that, in morbidly obese women, all postpartum complications occurred in those undergoing Caesarean section and not in those having vaginal delivery [51]. In general surgical patients, pre-operative pulmonary function tests have been shown to predict postoperative pulmonary complications in obese patients [77] and an extrapolation for obese parturients may be true.

Pain control should be adequate in the postoperative period to facilitate mobilisation and chest physiotherapy, as it is one of the determinants of postoperative maternal morbidity. Epidural analgesia has been shown to improve
postoperative respiratory function in patients undergoing abdominal surgery [114]. Epidural infusion of local anaesthetic with opioids improves the quality of dynamic postoperative pain relief [115]. Patient controlled intravenous opioids have also been successfully used for postoperative pain relief in the morbidly obese [116].

Thrombo-embolic episodes remain the leading cause of direct maternal deaths in the UK. Obesity is a known independent risk factor for deep vein thrombosis. Both pharmacological and mechanical strategies are used for thromboprophylaxis and an adequate dose of an anti-coagulant for an appropriate duration is recommended [117]. Obesity cardiomyopathy is a well-recognised clinical entity and at least three cases of peripartum cardiomyopathy in obese patients have been reported [51, 118, 119]. Although not established yet, obesity may well be a risk factor for peripartum cardiomyopathy [119].

Wound complications occur more frequently in obese than in non-obese patients and often lead to prolonged recovery. They have been found to be increased with midline abdominal incision compared to a Pfannenstiel incision [120]. An increased incidence of postoperative complications and antepartum medical disease probably contributes significantly to longer hospitalisation for the morbidly obese. Hospital stay and costs have been found to be increased for morbidly obese patients after both vaginal delivery and Caesarean section [121].

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Practice Guidelines for Obstetric Anesthesia

An Updated Report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia

PRACTICE guidelines are systematically developed recommendations that assist the practitioner and patient in making decisions about health care. These recommendations may be adopted, modified, or rejected according to clinical needs and constraints and are not intended to replace local institutional policies. In addition, practice guidelines are not intended as standards or absolute requirements, and their use cannot guarantee any specific outcome. Practice guidelines are subject to revision as warranted by the evolution of medical knowledge, technology, and practice. They provide basic recommendations that are supported by a synthesis and analysis of the current literature, expert opinion, open forum commentary, and clinical feasibility data.

This update includes data published since the “Practice Guidelines for Obstetrical Anesthesia” were adopted by the American Society of Anesthesiologists in 1998; it also includes data and recommendations for a wider range of techniques than was previously addressed.

Methodology

A. Definition of Perioperative Obstetric Anesthesia

For the purposes of these Guidelines, obstetric anesthesia refers to peripartum anesthetic and analgesic activities performed during labor and vaginal delivery, cesarean delivery, removal of retained placenta, and postpartum tubal ligation.

B. Purposes of the Guidelines

The purposes of these Guidelines are to enhance the quality of anesthetic care for obstetric patients, improve patient safety by reducing the incidence and severity of anesthesia-related complications, and increase patient satisfaction.

C. Focus

These Guidelines focus on the anesthetic management of pregnant patients during labor, nonoperative delivery, operative delivery, and selected aspects of postpartum care and analgesia (i.e., neuraxial opioids for postpartum analgesia after neuraxial anesthesia for cesarean delivery). The intended patient population includes, but is not limited to, intrapartum and postpartum patients with uncomplicated pregnancies or with common obstetric problems. The Guidelines do not apply to patients undergoing surgery during pregnancy, gynecologic patients, or parturients with chronic medical disease (e.g., severe cardiac, renal, or neurologic disease). In addition, these Guidelines do not address (1) postpartum analgesia for vaginal delivery, (2) analgesia after tubal ligation, or (3) postoperative analgesia after general anesthesia (GA) for cesarean delivery.

D. Application

These Guidelines are intended for use by anesthesiologists. They also may serve as a resource for other anesthesia providers and healthcare professionals who advise or care for patients who will receive anesthetic care during labor, delivery, and the immediate postpartum period.

E. Task Force Members and Consultants

The American Society of Anesthesiologists (ASA) appointed a Task Force of 11 members to (1) review the published evidence, (2) obtain the opinion of a panel of consultants including anesthesiologists and nonanesthesiologist physicians concerned with obstetric anesthesia and analgesia, and (3) obtain opinions from practitioners likely to be affected by the Guidelines. The Task Force included anesthesiologists in both private and academic practices from various geographic areas of the United States and two consulting methodologists from the ASA Committee on Standards and Practice Parameters.

The Task Force developed the Guidelines by means of

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This article is featured in “This Month in Anesthesiology.” Please see this issue of ANESTHESIOLOGY, page 5A.
a seven-step process. First, they reached consensus on the criteria for evidence. Second, original published research studies from peer-reviewed journals relevant to obstetric anesthesia were reviewed. Third, the panel of expert consultants was asked to (1) participate in opinion surveys on the effectiveness of various peripartum management strategies and (2) review and comment on a draft of the Guidelines developed by the Task Force. Fourth, opinions about the Guideline recommendations were solicited from active members of the ASA who provide obstetric anesthesia. Fifth, the Task Force held open forums at two major national meetings† to solicit input on its draft recommendations. Sixth, the consultants were surveyed to assess their opinions on the feasibility of implementing the Guidelines. Seventh, all available information was used to build consensus within the Task Force to finalize the Guidelines (appendix 1).

F. Availability and Strength of Evidence
Preparation of these Guidelines followed a rigorous methodologic process (appendix 2). To convey the findings in a concise and easy-to-understand fashion, these Guidelines use several descriptive terms. When sufficient numbers of studies are available for evaluation, the following terms describe the strength of the findings.

Support: Meta-analysis of a sufficient number of randomized controlled trials‡ indicates a statistically significant relationship \( (P < 0.01) \) between a clinical intervention and a clinical outcome.
Suggest: Information from case reports and observational studies permits inference of a relationship between an intervention and an outcome. A meta-analytic assessment of this type of qualitative or descriptive information is not conducted.
Equivocal: Either a meta-analysis has not found significant differences among groups or conditions, or there is insufficient quantitative information to conduct a meta-analysis and information collected from case reports and observational studies does not permit inference of a relationship between an intervention and an outcome.
Silent: No identified studies address the specified relationship between an intervention and outcome.
Insufficient: There are too few published studies to investigate a relationship between an intervention and outcome.

Inadequate: The available studies cannot be used to assess the relationship between an intervention and an outcome. These studies either do not meet the criteria for content as defined in the Focus section of these Guidelines, or do not permit a clear causal interpretation of findings due to methodologic concerns.

Formal survey information is collected from consultants and members of the ASA. The following terms describe survey responses for any specified issue. Responses are solicited on a five-point scale ranging from 1 (strongly disagree) to 5 (strongly agree), with a score of 3 being equivocal. Survey responses are summarized based on median values as follows:

Strongly Agree: Median score of 5 (at least 50% of the responses are 5)
Agree: Median score of 4 (at least 50% of the responses are 4 or 4 and 5)
Equivocal: Median score of 3 (at least 50% of the responses are 3, or no other response category or combination of similar categories contain at least 50% of the responses)
Disagree: Median score of 2 (at least 50% of the responses are 2 or 1 and 2)
Strongly Disagree: Median score of 1 (at least 50% of the responses are 1)

Guidelines
I. Perianesthetic Evaluation
History and Physical Examination. Although comparative studies are insufficient to evaluate the peripartum impact of conducting a focused history (e.g., reviewing medical records) or a physical examination, the literature reports certain patient or clinical characteristics that may be associated with obstetric complications. These characteristics include, but are not limited to, preeclampsia, pregnancy-related hypertensive disorders, HELLP syndrome, obesity, and diabetes.

The consultants and ASA members both strongly agree that a directed history and physical examination, as well as communication between anesthetic and obstetric providers, reduces maternal, fetal, and neonatal complications.

Recommendations. The anesthesiologist should conduct a focused history and physical examination before providing anesthesia care. This should include, but is not limited to, a maternal health and anesthetic history, a relevant obstetric history, a baseline blood pressure measurement, and an airway, heart, and lung examination, consistent with the ASA “Practice Advisory for Preanesthesia Evaluation.”§ When a neuraxial anesthetic is planned or placed, the patient’s back should be examined.

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‡ A prospective nonrandomized controlled trial may be included in a meta-analysis under certain circumstances if specific statistical criteria are met.
Recognition of significant anesthetic or obstetric risk factors should encourage consultation between the obstetrician and the anesthesiologist. A communication system should be in place to encourage early and ongoing contact between obstetric providers, anesthesiologists, and other members of the multidisciplinary team.

Intrapartum Platelet Count. The literature is insufficient to assess whether a routine platelet count can predict anesthesia-related complications in uncomplicated parturients. The literature suggests that a platelet count is clinically useful for parturients with suspected pregnancy-related hypertensive disorders, such as preeclampsia or HELLP syndrome, and for other disorders associated with coagulopathy.

The ASA members are equivocal, but the consultants agree that obtaining a routine intrapartum platelet count does not reduce maternal anesthetic complications. Both the consultants and ASA members agree that, for patients with suspected preeclampsia, a platelet count reduces maternal anesthetic complications. The consultants strongly agree and the ASA members agree that a platelet count reduces maternal anesthetic complications for patients with suspected coagulopathy.

Recommendations. A specific platelet count predictive of neuraxial anesthetic complications has not been determined. The anesthesiologist’s decision to order or require a platelet count should be individualized and based on a patient’s history, physical examination, and clinical signs. A routine platelet count is not necessary in the healthy parturient.

Blood Type and Screen. The literature is insufficient to determine whether obtaining a blood type and screen is associated with fewer maternal anesthetic complications. In addition, the literature is insufficient to determine whether a blood cross-match is necessary for healthy and uncomplicated parturients. The consultants and ASA members agree that an intrapartum blood sample should be sent to the blood bank for all parturients.

Recommendations. A specific fasting time for solids that is predictive of neuraxial anesthetic complications has not been determined. There is insufficient published evidence to draw conclusions about the relationship between fasting times for clear liquids and the risk of emesis/reflux or pulmonary aspiration during labor. The consultants and ASA members both agree that oral intake of clear liquids during labor improves maternal comfort and satisfaction. Although the ASA members are equivocal, the consultants agree that oral intake of clear liquids during labor does not increase maternal complications.

Recommendations. The oral intake of modest amounts of clear liquids may be allowed for uncomplicated laboring patients. The uncomplicated patient undergoing elective cesarean delivery may have modest amounts of clear liquids up to 2 h before induction of anesthesia. Examples of clear liquids include, but are not limited to, water, fruit juices without pulp, carbonated beverages, clear tea, black coffee, and sports drinks. The volume of liquid ingested is less important than the presence of particulate matter in the liquid ingested. However, patients with additional risk factors for aspiration (e.g., morbid obesity, diabetes, difficult airway) or patients at increased risk for operative delivery (e.g., nonreassuring fetal heart rate pattern) may have further restrictions of oral intake, determined on a case-by-case basis.

Solids. A specific fasting time for solids that is predictive of maternal anesthetic complications has not been determined. There is insufficient published evidence to address the safety of any particular fasting period for solids in obstetric patients. The consultants and ASA members both agree that the oral intake of solids during labor increases maternal complications. They both strongly agree that patients undergoing either elective cesarean delivery or postpartum tubal ligation should undergo a fasting period of 6–8 h depending on the type of food ingested (e.g., fat content). The Task Force recognizes that in laboring patients the timing of delivery is uncertain; therefore, compliance with a predetermined fasting period before nonelective surgical procedures is not always possible.

Recommendations. Solid foods should be avoided in laboring patients. The patient undergoing elective surgery (e.g., scheduled cesarean delivery or postpartum tubal ligation) should undergo a fasting period for solids...
of 6–8 h depending on the type of food ingested (e.g., fat content).

**Antacids, H₂ Receptor Antagonists, and Metoclopramide.** The literature does not sufficiently examine the relationship between reduced gastric acidity and the frequency of emesis, pulmonary aspiration, morbidity, or mortality in obstetric patients who have aspirated gastric contents. Published evidence supports the efficacy of preoperative nonparticulate antacids (e.g., sodium citrate, sodium bicarbonate) in decreasing gastric acidity during the peripartum period. However, the literature is insufficient to examine the impact of nonparticulate antacids on gastric volume. The literature suggests that H₂ receptor antagonists are effective in decreasing gastric acidity in obstetric patients and supports the efficacy of metoclopramide in reducing peripartum nausea and vomiting. The consultants and ASA members agree that neuraxial techniques improve the likelihood of vaginal delivery for patients attempting vaginal birth after previous cesarean delivery. For these patients, it is also appropriate to consider early placement of a neuraxial catheter that can be used later for labor analgesia, or for anesthesia in the event of operative delivery.

**Neuraxial Analgesia and Trial of Labor after Previous Cesarean Delivery.** Nonrandomized comparative studies suggest that epidural analgesia may be used in a trial of labor for previous cesarean delivery patients without adversely affecting the incidence of vaginal delivery. Randomized comparisons of epidural versus other anesthetic techniques were not found. The consultants and ASA members agree that neuraxial techniques improve the likelihood of vaginal delivery for patients attempting vaginal birth after cesarean delivery.

**Recommendations.** Neuraxial techniques should be offered to patients attempting vaginal birth after previous cesarean delivery. For these patients, it is also appropriate to consider early placement of a neuraxial catheter that can be used later for labor analgesia, or for anesthesia in the event of operative delivery.

**Early Insertion of a Spinal or Epidural Catheter for Complicated Parturients.** The literature is insufficient to assess whether, when caring for the complicated parturient, the early insertion of a spinal or epidural catheter, with later administration of analgesia, improves maternal or neonatal outcomes. The consultants and ASA members agree that early insertion of a spinal or epidural catheter for complicated parturients reduces maternal complications.

**Recommendations.** Early insertion of a spinal or epidural catheter for obstetric (e.g., twin gestation or pre-eclampsia) or anesthetic indications (e.g., anticipated difficult airway or obesity) should be considered to reduce the need for GA if an emergent procedure becomes necessary. In these cases, the insertion of a spinal or...
epidural catheter may precede the onset of labor or a patient’s request for labor analgesia.

**Continuous Infusion Epidural Analgesia.**

*CIE Compared with Parenteral Opioids.* The literature suggests that the use of continuous infusion epidural (CIE) local anesthetics with or without opioids provides greater quality of analgesia compared with parenteral (i.e., intravenous or intramuscular) opioids. The consultants and ASA members strongly agree that CIE local anesthetics with or without opioids provide improved analgesia compared with parenteral opioids.

Meta-analysis of the literature indicates that there is a longer duration of labor, with an average duration of 24 min for the second stage, and a lower frequency of spontaneous vaginal delivery when continuous epidural local anesthetics are administered compared with *intravenous* opioids. Meta-analysis of the literature determined that there are no differences in the frequency of cesarean delivery. Neither the consultants nor ASA members agree that CIE local anesthetics compared with parenteral opioids significantly (1) increase the duration of labor, (2) decrease the chance of spontaneous delivery, (3) increase maternal side effects, or (4) increase fetal and neonatal side effects.

*CIE Compared with Single-injection Spinal.* There is insufficient literature to assess the analgesic efficacy of CIE local anesthetics with or without opioids compared to *single-injection spinal opioids* with or without local anesthetics. The consultants are equivocal, but the ASA members agree that CIE local anesthetics improve analgesia compared with single-injection spinal opioids; both the consultants and ASA members are equivocal regarding the frequency of motor block. The consultants are equivocal, but the ASA members disagree that the use of CIE compared with single-injection spinal opioids increases the duration of labor. They both *disagree* that CIE local anesthetics with or without opioids compared to single-injection spinal opioids with or without local anesthetics decreases the likelihood of spontaneous delivery or increases maternal, fetal, or neonatal side effects.

*CIE with and without Opioids.* The literature supports the *induction* of analgesia using epidural local anesthetics combined with *opioids* compared with equal concentrations of epidural local anesthetics *without opioids* for improved quality and longer duration of analgesia. The consultants strongly agree and the ASA members agree that the addition of opioids to epidural local anesthetics improves analgesia; they both disagree that fetal or neonatal side effects are increased. The consultants disagree, but the ASA members are equivocal regarding whether the addition of opioids increases maternal side effects.

The literature is insufficient to determine whether induction of analgesia using local anesthetics with opioids compared with *higher concentrations* of epidural local anesthetics without opioids provides improved quality or duration of analgesia. The consultants and ASA members are equivocal regarding improved analgesia, and they both disagree that maternal, fetal, or neonatal side effects are increased using lower concentrations of epidural local anesthetics with opioids.

For *maintenance of analgesia*, the literature suggests that there are no differences in the analgesic efficacy of *low concentrations* of epidural local anesthetics with opioids compared with *higher concentrations* of epidural local anesthetics without opioids. The Task Force notes that the addition of an opioid to a local anesthetic infusion allows an even lower concentration of local anesthetic for providing equally effective analgesia. However, the literature is insufficient to examine whether a bupivacaine infusion concentration of less than or equal to 0.125% with an opioid provides comparable or improved analgesia compared with a bupivacaine concentration greater than 0.125% without an opioid.# Meta-analysis of the literature determined that low concentrations of epidural local anesthetics with opioids compared with higher concentrations of epidural local anesthetics without opioids are associated with reduced motor block. No differences in the duration of labor, mode of delivery, or neonatal outcomes are found when epidural local anesthetics with opioids are compared with epidural local anesthetics without opioids. The literature is insufficient to determine the effects of epidural local anesthetics with opioids on other maternal outcomes (e.g., hypotension, nausea, pruritus, respiratory depression, urinary retention).

The consultants and ASA members both agree that maintenance of epidural analgesia using *low concentrations* of local anesthetics with opioids provides improved analgesia compared with *higher concentrations* of local anesthetics without opioids. The consultants agree, but the ASA members are equivocal regarding the improved likelihood of spontaneous delivery when lower concentrations of local anesthetics with opioids are used. The consultants strongly agree and the ASA members agree that motor block is reduced. They agree that maternal side effects are reduced with this drug combination. They are both equivocal regarding a reduction in fetal and neonatal side effects.

**Recommendations.** The selected analgesic/anesthetic technique should reflect patient needs and preferences, practitioner preferences or skills, and available resources. The continuous epidural infusion technique may be used for effective analgesia for labor and delivery. When a continuous epidural infusion of local anesthetic is selected, an opioid may be added to reduce the

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# References to bupivacaine are included for illustrative purposes only, and because bupivacaine is the most extensively studied local anesthetic for continuous infusion epidural analgesia. The Task Force recognizes that other local anesthetics are appropriate for continuous infusion epidural analgesia.
concentration of local anesthetic, improve the quality of analgesia, and minimize motor block.

Accurate analgesia for uncomplicated labor and delivery should be administered with the secondary goal of producing as little motor block as possible by using dilute concentrations of local anesthetics with opioids. The lowest concentration of local anesthetic infusion that provides adequate maternal analgesia and satisfaction should be administered. For example, an infusion concentration greater than 0.125% bupivacaine is unnecessary for labor analgesia in most patients.

Single-injection Spinal Opioids with or without Local Anesthetics. The literature suggests that spinal opioids with or without local anesthetics provide effective analgesia during labor without altering the incidence of neonatal complications. There is insufficient literature to compare spinal opioids with parenteral opioids. There is also insufficient literature to compare single-injection spinal opioids with local anesthetics versus single-injection spinal opioids without local anesthetics.

The consultants strongly agree and the ASA members agree that spinal opioids provide improved analgesia compared with parenteral opioids. They both disagree that, compared with parenteral opioids, spinal opioids increase the duration of labor, decrease the chance of spontaneous delivery, or increase fetal and neonatal side effects. The consultants are equivocal, but the ASA members disagree that maternal side effects are increased with spinal opioids.

Compared with spinal opioids without local anesthetics, the consultants and ASA members both agree that spinal opioids with local anesthetics provide improved analgesia. They both disagree that the chance of spontaneous delivery is decreased and that fetal and neonatal side effects are increased. They are both equivocal regarding an increase in maternal side effects. However, they both agree that motor block is increased when local anesthetics are added to spinal opioids. Finally, the consultants disagree, but the ASA members are equivocal regarding an increase in the duration of labor.

Recommendations. Single-injection spinal opioids with or without local anesthetics may be used to provide effective, although time-limited, analgesia for labor when spontaneous vaginal delivery is anticipated. If labor is expected to last longer than the analgesic effects of the spinal drugs chosen or if there is a good possibility of operative delivery, a catheter technique instead of a single injection technique should be considered. A local anesthetic may be added to a spinal opioid to increase duration and improve quality of analgesia. The Task Force notes that the rapid onset of analgesia provided by single-injection spinal techniques may be advantageous for selected patients (e.g., those in advanced labor).

Pencil-point Spinal Needles. The literature supports the use of pencil-point spinal needles compared with cutting-bevel spinal needles to reduce the frequency of post-dural puncture headache. The consultants and ASA members both strongly agree that the use of pencil-point spinal needles reduces maternal complications.

Recommendations. Pencil-point spinal needles should be used instead of cutting-bevel spinal needles to minimize the risk of post-dural puncture headache.

Combined Spinal– Epidural Analgesia. The literature supports a faster onset time and equivalent analgesia with combined spinal–epidural (CSE) local anesthetics with opioids versus epidural local anesthetics with opioids. The literature is equivocal regarding the impact of CSE versus epidural local anesthetics on maternal satisfaction with analgesia, mode of delivery, hypotension, motor block, nausea, fetal heart rate changes, and Apgar scores. Meta-analysis of the literature indicates that the frequency of pruritus is increased with CSE.

The consultants and ASA members both agree that CSE local anesthetics with opioids provide improved early analgesia compared with epidural local anesthetics with opioids. They are equivocal regarding the impact of CSE with opioids on overall analgesic efficacy, duration of labor, and motor block. The consultants and ASA members both disagree that CSE increases the risk of fetal or neonatal side effects. The consultants disagree, but the ASA members are equivocal regarding whether CSE increases the incidence of maternal side effects.

Recommendations. Combined spinal– epidural techniques may be used to provide effective and rapid onset of analgesia for labor.

Patient-controlled Epidural Analgesia. The literature supports the efficacy of patient-controlled epidural analgesia (PCEA) versus CIE in providing equivalent analgesia with reduced drug consumption. Meta-analysis of the literature indicates that the duration of labor is longer with PCEA compared with CIE for the first stage (e.g., an average of 36 min) but not the second stage of labor. Meta-analysis of the literature also determined that mode of delivery, frequency of motor block, and Apgar scores are equivalent when PCEA administration is compared with CIE. The literature supports greater analgesic efficacy for PCEA with a background infusion compared with PCEA without a background infusion; meta-analysis of the literature also indicates no differences in the mode of delivery or frequency of motor block. The consultants and ASA members agree that PCEA compared with CIE improves analgesia and reduces the need for anesthetic interventions; they also agree that PCEA improves maternal satisfaction. The consultants and ASA members are equivocal regarding a reduction in motor block, an increased likelihood of spontaneous delivery, or a decrease in maternal side effects with PCEA compared with CIE. They both agree that PCEA with a background infusion improves analgesia, improves maternal satisfaction, and reduces the need for anesthetic intervention. The ASA members are equivocal, but the consultants disagree that a background infusion decreases the chance of sponta-
neous delivery or increases maternal side effects. The consultants and ASA members are equivocal regarding the effect of a background infusion on the incidence of motor block.

Recommendations. Patient-controlled epidural analgesia may be used to provide an effective and flexible approach for the maintenance of labor analgesia. The Task Force notes that the use of PCEA may be preferable to fixed-rate CIE for providing fewer anesthetic interventions and reduced dosages of local anesthetics. PCEA may be used with or without a background infusion.

IV. Removal of Retained Placenta

Anesthetic Techniques. The literature is insufficient to assess whether a particular type of anesthetic is more effective than another for removal of retained placenta. The consultants strongly agree and the ASA members agree that, if a functioning epidural catheter is in place and the patient is hemodynamically stable, epidural anesthesia is the preferred technique for the removal of retained placenta. The consultants and ASA members both agree that, in cases involving major maternal hemorrhage, GA is preferred over neuraxial anesthesia.

Recommendations. The Task Force notes that, in general, there is no preferred anesthetic technique for removal of retained placenta. However, if an epidural catheter is in place and the patient is hemodynamically stable, epidural anesthesia is preferable. Hemodynamic status should be assessed before administering neuraxial anesthesia. Aspiration prophylaxis should be considered. Sedation/analgesia should be titrated carefully due to the potential risks of respiratory depression and pulmonary aspiration during the immediate postpartum period. In cases involving major maternal hemorrhage, GA with an endotrachcal tube may be preferable to neuraxial anesthesia.

Uterine Relaxation. The literature suggests that nitroglycerin is effective for uterine relaxation during the removal of retained placenta. The consultants and ASA members both agree that the administration of nitroglycerin for uterine relaxation improves success in removing a retained placenta.

Recommendations. Nitroglycerin may be used as an alternative to terbutaline sulfate or general endotrachcal anesthesia with halogenated agents for uterine relaxation during removal of retained placental tissue. Initiating treatment with incremental doses of intravenous or sublingual (i.e., metered dose spray) nitroglycerin may relax the uterus sufficiently while minimizing potential complications (e.g., hypotension).

V. Anesthetic Choices for Cesarean Delivery

Equipment, Facilities, and Support Personnel. The literature is insufficient to evaluate the benefit of providing equipment, facilities and support personnel in the labor and delivery operating suite comparable to that available in the main operating suite. The consultants and ASA members strongly agree that the available equipment, facilities, and support personnel should be comparable.

Recommendations. Equipment, facilities, and support personnel available in the labor and delivery operating suite should be comparable to those available in the main operating suite. Resources for the treatment of potential complications (e.g., failed intubation, inadequate analgesia, hypotension, respiratory depression, pruritus, vomiting) should also be available in the labor and delivery operating suite. Appropriate equipment and personnel should be available to care for obstetric patients recovering from major neuraxial anesthesia or GA.

General, Epidural, Spinal, or Combined Spinal–Epidural Anesthesia. The literature suggests that induction-to-delivery times for GA are lower compared with epidural or spinal anesthesia and that a higher frequency of maternal hypotension may be associated with epidural or spinal techniques. Meta-analysis of the literature found that Apgar scores at 1 and 5 min are lower for GA compared with epidural anesthesia and suggests that Apgar scores are lower for GA versus spinal anesthesia. The literature is equivocal regarding differences in umbilical artery pH values when GA is compared with epidural or spinal anesthesia.

The consultants and ASA members agree that GA reduces the time to skin incision when compared with either epidural or spinal anesthesia; they also agree that GA increases maternal complications. The consultants are equivocal and the ASA members agree that GA increases fetal and neonatal complications. The consultants and ASA members both agree that epidural anesthesia increases the time to skin incision and decreases the quality of anesthesia compared with spinal anesthesia. They both disagree that epidural anesthesia increases maternal complications.

When spinal anesthesia is compared with epidural anesthesia, meta-analysis of the literature found that induction-to-delivery times are shorter for spinal anesthesia. The literature is equivocal regarding hypotension, umbilical pH values, and Apgar scores. The consultants and ASA members agree that epidural anesthesia increases time to skin incision and reduces the quality of anesthesia when compared with spinal anesthesia. They both disagree that epidural anesthesia increases maternal complications.

When CSE is compared with epidural anesthesia, meta-analysis of the literature found no differences in the frequency of hypotension or in 1-min Apgar scores; the literature is insufficient to evaluate outcomes associated with the use of CSE compared with spinal anesthesia. The consultants and ASA members agree that CSE anesthesia improves anesthesia and reduces time to skin incision when compared with epidural anesthesia. The
ASA members are equivocal, but the consultants disagree that maternal side effects are reduced. The consultants and ASA members both disagree that CSE improves anesthesia compared with spinal anesthesia. The ASA members are equivocal, but the consultants disagree that maternal side effects are reduced. The consultants strongly agree and the ASA members agree that CSE compared with spinal anesthesia increases flexibility of prolonged procedures, and they both agree that the time to skin incision is increased.

**Recommendations.** The decision to use a particular anesthetic technique for cesarean delivery should be individualized, based on several factors. These include anesthetic, obstetric, or fetal risk factors (e.g., elective vs emergency), the preferences of the patient, and the judgment of the anesthesiologist. Neuraxial techniques are preferred to GA for most cesarean deliveries. An indwelling epidural catheter may provide equivalent onset of anesthesia compared with initiation of spinal anesthesia for urgent cesarean delivery. If spinal anesthesia is chosen, pencil-point spinal needles should be used instead of cutting-bevel spinal needles. However, GA may be the most appropriate choice in some circumstances (e.g., profound fetal bradycardia, ruptured uterus, severe hemorrhage, severe placental abruption). Uterine displacement (usually left displacement) should be maintained until delivery regardless of the anesthetic technique used.

**Intravenous Fluid Preloading.** The literature supports and the consultants and ASA members agree that intravenous fluid preloading for spinal anesthesia reduces the frequency of maternal hypotension when compared with no fluid preloading.

**Recommendations.** Intravenous fluid preloading may be used to reduce the frequency of maternal hypotension after spinal anesthesia for cesarean delivery. Although fluid preloading reduces the frequency of maternal hypotension, initiation of spinal anesthesia should not be delayed to administer a fixed volume of intravenous fluid.

**Ephedrine or Phenylephrine.** The literature supports the administration of ephedrine and suggests that phenylephrine is effective in reducing maternal hypotension during neuraxial anesthesia for cesarean delivery. The literature is equivocal regarding the relative frequency of patients with breakthrough hypotension when infusions of ephedrine are compared with phenylephrine; however, lower umbilical cord pH values are reported after ephedrine administration. The consultants agree and the ASA members strongly agree that ephedrine is acceptable for treating hypotension during neuraxial anesthesia. The consultants strongly agree and the ASA members agree that phenylephrine is an acceptable agent for the treatment of hypotension.

**Recommendations.** Intravenous ephedrine and phenylephrine are both acceptable drugs for treating hypotension during neuraxial anesthesia. In the absence of maternal bradycardia, phenylephrine may be preferable because of improved fetal acid–base status in uncomplicated pregnancies.

**Neuraxial Opioids for Postoperative Analgesia.** For improved postoperative analgesia after cesarean delivery during epidural anesthesia, the literature supports the use of epidural opioids compared with intermittent injections of intravenous or intramuscular opioids. However, a higher frequency of pruritus was found with epidural opioids. The literature is insufficient to evaluate the impact of epidural opioids compared with intravenous PCA. In addition, the literature is insufficient to evaluate spinal opioids compared with parenteral opioids. The consultants strongly agree and the ASA members agree that neuraxial opioids for postoperative analgesia improve analgesia and maternal satisfaction.

**Recommendations.** For postoperative analgesia after neuraxial anesthesia for cesarean delivery, neuraxial opioids are preferred over intermittent injections of parenteral opioids.

VI. Postpartum Tubal Ligation

There is insufficient literature to evaluate the benefits of neuraxial anesthesia compared with GA for postpartum tubal ligation. In addition, the literature is insufficient to evaluate the impact of the timing of a postpartum tubal ligation on maternal outcome. The consultants and ASA members both agree that neuraxial anesthesia for postpartum tubal ligation reduces complications compared with GA. The ASA members are equivocal but the consultants agree that a postpartum tubal ligation within 8 h of delivery does not increase maternal complications.

**Recommendations.** For postpartum tubal ligation, the patient should have no oral intake of solid foods within 6–8 h of the surgery, depending on the type of food ingested (e.g., fat content). Absorption prophylaxis should be considered. Both the timing of the procedure and the decision to use a particular anesthetic technique (i.e., neuraxial vs. general) should be individualized, based on anesthetic risk factors, obstetric risk factors (e.g., blood loss), and patient preferences. However, neuraxial techniques are preferred to GA for most postpartum tubal ligations. The anesthesiologist should be aware that gastric emptying will be delayed in patients who have received opioids during labor, and that an epidural catheter placed for labor may be more likely to fail with longer postdelivery time intervals. If a postpartum tubal ligation is to be performed before the patient is discharged from the hospital, the procedure should not be attempted at a time when it might compromise other aspects of patient care on the labor and delivery unit.
Table 1. Suggested Resources for Obstetric Hemorrhagic Emergencies

- Large-bore intravenous catheters
- Fluid warmer
- Forced-air body warmer
- Availability of blood bank resources
- Equipment for infusing intravenous fluids and blood products rapidly. Examples include, but are not limited to, hand-squeezed fluid chambers, hand-inflated pressure bags, and automatic infusion devices

The items listed represent suggestions. The items should be customized to meet the specific needs, preferences, and skills of the practitioner and healthcare facility.

VII. Management of Obstetric and Anesthetic Emergencies

Resources for Management of Hemorrhagic Emergencies. Observational studies and case reports suggest that the availability of resources for hemorrhagic emergencies may be associated with reduced maternal complications. The consultants and ASA members both strongly agree that the availability of resources for managing hemorrhagic emergencies reduces maternal complications.

Recommendations. Institutions providing obstetric care should have resources available to manage hemorrhagic emergencies (table 1). In an emergency, the use of type-specific or O negative blood is acceptable. In cases of intractable hemorrhage when banked blood is not available or the patient refuses banked blood, intraoperative cell-salvage should be considered if available.

Central Invasive Hemodynamic Monitoring. There is insufficient literature to examine whether pulmonary artery catheterization is associated with improved maternal, fetal, or neonatal outcomes in patients with pregnancy-related hypertensive disorders. The literature is silent regarding the management of obstetric patients with central venous catheterization alone. The consultants and ASA members agree that the routine use of central venous or pulmonary artery catheterization does not reduce maternal complications in severely preeclamptic patients.

Recommendations. The decision to perform invasive hemodynamic monitoring should be individualized and based on clinical indications that include the patient’s medical history and cardiovascular risk factors. The Task Force recognizes that not all practitioners have access to resources for use of central venous or pulmonary artery catheters in obstetric units.

Equipment for Management of Airway Emergencies. Case reports suggest that the availability of equipment for the management of airway emergencies may be associated with reduced maternal, fetal, and neonatal complications. The consultants and ASA members both strongly agree that the immediate availability of equipment for the management of airway emergencies reduces maternal, fetal, and neonatal complications.

Recommendations. Labor and delivery units should have personnel and equipment readily available to manage airway emergencies, to include a pulse oximeter and qualitative carbon dioxide detector, consistent with the ASA Practice Guidelines for Management of the Difficult Airway.** Basic airway management equipment should be immediately available during the provision of neuraxial analgesia (table 2). In addition, portable equipment for difficult airway management should be readily available in the operative area of labor and delivery units (table 3). The anesthesiologist should have a preformulated strategy for intubation of the difficult airway. When tracheal intubation has failed, ventilation with mask and cricoid pressure, or with a laryngeal mask airway or supraglottic airway device (e.g., Combitube®), Intubating

Table 2. Suggested Resources for Airway Management during Initial Provision of Neuraxial Anesthesia

- Laryngoscope and assorted blades
- Endotracheal tubes, with stylets
- Oxygen source
- Suction source with tubing and catheters
- Self-inflating bag and mask for positive-pressure ventilation
- Medications for blood pressure support, muscle relaxation, and hypnosis
- Qualitative carbon dioxide detector
- Pulse oximeter

The items listed represent suggestions. The items should be customized to meet the specific needs, preferences, and skills of the practitioner and healthcare facility.

Table 3. Suggested Contents of a Portable Storage Unit for Difficult Airway Management for Cesarean Delivery Rooms

- Rigid laryngoscope blades of alternate design and size from those routinely used
- Laryngeal mask airway
- Endotracheal tubes of assorted size
- Endotracheal tube guides. Examples include, but are not limited to, semirigid stylets with or without a hollow core for jet ventilation, light wands, and forceps designed to manipulate the distal portion of the endotracheal tube
- Retrograde intubation equipment
- At least one device suitable for emergency nonsurgical airway ventilation. Examples include, but are not limited to, a hollow jet ventilation stylet with a transtracheal jet ventilator, and a supraglottic airway device (e.g., Combitube®, Intubating LMA [Fastrach™])
- Fiberoptic intubation equipment
- Equipment suitable for emergency surgical airway access (e.g., cricothyotomy)
- An exhaled carbon dioxide detector
- Topical anesthetics and vasoconstrictors

The items listed represent suggestions. The items should be customized to meet the specific needs, preferences, and skills of the practitioner and healthcare facility.

LMA [Fastrach™] should be considered for maintaining an airway and ventilating the lungs. If it is not possible to ventilate or awaken the patient, an airway should be created surgically.

Cardiopulmonary Resuscitation. The literature is insufficient to evaluate the efficacy of cardiopulmonary resuscitation in the obstetric patient during labor and delivery. In cases of cardiac arrest, the American Heart Association has stated that 4–5 min is the maximum time rescuers will have to determine whether the arrest can be reversed by Basic Life Support and Advanced Cardiac Life Support interventions.†† Delivery of the fetus may improve cardiopulmonary resuscitation of the mother by relieving aortocaval compression. The American Heart Association further notes that “the best survival rate for infants >24 to 25 weeks in gestation occurs when the delivery of the infant occurs no more than 5 min after the mother’s heart stops beating. This typically requires that the provider begin the hysterotomy about 4 min after cardiac arrest.”†† The consultants and ASA members both strongly agree that the immediate availability of basic and advanced life-support equipment in the labor and delivery suite reduces maternal, fetal, and neonatal complications.

Recommendations. Basic and advanced life-support equipment should be immediately available in the operative area of labor and delivery units. If cardiac arrest occurs during labor and delivery, standard resuscitative measures should be initiated. In addition, uterine displacement (usually left displacement) should be maintained. If maternal circulation is not restored within 4 min, cesarean delivery should be performed by the obstetrics team.

Appendix 1: Summary of Recommendations

I. Perianesthetic Evaluation

• Conduct a focused history and physical examination before providing anesthesia care
  - Maternal health and anesthetic history
  - Relevant obstetric history
  - Airway and heart and lung examination
  - Baseline blood pressure measurement
  - Back examination when neuraxial anesthesia is planned or placed

A communication system should be in place to encourage early and ongoing contact between obstetric providers, anesthesiologists, and other members of the multidisciplinary team

• Order or require a platelet count based on a patient’s history, physical examination, and clinical signs; a routine intrapartum platelet count is not necessary in the healthy parturient

• Order or require an intrapartum blood type and screen or cross-match based on maternal history, anticipated hemorrhagic complications (e.g., placenta accreta in a patient with placenta previa and previous uterine surgery), and local institutional policies; a routine blood cross-match is not necessary for healthy and uncomplicated parturients

• The fetal heart rate should be monitored by a qualified individual before and after administration of neuraxial analgesia for labor; continuous electronic recording of the fetal heart rate may not be necessary in every clinical setting and may not be possible during initiation of neuraxial anesthesia

II. Aspiration Prophylaxis

• Oral intake of modest amounts of clear liquids may be allowed for uncomplicated laboring patients

• The uncomplicated patient undergoing elective cesarean delivery may have modest amounts of clear liquids up to 2 h before induction of anesthesia

• The volume of liquid ingested is less important than the presence of particulate matter in the liquid ingested

• Patients with additional risk factors for aspiration (e.g., morbid obesity, diabetes, difficult airway) or patients at increased risk for operative delivery (e.g., nonreassuring fetal heart rate pattern) may have further restrictions of oral intake, determined on a case-by-case basis

• Solid foods should be avoided in laboring patients

• Patients undergoing elective surgery (e.g., scheduled cesarean delivery or postpartum tubal ligation) should undergo a fasting period for solids of 6–8 h depending on the type of food ingested (e.g., fat content)

• Before surgical procedures (i.e., cesarean delivery, postpartum tubal ligation), practitioners should consider timely administration of nonparticulate antacids, H2 receptor antagonists, and/or metoclopramide for aspiration prophylaxis

III. Anesthetic Care for Labor and Delivery

Neuraxial Techniques: Availability of Resources.

• When neuraxial techniques that include local anesthetics are chosen, appropriate resources for the treatment of complications (e.g., hypotension, systemic toxicity, high spinal anesthesia) should be available

• If an opioid is added, treatments for related complications (e.g., pruritus, nausea, respiratory depression) should be available

• An intravenous infusion should be established before the initiation of neuraxial analgesia or anesthesia and maintained throughout the duration of the neuraxial analgesic or anesthetic

• Administration of a fixed volume of intravenous fluid is not required before neuraxial analgesia is initiated

Timing of Neuraxial Analgesia and Outcome of Labor.

• Neuraxial analgesia should not be withheld on the basis of achieving an arbitrary cervical dilation, and should be offered on an individualized basis when this service is available

• Patients may be reassured that the use of neuraxial analgesia does not increase the incidence of cesarean delivery

Neuraxial Analgesia and Trial of Labor after Previous Cesarean Delivery.

• Neuraxial techniques should be offered to patients attempting vaginal birth after previous cesarean delivery

• For these patients, it is also appropriate to consider early placement of a neuraxial catheter that can be used later for labor analgesia or for anesthesia in the event of operative delivery

Early Insertion of Spinal or Epidural Catheter for Complicated Parturients.

• Early insertion of a spinal or epidural catheter for obstetric (e.g., twin gestation or preeclampsia) or anesthetic indications (e.g., anticipated...
difficult airway or obesity) should be considered to reduce the need for general anesthesia if an emergent procedure becomes necessary

- In these cases, the insertion of a spinal or epidural catheter may precede the onset of labor or a patient's request for labor analgesia

Continuous Infusion Epidural (CIE) Analgesia.

- The selected analgesic/anesthetic technique should reflect patient needs and preferences, practitioner preferences or skills, and available resources
- CIE may be used for effective analgesia for labor and delivery
- When a continuous epidural infusion of local anesthetic is selected, an opioid may be added to reduce the concentration of local anesthetic, improve the quality of analgesia, and minimize motor block
- Adequate analgesia for uncomplicated labor and delivery should be administered with the secondary goal of producing as little motor block as possible by using dilute concentrations of local anesthetics with opioids
- The lowest concentration of local anesthetic infusion that provides adequate maternal analgesia and satisfaction should be administered

Single-injection Spinal Opioids with or without Local Anesthetics.

- Single-injection spinal opioids with or without local anesthetics may be used to provide effective, although time-limited, analgesia for labor when spontaneous vaginal delivery is anticipated
- If labor is expected to last longer than the analgesic effects of the spinal drugs chosen or if there is a good possibility of operative delivery, a catheter technique instead of a single injection technique should be considered
- A local anesthetic may be added to a spinal opioid to increase duration and improve quality of analgesia

Pencil-point Spinal Needles.

- Pencil-point spinal needles should be used instead of cutting-bevel spinal needles to minimize the risk of post-dural puncture headache


- CSE techniques may be used to provide effective and rapid analgesia for labor

Patient-controlled Epidural Analgesia (PCEA).

- PCEA may be used to provide an effective and flexible approach for the maintenance of labor analgesia
- PCEA may be preferable to CIE for providing fewer anesthetic interventions, reduced dosages of local anesthetics, and less motor blockade than fixed-rate continuous epidural infusions
- PCEA may be used with or without a background infusion

IV. Removal of Retained Placenta

- In general, there is no preferred anesthetic technique for removal of retained placenta

  - If an epidural catheter is in place and the patient is hemodynamically stable, epidural anesthesia is preferable
- Hemodynamic status should be assessed before administering neuraxial anesthesia
- Aspiration prophylaxis should be considered
- Sedation/analgesia should be titrated carefully due to the potential risks of respiratory depression and pulmonary aspiration during the immediate postpartum period
- In cases involving major maternal hemorrhage, general anesthesia with an endotracheal tube may be preferable to neuraxial anesthesia
- Nitroglycerin may be used as an alternative to terbutaline sulfate or general endotracheal anesthesia with halogenated agents for uterine relaxation during removal of retained placental tissue

  - Initiating treatment with incremental doses of intravenous or sublingual (i.e., metered dose spray) nitroglycerin may relax the uterus sufficiently while minimizing potential complications (e.g., hypotension)

V. Anesthetic Choices for Cesarean Delivery

- Equipment, facilities, and support personnel available in the labor and delivery operating suite should be comparable to those available in the main operating suite

  - Resources for the treatment of potential complications (e.g., failed intubation, inadequate analgesia, hypotension, respiratory depression, pruritus, vomiting) should be available in the labor and delivery operating suite
  - Appropriate equipment and personnel should be available to care for obstetric patients recovering from major neuraxial or general anesthesia

- The decision to use a particular anesthetic technique should be individualized based on anesthetic, obstetric, or fetal risk factors (e.g., elective vs. emergency), the preferences of the patient, and the judgment of the anesthesiologist

  - Neuraxial techniques are preferred to general anesthesia for most cesarean deliveries
  - An indwelling epidural catheter may provide equivalent onset of anesthesia compared with initiation of spinal anesthesia for urgent cesarean delivery
  - If spinal anesthesia is chosen, pencil-point spinal needles should be used instead of cutting-bevel spinal needles
  - General anesthesia may be the most appropriate choice in some circumstances (e.g., profound fetal bradycardia, ruptured uterus, severe hemorrhage, severe placental abruption)
  - Uterine displacement (usually left displacement) should be maintained until delivery regardless of the anesthetic technique used
  - Intravenous fluid preloading may be used to reduce the frequency of maternal hypotension after spinal anesthesia for cesarean delivery
  - Initiation of spinal anesthesia should not be delayed to administer a fixed volume of intravenous fluid
  - Intravenous ephedrine and phenylephrine are both acceptable drugs for treating hypotension during neuraxial anesthesia

  - In the absence of maternal bradycardia, phenylephrine may be preferable because of improved fetal acid–base status in uncomplicated pregnancies

- For postoperative analgesia after neuraxial anesthesia for cesarean delivery, neuraxial opioids are preferred over intermittent injections of parenteral opioids

VI. Postpartum Tubal Ligation

- For postpartum tubal ligation, the patient should have no oral intake of solid foods within 6–8 h of the surgery, depending on the type of food ingested (e.g., fat content)
- Aspiration prophylaxis should be considered
- Both the timing of the procedure and the decision to use a particular anesthetic technique (i.e., neuraxial vs. general) should be individualized, based on anesthetic risk factors, obstetric risk factors (e.g., blood loss), and patient preferences
- Neuraxial techniques are preferred to general anesthesia for most postpartum tubal ligations

  - Be aware that gastric emptying will be delayed in patients who have received opioids during labor and that an epidural catheter placed
for labor may be more likely to fail with longer postdelivery time intervals

- If a postpartum tubal ligation is to be performed before the patient is discharged from the hospital, the procedure should not be attempted at a time when it might compromise other aspects of patient care on the labor and delivery unit

VII. Management of Obstetric and Anesthetic Emergencies

- Institutions providing obstetric care should have resources available to manage hemorrhagic emergencies
  - In an emergency, the use of type-specific or O negative blood is acceptable
  - In cases of intractable hemorrhage when banked blood is not available or the patient refuses banked blood, intraoperative cell-salvage should be considered if available
  - The decision to perform invasive hemodynamic monitoring should be individualized and based on clinical indications that include the patient’s medical history and cardiovascular risk factors

- Labor and delivery units should have personnel and equipment readily available to manage airway emergencies, to include a pulse oximeter and qualitative carbon dioxide detector, consistent with the ASA Practice Guidelines for Management of the Difficult Airway
  - Basic airway management equipment should be immediately available during the provision of neuraxial analgesia
  - Portable equipment for difficult airway management should be readily available in the operative area of labor and delivery units
  - The anesthesiologist should have a preformulated strategy for intubation of the difficult airway
  - When tracheal intubation has failed, ventilation with mask and cricoid pressure, or with a laryngeal mask airway or supraglottic airway device (e.g., Combitube®, Intubating LMA [Fastrach™]) should be considered for maintaining an airway and ventilating the lungs
  - If it is not possible to ventilate or awaken the patient, an airway should be created surgically

- Basic and advanced life-support equipment should be immediately available in the operative area of labor and delivery units
- If cardiac arrest occurs during labor and delivery, standard resuscitative measures should be initiated
  - Uterine displacement (usually left displacement) should be maintained
  - If maternal circulation is not restored within 4 min, cesarean delivery should be performed by the obstetrics team

Appendix 2: Methods and Analyses

The scientific assessment of these Guidelines was based on evidence linkages or statements regarding potential relationships between clinical interventions and outcomes. The interventions listed below were examined to assess their impact on a variety of outcomes related to obstetric anesthesia.†‡

†‡ Unless otherwise specified, outcomes for the listed interventions refer to the reduction of maternal, fetal, and neonatal complications

§§ Additional outcomes include improved analgesia, analgesic use, maternal comfort, and satisfaction.

1. Perianesthetic Evaluation
   i. A directed history and physical examination
   ii. Communication between anesthetic and obstetric providers
   iii. A routine intrapartum platelet count does not reduce maternal anesthetic complications
   iv. For suspected preeclampsia or coagulopathy an intrapartum platelet count
   v. An intrapartum blood type and screen for all parturients reduces maternal complications
   vi. For healthy and uncomplicated parturients, a blood cross-match is unnecessary
   vii. Perianesthetic recording of the fetal heart rate reduces fetal and neonatal complications

2. Aspiration Prophylaxis in the Obstetric Patient
   i. Oral intake of clear liquids during labor improves patient comfort and satisfaction but does not increase maternal complications
   ii. Oral intake of solids during labor increases maternal complications
   iii. A fasting period for solids of 6 - 8 h before an elective cesarean reduces maternal complications
   iv. Nonparticulate antacids versus no antacids before operative procedures (excluding operative vaginal delivery) reduces maternal complications

3. Anesthetic Care for Labor and Delivery§§
   i. Neuromuscular techniques
     a. Prophylactic spinal or epidural catheter insertion for complicated parturients reduces maternal complications
     b. Continuous epidural infusion of local anesthetics with or without opioids versus parenteral opioids
     c. Continuous epidural infusion of local anesthetics with or without opioids versus spinal opioids with or without local anesthetics
     d. Induction of epidural analgesia using local anesthetics with opioids versus equal concentrations of epidural local anesthetics without opioids
     e. Induction of epidural analgesia using local anesthetics with opioids versus higher concentrations of epidural local anesthetics without opioids
     f. Maintenance of epidural infusion of lower concentrations of local anesthetics with opioids versus higher concentrations of local anesthetics without opioids (e.g., bupivacaine concentrations < 0.125% with opioids vs. concentrations > 0.125% without opioids)
     g. Single-injection spinal opioids with or without local anesthetics versus parenteral opioids
     h. Single-injection spinal opioids with local anesthetics versus spinal opioids without local anesthetics
   ii. Combined spinal–epidural (CSE) techniques
     a. CSE local anesthetics with opioids versus epidural local anesthetics with opioids
     iii. Patient-controlled epidural analgesia (PCEA)
        a. PCEA versus continuous infusion epidurals
        b. PCEA with a background infusion versus PCEA without a background infusion
   iv. Neuromuscular analgesia, timing of initiation, and progress of labor
      a. Administering epidural analgesia at cervical dilations of < 5 cm (vs. ≥ 5 cm)
      b. Neuromuscular techniques for patients attempting vaginal birth after previous cesarean delivery

4. Removal of Retained Placenta
   i. If an epidural catheter is in situ and the patient is hemodynamically stable, epidural anesthesia is preferred over general or spinal anesthesia to improve the success at removing retained placenta
5. Anesthetic Choices for Cesarean Delivery

- General anesthesia versus epidural anesthesia
- General anesthesia versus spinal anesthesia
- Epidural anesthesia versus spinal anesthesia
- CSE anesthesia versus epidural anesthesia
- CSE anesthesia versus spinal anesthesia

6. Postpartum Tubal Ligation

- Neuraxial opioids versus parenteral opioids for postoperative analgesia after neuraxial anesthesia for cesarean delivery

7. Management of Complications

- Availability of resources for management of hemorrhagic emergencies
- Immediate availability of equipment for management of airway emergencies
- Immediate availability of basic and advanced life-support equipment in the labor and delivery suite
- Invasive hemodynamic monitoring for severely preeclamptic patients

Consensus was obtained from multiple sources, including:

1. Survey opinion from consultants who were selected based on their knowledge or expertise in obstetric anesthesia or maternal and fetal medicine.
2. Survey opinions solicited from active members of the ASA.
3. Testimony from attendees of publicly held open forums at two national anesthesia meetings.
4. Internet commentary.
5. Task Force opinion and interpretation.

The consultants were asked to indicate which, if any, of the evidence linkages would change their clinical practices if the Guidelines were instituted. The rate of return was 35% (n = 56). The percent of responding consultants expecting no change associated with each linkage were as follows:

- Perianesthetic evaluation—97%; aspiration prophylaxis—83%; analgesic care for labor and delivery—89%; removal of retained placenta—97%; aesthetic choices for cesarean delivery—97%; postpartum tubal ligation—97%; and management of complications—94%. Ninety-seven percent of the respondents indicated that the Guidelines would have no effect on the amount of time spent on a typical case. One respondent indicated that there would be an increase of 5 min in the amount of time spent on a typical case with the implementation of these Guidelines.
Table 4. Meta-analysis Summary

<table>
<thead>
<tr>
<th>Linkages</th>
<th>Fisher Chi-square</th>
<th>Weighted Stouffer Zc</th>
<th>Effect Size</th>
<th>Mantel-Haenszel OR</th>
<th>CI</th>
<th>Significance</th>
<th>Effect Size</th>
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<td><strong>Aspiration Prophylaxis</strong></td>
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<td>Nonparticulate antacids vs. no antacids</td>
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<td>Gastric pH*</td>
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<td>Metoclopramide vs. no metoclopramide</td>
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<td>Nausea</td>
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<td>Vomiting</td>
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<td><strong>Anesthetic Care for Labor and Vaginal Delivery</strong></td>
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<td>CIE local anesthetics vs. opioids vs. IV opioids</td>
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<td>Duration of labor 1st stage</td>
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<td>Duration of labor 2nd stage</td>
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<td>Spontaneous delivery</td>
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<td>5-min Apgar</td>
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<td><strong>Epidural induction LA + O vs. equal LA doses</strong></td>
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<td>Analgesia (pain relief)</td>
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<td>Duration of labor</td>
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<td>Hypotension</td>
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<td>Motor block*</td>
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<td>Pruritus</td>
<td>7 — — — — — 6.15 3.22–11.74 — NS</td>
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<td>Pencil-point vs. cutting-bevel spinal needles</td>
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<td>Fluid preloading vs. no preloading</td>
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* Nonrandomized comparative studies included in analysis. † DerSimonian-Laird random effects odds ratio (OR).

CI = confidence interval; CIE = continuous infusion epidural; CSE = combined spinal–epidural; GA = general anesthesia; IV = intravenous; LA = local anesthetics; LA + O = local anesthetics with opioids; NS = not significant; O = opioids; PCEA = patient-controlled epidural analgesia.
<table>
<thead>
<tr>
<th>Table 5. Consultant Survey Responses</th>
<th>Percent Responding to Each Item</th>
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<td>Perianesthetic Evaluation</td>
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<td>1. Directed history and physical examination reduces maternal, fetal, and neonatal complications</td>
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<tr>
<td>2. Communication between anesthetic and obstetric providers reduces maternal, fetal, and neonatal complications</td>
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<tr>
<td>3. A routine intrapartum platelet count does not reduce maternal anesthetic complications</td>
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<tr>
<td>4. An intrapartum platelet count reduces maternal anesthetic complications:</td>
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<td>For suspected preeclampsia</td>
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<td>For suspected coagulopathy</td>
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<td>5. All parturients should have an intrapartum blood sample sent to the blood bank to reduce maternal complications</td>
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<tr>
<td>6. Perianesthetic recording of the fetal heart rate reduces fetal and neonatal complications</td>
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<td>Aspiration Prophylaxis</td>
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<td>7a. Oral intake of clear liquids during labor improves patient comfort and satisfaction</td>
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</tr>
<tr>
<td>7b. Oral intake of clear liquids during labor does not increase maternal complications</td>
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<tr>
<td>8a. Oral intake of solids during labor increases maternal complications</td>
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<td>8b. The patient undergoing elective cesarean delivery should undergo a fasting period for solids of 6–8 h depending on the type of food ingested (e.g., fat content)</td>
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<td>8c. The patient undergoing elective postpartum tubal ligation should undergo a fasting period for solids of 6–8 h depending on the type of food ingested (e.g., fat content)</td>
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<td>9. Administration of a nonparticulate antacid before operative procedures reduces maternal complications</td>
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<td>Neuraxial techniques:</td>
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<td>10. Prophylactic spinal or epidural catheter insertion for complicated parturients reduces maternal complications</td>
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<td>11. Continuous epidural infusion using local anesthetics with or without opioids vs. parenteral opioids:</td>
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<td>Improves analgesia</td>
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<tr>
<td>Increases the duration of labor</td>
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<tr>
<td>Decreases the chance of spontaneous delivery</td>
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<tr>
<td>Increases maternal side effects</td>
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<tr>
<td>Increases fetal and neonatal side effects</td>
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<td>12. Continuous epidural infusion using local anesthetics with or without opioids vs. spinal opioids with or without local anesthetics:</td>
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<td>Increases the duration of labor</td>
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<td>Increases maternal motor block</td>
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<tr>
<td>Increases maternal side effects</td>
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<td>Increases fetal and neonatal side effects</td>
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<td>13a. Induction of epidural analgesia using local anesthetics with opioids vs. epidural analgesia with equal concentrations of local anesthetics without opioids:</td>
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<td>Increases maternal side effects</td>
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<td>13b. Induction of epidural analgesia using low-dose local anesthetics with opioids vs. higher concentrations of epidural local anesthetics without opioids:</td>
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<td>Increases fetal and neonatal side effects</td>
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<td>14a. Maintenance of epidural infusion of lower concentrations of local anesthetics with opioids vs. higher concentrations of local anesthetics without opioids:</td>
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<td>Reduces maternal motor block</td>
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<td>14b. Maintenance of epidural analgesia using bupivacaine ( \leq 0.125% ) with opioids vs. bupivacaine concentrations &gt; 0.125% without opioids:</td>
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<td>Reduces maternal motor block</td>
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<td>Reduces fetal and neonatal side effects</td>
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Table 5. Continued

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<th>15. Single-injection spinal opioids with or without local anesthetics vs. parenteral opioids:</th>
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<th>Percent Responding to Each Item</th>
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<td>Increase fetal and neonatal side effects</td>
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<tr>
<td>Decrease the chance of spontaneous delivery</td>
<td>74</td>
<td>0.0</td>
</tr>
<tr>
<td>Reduce maternal motor block</td>
<td>74</td>
<td>5.4</td>
</tr>
<tr>
<td>Increase maternal side effects</td>
<td>74</td>
<td>0.0</td>
</tr>
<tr>
<td>Increase fetal and neonatal side effects</td>
<td>74</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Combined spinal–epidural (CSE) techniques:

<table>
<thead>
<tr>
<th>17. CSE local anesthetics with opioids vs. epidural local anesthetics with opioids:</th>
<th>n</th>
<th>Percent Responding to Each Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve analgesia</td>
<td>74</td>
<td>48.6</td>
</tr>
<tr>
<td>Improve overall analgesia</td>
<td>74</td>
<td>18.9</td>
</tr>
<tr>
<td>Decrease the duration of labor</td>
<td>74</td>
<td>4.1</td>
</tr>
<tr>
<td>Improve overall analgesia</td>
<td>75</td>
<td>23.0</td>
</tr>
<tr>
<td>Decrease the chance of spontaneous delivery</td>
<td>75</td>
<td>0.0</td>
</tr>
<tr>
<td>Reduce maternal motor block</td>
<td>75</td>
<td>9.3</td>
</tr>
<tr>
<td>Increases maternal side effects</td>
<td>74</td>
<td>5.3</td>
</tr>
</tbody>
</table>

Patient-controlled epidural analgesia (PCEA):

<table>
<thead>
<tr>
<th>18. PCEA vs. continuous infusion epidurals:</th>
<th>n</th>
<th>Percent Responding to Each Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve analgesia</td>
<td>75</td>
<td>16.0</td>
</tr>
<tr>
<td>Improve overall analgesia</td>
<td>75</td>
<td>41.3</td>
</tr>
<tr>
<td>Reduce the need for anesthetic interventions</td>
<td>75</td>
<td>42.7</td>
</tr>
<tr>
<td>Increase maternal side effects</td>
<td>74</td>
<td>9.3</td>
</tr>
<tr>
<td>Decreases maternal side effects</td>
<td>75</td>
<td>5.3</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>19. PCEA with a background infusion vs. PCEA without a background infusion:</th>
<th>n</th>
<th>Percent Responding to Each Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve analgesia</td>
<td>74</td>
<td>23.0</td>
</tr>
<tr>
<td>Improve overall analgesia</td>
<td>75</td>
<td>24.3</td>
</tr>
<tr>
<td>Reduce the need for anesthetic interventions</td>
<td>75</td>
<td>21.6</td>
</tr>
<tr>
<td>Decrease the chance of spontaneous delivery</td>
<td>74</td>
<td>0.0</td>
</tr>
<tr>
<td>Increases maternal motor block</td>
<td>74</td>
<td>1.4</td>
</tr>
<tr>
<td>Increases maternal side effects</td>
<td>75</td>
<td>1.3</td>
</tr>
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</table>

Neuraxial Analgesia, Timing of Initiation, and Progress of Labor

<table>
<thead>
<tr>
<th>20. Administering epidural analgesia at cervical dilations of &lt;5 centimeters (vs. ≥5 cm):</th>
<th>n</th>
<th>Percent Responding to Each Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve analgesia</td>
<td>75</td>
<td>50.7*</td>
</tr>
<tr>
<td>Reduce the duration of labor</td>
<td>75</td>
<td>0.0</td>
</tr>
<tr>
<td>Improve overall analgesia</td>
<td>74</td>
<td>0.0</td>
</tr>
<tr>
<td>Decrease the chance of spontaneous delivery</td>
<td>75</td>
<td>1.3</td>
</tr>
<tr>
<td>Decrease maternal side effects</td>
<td>75</td>
<td>1.3</td>
</tr>
<tr>
<td>Increases fetal and neonatal side effects</td>
<td>75</td>
<td>0.0</td>
</tr>
</tbody>
</table>

21. Neuraxial techniques improve the likelihood of vaginal delivery for patients attempting vaginal birth after previous cesarean delivery

<table>
<thead>
<tr>
<th>22. If an epidural catheter is in situ and the patient is hemodynamically stable, epidural anesthesia is the preferred technique</th>
<th>n</th>
<th>Percent Responding to Each Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve analgesia</td>
<td>74</td>
<td>66.7*</td>
</tr>
<tr>
<td>Improve overall analgesia</td>
<td>75</td>
<td>30.7</td>
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</tbody>
</table>

23. In cases involving major maternal hemorrhage, a general endotracheal anesthetic is preferred over neuraxial anesthesia

<table>
<thead>
<tr>
<th>24. Administration of nitroglycerin for uterine relaxation improves success at removing retained placenta</th>
<th>n</th>
<th>Percent Responding to Each Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve analgesia</td>
<td>74</td>
<td>82.4*</td>
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</tbody>
</table>

Anesthetic Choices for Cesarean Delivery

<table>
<thead>
<tr>
<th>25. Equipment, facilities, and support personnel available in the labor and delivery operating suite should be comparable to that available in the main operating suite</th>
<th>n</th>
<th>Percent Responding to Each Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve analgesia</td>
<td>74</td>
<td>40.5</td>
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<tr>
<td>Improve overall analgesia</td>
<td>74</td>
<td>37.8</td>
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<tr>
<td>Improve overall analgesia</td>
<td>74</td>
<td>14.9</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>26. General anesthesia vs. epidural anesthesia:</th>
<th>n</th>
<th>Percent Responding to Each Item</th>
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</thead>
<tbody>
<tr>
<td>Improve analgesia</td>
<td>74</td>
<td>20.3</td>
</tr>
<tr>
<td>Improve overall analgesia</td>
<td>74</td>
<td>33.8</td>
</tr>
<tr>
<td>Improve overall analgesia</td>
<td>74</td>
<td>12.2</td>
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(continued)
### Table 5. Continued

<table>
<thead>
<tr>
<th>Percent Responding to Each Item</th>
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<th>Agree</th>
<th>Uncertain</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
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<tr>
<td>28. Epidural anesthesia vs. spinal anesthesia:</td>
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<td></td>
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<tr>
<td>Increases time to skin incision</td>
<td>74</td>
<td>43.2</td>
<td>8.1</td>
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<td>0.0</td>
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<tr>
<td>Reduces quality of anesthesia</td>
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<td>12.2</td>
<td>56.8*</td>
<td>9.5</td>
<td>17.6</td>
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<td>Increases maternal complications</td>
<td>74</td>
<td>1.4</td>
<td>13.5</td>
<td>28.4</td>
<td>48.6*</td>
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<td>29. CSE anesthesia vs. epidural anesthesia:</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Improves anesthesia</td>
<td>73</td>
<td>20.5</td>
<td>47.9*</td>
<td>20.5</td>
<td>11.0</td>
</tr>
<tr>
<td>Reduces time to skin incision</td>
<td>73</td>
<td>17.8</td>
<td>53.4*</td>
<td>12.3</td>
<td>16.4</td>
</tr>
<tr>
<td>Reduces maternal side effects</td>
<td>73</td>
<td>2.7</td>
<td>12.3</td>
<td>30.1</td>
<td>52.1*</td>
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<tr>
<td>30. CSE anesthesia vs. spinal anesthesia:</td>
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<td></td>
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<td>Improves anesthesia</td>
<td>72</td>
<td>1.4</td>
<td>15.3</td>
<td>25.0</td>
<td>52.8*</td>
</tr>
<tr>
<td>Increases flexibility for prolonged procedures</td>
<td>73</td>
<td>61.6*</td>
<td>32.9</td>
<td>4.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Increases time to skin incision</td>
<td>73</td>
<td>6.8</td>
<td>49.3*</td>
<td>17.8</td>
<td>21.9</td>
</tr>
<tr>
<td>Reduces maternal side effects</td>
<td>73</td>
<td>1.4</td>
<td>11.0</td>
<td>37.0</td>
<td>47.9*</td>
</tr>
<tr>
<td>31. Use of pencil-point spinal needles vs. cutting-bevel spinal needles reduces maternal complications</td>
<td>73</td>
<td>75.3*</td>
<td>23.3</td>
<td>1.4</td>
<td>0.0</td>
</tr>
<tr>
<td>32. Intravenous fluid preloading vs. no intravenous fluid preloading for spinal anesthesia reduces maternal hypotension</td>
<td>73</td>
<td>30.1</td>
<td>46.6*</td>
<td>12.3</td>
<td>9.6</td>
</tr>
<tr>
<td>33a. Intravenous ephedrine is an acceptable agent to treat hypotension during neuraxial anesthesia</td>
<td>75</td>
<td>48.0</td>
<td>49.3*</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>33b. Intravenous phenylephrine is an acceptable agent to treat hypotension during neuraxial anesthesia</td>
<td>75</td>
<td>50.7*</td>
<td>40.0</td>
<td>6.7</td>
<td>2.7</td>
</tr>
<tr>
<td>34. Neuraxial opioids vs. parenteral opioids for postoperative analgesia after regional anesthesia for cesarean delivery:</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improves analgesia</td>
<td>69</td>
<td>60.9*</td>
<td>33.3</td>
<td>5.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Improves maternal satisfaction</td>
<td>69</td>
<td>52.2*</td>
<td>33.3</td>
<td>8.7</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Postpartum Tubal Ligation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35. Neuraxial vs. general anesthesia reduces maternal complications</td>
<td>70</td>
<td>24.3</td>
<td>58.6*</td>
<td>12.9</td>
<td>2.9</td>
</tr>
<tr>
<td>36. An immediate (≤ 8 h) postpartum tubal ligation does not increase maternal complications</td>
<td>70</td>
<td>14.3</td>
<td>50.0*</td>
<td>22.9</td>
<td>11.4</td>
</tr>
<tr>
<td><strong>Management of Complications</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37. Availability of resources for management of hemorrhagic emergencies reduces maternal complications</td>
<td>70</td>
<td>74.3*</td>
<td>25.7</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>38. Immediate availability of equipment for management of airway emergencies reduces maternal, fetal, and neonatal complications</td>
<td>70</td>
<td>80.0*</td>
<td>20.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>39. Immediate availability of basic and advanced life-support equipment in the labor and delivery suite reduces maternal, fetal, and neonatal complications</td>
<td>70</td>
<td>78.6*</td>
<td>21.4</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>40. Routine use of central venous or pulmonary artery catheterization reduces maternal complications in severely preeclamptic patients</td>
<td>70</td>
<td>0.0</td>
<td>10.0</td>
<td>12.9</td>
<td>55.7*</td>
</tr>
</tbody>
</table>

* Median.

n = number of consultants who responded to each item.
Table 6. ASA Membership Survey Responses

<table>
<thead>
<tr>
<th>Peri-anesthetic Evaluation</th>
<th>Percent Responding to Each Item</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>1. Directed history and physical examination reduces maternal, fetal, and neonatal complications</td>
<td>2,324</td>
</tr>
<tr>
<td>2. Communication between anesthetic and obstetric providers reduces maternal, fetal, and neonatal complications</td>
<td>2,321</td>
</tr>
<tr>
<td>3. A routine intrapartum platelet count does not reduce maternal anesthetic complications</td>
<td>2,320</td>
</tr>
<tr>
<td>4. An intrapartum platelet count reduces maternal anesthetic complications:</td>
<td></td>
</tr>
<tr>
<td>For suspected preeclampsia</td>
<td>2,326</td>
</tr>
<tr>
<td>For suspected coagulopathy</td>
<td>2,323</td>
</tr>
<tr>
<td>5. All parturients should have an intrapartum blood sample sent to the blood bank to reduce maternal complications</td>
<td>2,317</td>
</tr>
<tr>
<td>6. Peri-anesthetic recording of the fetal heart rate reduces fetal and neonatal complications</td>
<td>2,319</td>
</tr>
</tbody>
</table>

**Aspiration Prophylaxis**

| 7a. Oral intake of clear liquids during labor improves patient comfort and satisfaction | 2,283 | 15.4    | 65.5* | 12.1   | 6.2      | 0.8          |
| 7b. Oral intake of clear liquids during labor does not increase maternal complications | 2,285 | 6.7     | 40.2  | 23.6*  | 23.6     | 6.0          |
| 8a. Oral intake of solids during labor increases maternal complications                  | 2,284 | 48.2    | 38.0* | 9.9    | 2.8      | 1.1          |
| 8b. The patient undergoing elective cesarean delivery should undergo a fasting period for solids of 6-8 h depending on the type of food ingested (e.g., fat content) | 2,283 | 66.8*   | 30.3  | 1.1    | 1.3      | 0.5          |
| 8c. The patient undergoing elective postpartum tubal ligation should undergo a fasting period for solids of 6-8 h depending on the type of food ingested (e.g., fat content) | 2,281 | 66.9*   | 30.2  | 1.1    | 1.4      | 0.4          |
| 9. Administration of a nonparticulate antacid before operative procedures reduces maternal complications | 2,281 | 24.5    | 43.3* | 24.0   | 7.2      | 1.1          |

**Anesthetic Care for Labor and Delivery**

**Neuraxial techniques:**

| 10. Prophylactic spinal or epidural catheter insertion for complicated parturients reduces maternal complications | 2,071 | 17.6    | 42.4* | 26.9   | 11.8     | 1.2          |

**Continuous epidural infusion using local anesthetics with or without opioids vs. parenteral opioids:**

| Improves analgesia                                                                      | 2,170 | 73.6*   | 25.1  | 0.8    | 0.4      | 0.1          |
| Increases the duration of labor                                                        | 2,174 | 7.2     | 14.4  | 19.0   | 51.7*     | 13.8         |
| Decreases the chance of spontaneous delivery                                          | 2,171 | 0.8     | 7.4   | 16.9   | 53.3*     | 21.6         |
| Increases maternal side effects                                                        | 2,169 | 0.6     | 12.0  | 9.8    | 58.9*     | 18.7         |
| Increases fetal and neonatal side effects                                              | 2,168 | 0.3     | 3.0   | 7.5    | 61.3*     | 27.9         |

**Continuous epidural infusion using local anesthetics with or without opioids vs. spinal opioids with or without local anesthetics:**

| Improves analgesia                                                                      | 2,160 | 17.4    | 36.5* | 24.8   | 20.2      | 1.2          |
| Increases the duration of labor                                                        | 2,161 | 0.8     | 8.9   | 31.8   | 49.7*     | 8.8          |
| Decreases the chance of spontaneous delivery                                          | 2,158 | 0.6     | 5.8   | 27.7   | 53.7*     | 12.3         |
| Increases maternal motor block                                                         | 2,149 | 3.7     | 36.0  | 16.1*  | 38.7      | 5.4          |
| Increases maternal side effects                                                        | 2,152 | 0.7     | 10.2  | 21.9   | 58.4*     | 8.8          |
| Increases fetal and neonatal side effects                                              | 2,153 | 0.4     | 4.2   | 20.9   | 61.2*     | 13.3         |

**Induction of epidural analgesia using local anesthetics with or without epidural analgesia with equal concentrations of local anesthetics without opioids:**

| Improves analgesia                                                                      | 2,153 | 34.6    | 46.1* | 6.2    | 10.8      | 2.3          |
| Increases maternal side effects                                                        | 2,150 | 2.6     | 38.0  | 12.8*  | 40.4      | 6.2          |
| Increases fetal and neonatal side effects                                              | 2,142 | 0.7     | 7.5   | 17.5   | 63.1*     | 11.3         |

**Induction of epidural analgesia using low-dose local anesthetics with opioids vs. higher concentrations of epidural local anesthetics without opioids:**

| Improves analgesia                                                                      | 2,155 | 31.3    | 31.7  | 26.9*  | 26.8      | 1.7          |
| Increases maternal side effects                                                        | 2,154 | 1.1     | 13.8  | 15.8   | 55.7*     | 13.6         |
| Increases fetal and neonatal side effects                                              | 2,147 | 0.6     | 4.5   | 19.3   | 60.8*     | 14.8         |

**Maintenance of epidural infusion of lower concentrations of local anesthetics with opioids vs. higher concentrations of local anesthetics without opioids:**

| Improves analgesia                                                                      | 1,977 | 17.2    | 38.5* | 24.0   | 19.2      | 1.0          |
| Reduces the duration of labor                                                          | 1,980 | 3.9     | 28.0  | 44.9*  | 21.6      | 1.6          |
| Improves the chance of spontaneous delivery                                            | 1,977 | 6.9     | 41.1  | 35.9*  | 15.1      | 1.0          |
| Reduces maternal motor block                                                          | 1,977 | 31.3    | 63.0* | 2.9    | 2.4       | 0.4          |
| Reduces maternal side effects                                                          | 1,971 | 47.1    | 38.8* | 26.8   | 14.0      | 0.9          |
| Reduces fetal and neonatal side effects                                               | 1,972 | 7.4     | 34.4  | 38.1*  | 18.6      | 1.5          |

**Maintenance of epidural analgesia using bupivacaine ≤ 0.125% with opioids vs. bupivacaine concentrations > 0.125% without opioids:**

| Improves analgesia                                                                      | 1,973 | 16.5    | 38.6* | 23.9   | 19.7      | 1.4          |
| Reduces the duration of labor                                                          | 1,975 | 4.4     | 25.6  | 46.9*  | 21.5      | 1.7          |
| Improves the chance of spontaneous delivery                                             | 1,973 | 6.1     | 36.9  | 38.9*  | 16.7      | 1.4          |
| Reduces maternal motor block                                                          | 1,967 | 23.4    | 63.7* | 5.3    | 6.5       | 1.1          |
| Reduces maternal side effects                                                          | 1,960 | 44.7    | 37.0  | 16.1   | 18.1      | 1.0          |
| Reduces fetal and neonatal side effects                                               | 1,957 | 6.3     | 31.3  | 39.0*  | 21.6      | 1.8          |

(continued)
Table 6. Continued

<table>
<thead>
<tr>
<th>Item</th>
<th>n</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Uncertain</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>15. Single-injection spinal opioids with or without local anesthetics vs. parenteral opioids:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improve analgesia</td>
<td>1,966</td>
<td>36.9</td>
<td>50.2</td>
<td>8.9</td>
<td>3.6</td>
<td>0.5</td>
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<tr>
<td>Increase the duration of labor</td>
<td>1,963</td>
<td>0.4</td>
<td>2.7</td>
<td>31.5</td>
<td>55.8</td>
<td>9.6</td>
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<tr>
<td>Decrease the chance of spontaneous delivery</td>
<td>1,967</td>
<td>0.4</td>
<td>2.8</td>
<td>27.9</td>
<td>58.3</td>
<td>10.7</td>
</tr>
<tr>
<td>Increase maternal side effects</td>
<td>1,958</td>
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<td>23.7</td>
<td>23.1</td>
<td>45.1</td>
<td>5.8</td>
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<tr>
<td>Increase fetal and neonatal side effects</td>
<td>1,960</td>
<td>0.7</td>
<td>7.7</td>
<td>25.6</td>
<td>55.9</td>
<td>10.2</td>
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<tr>
<td>16. Single-injection spinal opioids with local anesthetics vs. spinal opioids without local anesthetics:</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improve analgesia</td>
<td>1,961</td>
<td>29.2</td>
<td>55.6</td>
<td>9.4</td>
<td>5.5</td>
<td>0.4</td>
</tr>
<tr>
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<td>1,960</td>
<td>1.1</td>
<td>10.2</td>
<td>43.0</td>
<td>41.2</td>
<td>4.6</td>
</tr>
<tr>
<td>Decrease the chance of spontaneous delivery</td>
<td>1,959</td>
<td>0.8</td>
<td>8.1</td>
<td>38.4</td>
<td>47.1</td>
<td>5.7</td>
</tr>
<tr>
<td>Increase maternal motor block</td>
<td>1,955</td>
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<td>17. CSE local anesthetics with opioids vs. epidural local anesthetics:</td>
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<td>18. PCEA vs. continuous infusion epiduals:</td>
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<td>Neuraxial Analgesia, Timing of Initiation, and Progress of Labor</td>
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<td>20. Administering epidural analgesia at cervical dilations of &lt; 5 centimeters (vs. &gt; 5 cm):</td>
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<tr>
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<td>14.9</td>
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<td>Increases maternal side effects</td>
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<td>41.6</td>
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<td>Removal of Retained Placenta</td>
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<td>22. If an epidural catheter is in situ and the patient is hemodynamically stable, epidural anesthesia is the preferred technique</td>
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<td>6.9</td>
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<td>24. Administration of nitroglycerin for uterine relaxation improves success at removing retained placenta</td>
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<td>Anesthetic Choices for Cesarean Delivery</td>
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<td>25. Equipment, facilities, and support personnel available in the labor and delivery operating suite should be comparable to that available in the main operating suite</td>
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<tr>
<td>Reduce time to skin incision</td>
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<td>46.3</td>
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<tr>
<td>Increases maternal complications</td>
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(continued)
Table 6. Continued

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<td>Increases time to skin incision</td>
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<td>Reduces quality of anesthesia</td>
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<td>Reduces time to skin incision</td>
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<td>Reduces maternal side effects</td>
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<td>31. Use of pencil-point spinal needles vs. cutting-bevel spinal needles reduces maternal complications</td>
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<tr>
<td>32. Intravenous fluid preloading vs. no intravenous fluid preloading for spinal anesthesia reduces maternal hypotension</td>
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<td>33a. Intravenous ephedrine is an acceptable agent to treat hypotension during neuraxial anesthesia</td>
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<tr>
<td>33b. Intravenous phenylephrine is an acceptable agent to treat hypotension during neuraxial anesthesia</td>
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<td>34. Neuraxial opioids vs. parenteral opioids for postoperative analgesia after regional anesthesia for cesarean delivery:</td>
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<td>Improves analgesia</td>
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<td>Improves maternal satisfaction</td>
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<tr>
<td>Postpartum Tubal Ligation</td>
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<td>35. Neuraxial vs. general anesthesia reduces maternal complications</td>
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<td>36. An immediate (≤ 8 h) postpartum tubal ligation does not increase maternal complications</td>
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<td>Management of Complications</td>
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<td>37. Availability of resources for management of hemorrhagic emergencies reduces maternal complications</td>
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</tr>
<tr>
<td>38. Immediate availability of equipment for management of airway emergencies reduces maternal, fetal, and neonatal complications</td>
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</tr>
<tr>
<td>39. Immediate availability of basic and advanced life-support equipment in the labor and delivery suite reduces maternal, fetal, and neonatal complications</td>
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</tr>
<tr>
<td>40. Routine use of central venous or pulmonary artery catheterization reduces maternal complications in severely preeclamptic patients</td>
<td>1,822</td>
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</tbody>
</table>

* Median.

ASA — American Society of Anesthesiologists; n — number of members who responded to each item.
Spinal Hypotension During Elective Cesarean Delivery: Closer to a Solution

Robert A. Dyer, FCA (SA), PhD, and Anthony R. Reed, FRCA

Hypotension during spinal anesthesia for cesarean delivery should be minimized, both for maternal safety and comfort, and fetal wellbeing. Traditional teaching is that aortocaval compression predisposes the parturient to decreased venous return and hence cardiac output and blood pressure during spinal anesthesia for cesarean delivery. However, a variety of measures to improve venous return, including lateral tilt and numerous fluid administration regimens, have failed to eliminate hypotension. Recent studies focusing on the arterial circulation as a source for hypotension suggest that in the fluid-replete parturient undergoing elective cesarean delivery, moderate spinal hypotension (20% decrease from baseline) primarily reflects decreased systemic vascular resistance. In most cases, venous return is initially maintained and consequently there is a partial compensatory increase in cardiac output, mediated by an increase in stroke volume and heart rate. In this situation, the rapidly acting α-agonist phenylephrine seems to be the best option to restore baseline hemodynamics rapidly. Although ephedrine has traditionally been used to treat spinal anesthesia–induced hypotension, recent evidence suggests that ephedrine causes neonatal acidosis, and large doses may be harmful in a compromised fetus, by increasing oxygen demand and anaerobic metabolism. Ephedrine is also associated with a higher incidence of nausea and vomiting than phenylephrine.

The dose and method of administration of phenylephrine have been the subject of extensive investigation. In this issue of *Anesthesia & Analgesia*, 2 articles address this subject. First, Allen et al. compared placebo with the use of 4 different infusion rates of phenylephrine, in combination with a crystalloid colloid, and assessed “hemodynamic stability” by heart rate and blood pressure. The aim was to maintain blood pressure within 20% of baseline values. They demonstrated that infusing phenylephrine at a fixed rate of 75 or 100 μg/min is associated with more episodes of hypertension than placebo, or the lower infusion rates of 25 or 50 μg/min, respectively. Seven patients in the group receiving 100 μg/min developed sinus bradycardia and were given glycopyrrolate. It may be more appropriate to treat baroreceptor-mediated bradycardia associated with a well-maintained blood pressure by discontinuing the infusion than by the administration of an anticholinergic. This would avert the reactive hypertension reported by the authors. This work suggests that to reduce hypotension and avoid hypertension and bradycardia, slower infusion rates of phenylephrine are a better starting point, with supplementary boluses as necessary, in keeping with the pharmacokinetic principle of the use of a bolus followed by an infusion to increase steady-state concentrations. Alternatively, the authors speculate, varying infusion rates could be used. The fact that some patients experienced bradycardia and hypertension even at the slower infusion rates suggests that bolus administration of phenylephrine, titrated as required in the individual case, may be a better option than prophylactic infusions.

In the second important contribution, Stewart et al., using a suprasternal Doppler flow technique, described cardiac output changes associated with infusions of 25, 50, and 100 μg/min phenylephrine, respectively, after the administration of a rapid crystalloid preload, during spinal anesthesia for elective cesarean delivery. The aim was to maintain baseline blood pressure. The infusion of phenylephrine at 100 μg/min for 20 minutes was associated with a reduction in heart rate from 80 to 58 bpm and a reduction in cardiac output from 5.1 to 4.0 L/min. Neonatal outcomes were similar among groups. This is in agreement with a recent investigation of the hemodynamic effects of boluses of ephedrine and phenylephrine using pulse power analysis. Bolus administration of phenylephrine in response to hypotension (20% decrease from baseline blood pressure) was shown to reduce maternal cardiac output to close to baseline values (an effect strongly correlated with maternal heart rate) and restore blood pressure.

In the non-obstetric population, phenylephrine (1:20,000) added to epidural lidocaine, and IV methoxamine administered during spinal anesthesia, have been shown to reduce cardiac output. The studies published in this issue examining the effects of phenylephrine infusions during spinal anesthesia for cesarean delivery suggest that the use of phenylephrine in doses that cause hypertension and sinus bradycardia is inappropriate.

How does phenylephrine influence cardiac output? The effect of α-agonists on venous return is controversial. It is
likely that low doses of phenylephrine increase venous return, and thus cardiac output, by causing some degree of increase in splanchnic venous tone, particularly in the parturient at term, with her expanded blood volume. By contrast, high doses of phenylephrine cause a baroreceptor-mediated reduction in heart rate and dilation of splanchnic veins and a shift of blood into the splanchnic vasculature with a decrease in venous return. Although the indirect baroreceptor reflex-mediated sympathetic effects on the splanchnic circulation are blocked under spinal anesthesia, the heart rate- and direct receptor-mediated effects of high-dose phenylephrine persist. The latter may cause a significant increase in splanchnic arterial resistance, resulting in a decrease in splanchnic blood flow. Hepatic vein resistance may also be increased. Both effects would reduce venous return. It was interesting that Stewart et al. noted that larger doses of phenylephrine were required to maintain equivalent control of the blood pressure when the infusion rate was 100 μg/min. This would be in keeping with a dose-related decrease in venous return. Because the Corrected Flow Time Index is a measure of ventricular filling, the suprasternal Doppler flow technique, which incorporates this technology, could be used in future research to study a surrogate marker of cardiac filling and hence changes in venous return.

High-dose phenylephrine may also reduce cardiac output by decreasing stroke volume. Stroke volume may decrease in response to a marked increase in systemic vascular resistance and afterload. This decrease in stroke volume was not shown in the study by Stewart et al., because the effect is best demonstrated after bolus administration, using beat-by-beat measurements. A compensatory increase in stroke volume may occur via the Anrep effect, postulated to be the recovery from subendocardial ischemia induced by the increase in afterload, and subsequent correction by autoregulation of the coronary vascular bed. This effect would be undesirable if there is either coronary artery disease or ventricular dysfunction.

Animal studies have shown that under normal physiological conditions, uterine blood flow is higher than required for fetal oxygen demand, thus conferring a margin of safety under conditions of rapid changes in uterine flow. This could explain the lack of neonatal acidosis observed during the administration of large doses of phenylephrine, even in the face of decreases in cardiac output. However, as Stewart et al. rightly pointed out, significant reductions in maternal cardiac output could have deleterious effects on the outcome of a compromised fetus.

In the absence of cardiac output monitoring in everyday practice, heart rate is a good surrogate marker of cardiac output. Usually, the initial response to spinal anesthesia for elective cesarean delivery is an increase in heart rate and a well-maintained or increased cardiac output. In this situation, restoring the heart rate to the baseline value using phenylephrine in conjunction with a rapid fluid colloid should be the primary goal. Because a small proportion of patients respond to spinal anesthesia with hypotension and bradycardia, which usually reflects a decrease in cardiac output, anticholinergics and ephedrine (and occasionally epinephrine) do have a role to play, together with increasing lateral tilt and fluid administration.

The primary goal should thus be the maintenance of the baseline heart rate. In many cases, this can be achieved by simply using boluses of phenylephrine. Alternatively, variable rate infusions may be used, with supplementary boluses of phenylephrine (either administered as prophylaxis or in response to modest hypotension). These interventions will correct blood pressure and cardiac output simultaneously, and maintain the baseline resting physiological hemodynamics. This, after all, is what we are supposed to do as anaesthesiologists.

Further research should explore the exact dose-related effects of phenylephrine on venous return in the term parturient. This would enable the anaesthesiologist to fine-tune what is now a well-understood clinical scenario. The more difficult issue of establishing predictors for the rarer presentation of acute bradycardia and hypotension is far from resolved and requires further investigation.

REFERENCES


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Thrombocytopenia occurs in approximately 10% of pregnant women and may be caused by a variety of obstetric conditions (Table 1) [1]. Although some of these diseases are not associated with adverse effects or outcomes of pregnancy, others can be associated with serious maternal as well as fetal/neonatal morbidity and mortality. A multidisciplinary team approach involving obstetrician, haematologists, paediatricians and anaesthetists is essential for the optimal management of pregnant women with thrombocytopenia. Thrombocytopenia in the obstetric patient may be the result of a range of conditions, from benign disorders such as incidental gestational thrombocytopenia to life-threatening syndromes such as the ‘haemolysis, elevated liver enzymes, low platelets’ syndrome (HELLP) [2]. The diagnosis of specific disorders is often difficult because the time of onset of these disorders during pregnancy and their clinical manifestations often overlap.

The aim of this article is to review the differential diagnosis of thrombocytopenia in pregnancy and highlight the clinical features and management of the various diseases that cause thrombocytopenia, and to summarise the anaesthetic considerations in the management of thrombocytopenia in the parturient.
Pregnancy induced hypertension

Pseudothrombocytopenia (laboratory artefact with EDTA)

Incidental or gestational thrombocytopenia

Table 1

<table>
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<th>Causes of thrombocytopenia in pregnancy.</th>
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<tr>
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<tr>
<td>Disorders with increased platelet</td>
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<tr>
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<td>Immune thrombocytopenic purpura</td>
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<tr>
<td>Pregnancy induced hypertension / HELLP</td>
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<tr>
<td>syndrome</td>
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<tr>
<td>Haemolytic uraemic syndrome</td>
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<td>Infection-associated (HIV, malaria)</td>
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<tr>
<td>Drug-induced (heparin, sulphonamides,</td>
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<td>penicillin, rifampicin, quinine)</td>
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<td>Systemic lupus erythematosus</td>
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<td>Antiphospholipid syndrome</td>
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<td>Disseminated intravascular coagulation</td>
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<td>Amniotic embolism</td>
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<td>Disorders with reduced platelet</td>
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All blood coagulation factors except XI and XIII increase during normal pregnancy [4, 5]. The plasma fibrinogen concentration increases from non-pregnant levels of 2.5–4 g.l⁻¹ to 6 g.l⁻¹ in late pregnancy and labour. The increase in the concentration of the two components of the factor VIII complex, Factor VIII and von Willebrand factor (VWF) antigen, occur in parallel in the first half of pregnancy, but then diverge because of a two-fold increase in von Willebrand factor antigen. Factor XI concentrations decrease to approximately 60% of the non-pregnant values. Factor XIII concentrations fall to about 50% of the normal non-pregnant value at term. The increase in factors VII and X is highest in mid-pregnancy and remains high in the third trimester.

Most blood coagulation inhibitors are unchanged. Antithrombin and protein C levels are normal during pregnancy. However, the plasma concentration of free protein S decreases markedly during pregnancy and may contribute to the hypercoagulable state [6, 7]. The level of tissue factor pathway inhibitor increases in pregnancy.

Plasma fibrinolytic activity is reduced during pregnancy and labour, and returns to normal within 1 h after placental delivery. The diminished fibrinolysis is caused by increased concentrations of plasminogen activator-1 derived from endothelial cells and plasminogen activator inhibitor-2 derived from the placenta.

The normal platelet count range in non-pregnant women is 150–400 × 10⁹.l⁻¹. In uncomplicated pregnancies, recent studies have reported that the platelet count decreases by an average of 10% during the third trimester as a result of haemodilution or accelerated destruction leading to younger and larger platelets [8]. Incidental thrombocytopenia in pregnancy is usually benign. The mean platelet volume increases, suggesting that a compensated state of progressive platelet destruction occurs during the third trimester [9, 10]. The concentration of plasma β-thromboglobulin (a specific protein in the α-granules that is secreted during platelet activation) increases in the second and third trimesters of pregnancy [11].

Platelet activation, coagulation and fibrinolytic activity are enhanced during delivery [7]. Significant increases in fibrinogen degradation products occur in 21% of parturients during labour, with 32% showing the similar increases in the immediate postpartum period. At 24–72 h after delivery, fibrinogen degradation remains elevated in only 10% of women. Platelet count returns to normal 24–72 h postpartum [12, 13], and fibrinolytic activity decreases rapidly [7]. During placental separation, the clotting mechanism is activated and factor VIII activity transiently increases after delivery, shortening coagulation times [14].

In the pregnant women, thrombocytopenia is defined as a platelet count of less than 150 × 10⁹.l⁻¹; counts of 100–150 × 10⁹.l⁻¹ are defined as mild thrombocytopenia, counts of 50–100 × 10⁹.l⁻¹ as moderate thrombocytopenia, and counts of less than 50 × 10⁹.l⁻¹ as severe thrombocytopenia. Thrombocytopenia is caused either by increased platelet destruction or decreased platelet production. In pregnancy, increased platelet destruction may be mediated by immunological mechanisms, abnormal platelet activation, or platelet consumption [15]. Increased destruction or utilisation of platelets during pregnancy occurs in microangiopathies (exposure to abnormal blood vessels) such as thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, haemolysis, elevated liver enzymes, low platelet (HELLP) syndrome, and pre-eclampsia.

Gestational or incidental thrombocytopenia

Gestational or incidental thrombocytopenia, the most common cause of thrombocytopenia during pregnancy, occurs in 5–8% of all pregnant women and accounts for 75% of pregnancy-associated thrombocytopenia. The decreased platelet count may be related to haemodilution and/or accelerated platelet turnover with increased platelet production in the bone marrow, and increased trapping or destruction at the placenta [16]. The quantitative decrease in platelet count is balanced by enhanced platelet reactivity [17]. Some authors, however, have described decreased platelet activation mediated by a plasma factor that selectively inhibits prostaglandin-dependent activation during pregnancy [18].

The features of gestational thrombocytopenia include a platelet count usually below 70 × 10⁹.l⁻¹ which returns to
a normal level following delivery within 12 weeks. The women are asymptomatic with no history of bleeding and thrombocytopenia is usually detected as part of antenatal screening. The women have no history of thrombocytopenia prior to pregnancy but may have thrombocytopenia in previous pregnancies. Gestational thrombocytopenia is a diagnosis of exclusion. However, when a platelet count is below $70 \times 10^9 \text{L}^{-1}$, a pathological cause of thrombocytopenia becomes substantially more likely. Gestational thrombocytopenia usually occurs in the late second or third trimester. There is an extremely low risk of fetal or neonatal thrombocytopenia [19]. In non-hypertensive pregnant women, investigations are only required when thrombocytopenia occurs early in pregnancy or progressively decreases during the pregnancy or when the platelet count is less than $70 \times 10^9 \text{L}^{-1}$. Further investigations must be undertaken in pregnant women who are symptomatic or who do not regain a normal postpartum platelet count. If a thrombocytopenic but otherwise healthy pregnant woman has a platelet count $>70 \times 10^9 \text{L}^{-1}$ and no history of previous thrombocytopenia, a meticulous physical examination, careful blood pressure assessment and monitoring and a peripheral blood film examination should be undertaken. The confirmation of normal platelet count prior to pregnancy decreases the probability of an underlying immune thrombocytopenic purpura [20]. Antiplatelet antibody tests do not differentiate gestational thrombocytopenia from idiopathic thrombocytopenia. In a study of 250 pregnant women with thrombocytopenia (90 with idiopathic thrombocytopenia, 160 with presumed gestational thrombocytopenia) that evaluated eight different platelet antibodies, platelet-associated IgG was elevated in 69.5% of women with gestational thrombocytopenia and in 64.6% of women with idiopathic thrombocytopenia ($p = 0.24$). Although 85.9% of women with idiopathic thrombocytopenia had indirect IgG compared with 60.3% women with gestational thrombocytopenia ($p < 0.001$), significant overlap existed and limited its clinical value [21]. It appears that there are no specific diagnostic tests that can distinguish gestational thrombocytopenia from mild idiopathic thrombocytopenia. Therefore, the only means of differentiation is to monitor platelet counts closely, to detect levels that decrease below the $50–70 \times 10^9 \text{L}^{-1}$ range, to document a normal neonatal platelet count and a restoration of a normal maternal platelet count after delivery. Women with gestational thrombocytopenia are not at a risk of either maternal haemorrhage or fetal haemorrhage.

**Immune thrombocytopenic purpura (ITP)**

ITP is characterised by immunologically mediated platelet destruction and an increase in circulating megathrombocytes. The patient produces IgG antiplatelet antibodies that recognise platelet membrane glycoproteins. The antibody-coated platelets are then destroyed by the reticuloendothelial system (primarily the spleen) at a rate that exceeds the capacity of the bone marrow to produce new platelets. However, antiplatelet antibodies are present in only 80% of cases.

ITP occurs in approximately one case of thrombocytopenia per 1000 pregnancies and accounts for 5% of cases of pregnancy-associated thrombocytopenia [22]. It is the most common cause of significant thrombocytopenia in the first trimester. ITP is a diagnosis of exclusion because there are no pathognomonic signs, symptoms or laboratory tests. The four consistent features that are associated with the condition are persistent thrombocytopenia (platelet count $<100 \times 10^9 \text{L}^{-1}$) with or without peripheral megathrombocytes; normal or increased number of megakaryocytes detected by bone marrow aspiration; absence of splenomegaly; and exclusion of systemic diseases or drugs that are known to cause thrombocytopenia.

Most women with ITP have a history of bruising easily, petechiae, epistaxis, and gingival bleeding preceding pregnancy, although some may be asymptomatic. Symptoms of haemorrhage are rare unless the platelet count is $<20 \times 10^9 \text{L}^{-1}$. A history of prior thrombocytopenia, underlying autoimmune disease or a platelet count $<50 \times 10^9 \text{L}^{-1}$ makes the diagnosis of ITP more likely. In patients with mildly decreased platelet count and with no prior history of thrombocytopenia, it can be difficult to distinguish ITP from gestational thrombocytopenia, because platelet-associated IgG may be elevated in both diseases [21]. An immunological test that measures antibodies that react with specific platelet glycoproteins (monoclonal antibody immobilisation of platelets) cannot differentiate these two syndromes consistently [23]. From a clinical view, in the absence of a platelet count prior to pregnancy, a platelet count $<100 \times 10^9 \text{L}^{-1}$ in the first trimester that declines progressively as the pregnancy progresses is consistent with ITP. In contrast, mild thrombocytopenia occurring in the second or third trimester and not associated with proteinuria or hypertension indicates incidental or gestational thrombocytopenia [24]. ITP is an insidious disease with initial symptoms such as easy bruising and petechiae. Pregnancy does not alter the clinical course of ITP. However, there are anecdotal reports of deterioration of symptoms during pregnancy and improvement postpartum [2].

Patients with platelet counts $>30 \times 10^9 \text{L}^{-1}$ and no bleeding do not usually require immediate treatment. Platelet transfusion is indicated if bleeding occurs or if the platelet count is $<30 \times 10^9 \text{L}^{-1}$ [9, 23]. More aggressive measures may be required to increase the platelet count to
a level to allow epidural analgesia for labour and adequate haemostasis during delivery. A platelet count >50 × 10^9·L^{-1} is usually adequate in this regard, although some authors recommend a platelet count >100 × 10^9·L^{-1} [25]. Drug therapy usually commences with oral prednisone (1–2 mg·kg^{-1}·day^{-1}), with reduction of doses until the platelet count stabilises at 75–100 × 10^9·L^{-1}. However, steroid therapy increases the incidence of gestational diabetes, pregnancy-induced hypertension and premature rupture of placental membranes. Patients with low platelet counts should receive steroids at around 37 weeks of gestation in order to increase maternal and foetal platelet counts. Betamethasone or dexamethasone is preferred because placental enzymes inactivate a major portion of the prednisone dose that is presented to the placental circulation.

High doses of intravenous immunoglobulin (2 mg·kg^{-1}) have been recommended for pregnancy-associated ITP [24]. However, the responses are often transient and multiple courses of treatment may be required.

Splenectomy may be required during pregnancy to decrease platelet destruction in patients who are refractory to steroid or IgG therapy. It should be performed in the second trimester because surgery can cause premature labour in the first trimester and may be more difficult in the third trimester due to the large gravid uterus.

The maternal consequence of ITP is haemorrhage. Bleeding complications are usually associated with surgical incisions (such as episiotomy) and lacerations of the birth canal. The mother is not at a greater risk of abruptio placentae or placenta praevia than the general pregnant population [26]. They are not at higher risk for postpartum uterine bleeding because myometrial contractions produce mechanical haemostasis without a significant contribution from platelets. Platelet numbers should be maintained above 50 × 10^9·L^{-1} for delivery. Platelet counts below 20 × 10^9·L^{-1} should be augmented using platelet transfusions.

The neonate of a mother with ITP may develop ITP as a result of the transplacental transfer of maternal antiplatelet IgG [24]. At delivery, 10–20% of these neonates have platelet counts below 50 × 10^9·L^{-1} and, in 5%, platelet counts may be <20 × 10^9·L^{-1} [27]. The major fetal risk is intracranial haemorrhage causing neurological sequelae or death, but this is rare [28]. There is no consistent and reliable correlation between the fetal platelet numbers at delivery and the severity of maternal thrombocytopenia or the concentration of maternal antiplatelet IgG [21, 27]. The most reliable predictor of fetal thrombocytopenia is the presence of thrombocytopenia at delivery of a prior sibling [29]. Determination of fetal platelet count can only be achieved by fetal scalp sampling during labour or percutaneous umbilical blood sampling, although the latter is associated with bleeding and fetal bradycardia (~1%) [30].

In 1977, a case report of intracranial haemorrhage after a vaginal delivery of a thrombocytopenic infant to a mother with ITP led to the recommendation that women with ITP should be delivered by Caesarean section. However, this approach has not been subjected to randomised controlled studies and has been recently been questioned [31, 32]. Cook and colleagues reviewed literature that included 474 pregnant women with ITP and reported that the incidence of intracranial haemorrhage among neonates with severe thrombocytopenia (<50 × 10^9·L^{-1}) was 4% after Caesarean delivery and 5% after vaginal delivery [31]. A literature review of 18 studies on maternal ITP that involved 601 neonates showed that 12% of neonates had severe thrombocytopenia, but that intracranial haemorrhage only occurred in 1% (6/601) of neonates and was not related to the mode of delivery [33]. It is currently recommended that fetal platelet count using percutaneous umbilical blood samples should be measured first, and delivery by Caesarean section undertaken if the fetal platelet count is <50 × 10^9·L^{-1} [34].

Umbilical cord platelet counts should be measured from umbilical blood obtained at delivery regardless of the method of delivery. Daily monitoring of platelet numbers in the neonate is necessary because neonatal platelet count can decrease for 4–5 days post delivery. The neonate’s platelet count is usually normal by 1 month of age.

**Pre-eclampsia and HELLP syndrome**

Pre-eclampsia is characterised by hypertension and proteinuria (> 300 mg·24 h^{-1}) developing after 20 weeks of gestation, and occurs in 6% of all pregnancies [35]. The pathological lesions of pre-eclampsia involve deficient remodelling of the maternal uterine vasculature by the placental trophoblast early in pregnancy [36]. Abnormal expression of cell adhesion molecules, and vascular endothelial cell growth factor and its receptor by trophoblasts in pre-eclampsia have been reported [37, 38]. This causes uteroplacental vascular insufficiency leading to abnormal release and metabolism of nitric oxide, prostaglandins and endothelin by placental tissues. These changes lead to platelet activation, generalised endothelial dysfunction and hypertension [39]. Circulating platelets adhere to damaged or activated endothelium, causing enhanced platelet clearance. Although increased levels of platelet-associated IgG are detected in patients with pregnancy-induced hypertension (PIH), this finding is not specific and does not provide an immunological basis for the thrombocytopenia [40]. Clearance of
IgG-coated platelets may be further increased by the reticulo-endothelial system and platelet activation due to thrombin generation [2]. Platelet function may also be impaired in women with pre-eclampsia even if their platelet count is normal.

Pre-eclampsia is present in 21% of cases of maternal thrombocytopenia [28]. Thrombocytopenia occurs in 50% of pre-eclamptic patients and occasionally precedes other manifestations of the disease. The thrombocytopenia is usually moderate and clinical haemorrhage is uncommon unless the patient develops disseminated intravascular coagulopathy. A decreasing maternal platelet count is considered as an early sign of worsening of pre-eclampsia and may occur even before other clinical manifestations of the disease are apparent. The pathogenesis of thrombocytopenia in women with severe pre-eclampsia is unknown, although vascular endothelial damage, impaired prostacyclin production and increased deposition of fibrin within the vascular bed have been suggested. Accelerated platelet destruction, platelet activation, increased platelet volume and increased megakaryocyte production have been observed [2]. An increased response of platelet calcium to arginine vasopressin preceding thrombocytopenia as early as in the first trimester has been reported and has been proposed as a possible predictor of the development of the disease [41]. Activation of the coagulation cascade occurs in most pre-eclamptic patients, but routine tests such as activated partial thromboplastin time, prothrombin time and fibrinogen concentrations are normal. However, fibrinogen d-dimers and thrombin-antithrombin complexes are elevated in most cases.

Only neonates born prematurely are at risk of neonatal thrombocytopenia, and especially those with intrauterine growth retardation [15]. The platelet count in neonatal thrombocytopenia associated with pre-eclampsia is rarely below $20 \times 10^9\,\text{L}^{-1}$ and does not cause fetal bleeding complications [28]. Term infants of mothers with PIH are no more likely to be thrombocytopenic than those of normal mothers.

The HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome, a variant of pre-eclampsia, is characterised by microangiopathic anaemia, SGOT $>70\text{ units}\,\text{L}^{-1}$, and thrombocytopenia ($<100 \times 10^9\,\text{L}^{-1}$) and is associated with a maternal mortality of about 3.3%. Severe epigastric or right upper quadrant abdominal pain, which need not be associated by proteinuria and hypertension, are common symptoms. It is more common in multiparae, occurs in a slightly younger age group (19 years vs 25 years), and can manifest in approximately 30% of cases postpartum [42, 43]. It has been suggested that the underlying primary pathological lesion in the HELLP syndrome might be endothelial dysfunction and damage, which leads to platelet aggregation, consumption and eventually thrombocytopenia. Microthrombi deposited in the liver sinusoids cause obstruction to hepatic blood flow, consequently leading to liver distension and elevations of liver enzymes [42]. Although platelet activation has been suggested in the pathogenesis of pre-eclampsia or HELLP syndrome, prophylactic treatment of high-risk pregnant women with low-dose aspirin does not significantly decrease the incidence of pre-eclampsia [44].

The HELLP syndrome is associated with disseminated intravascular coagulation, placental abruption, acute renal failure, adult respiratory distress syndrome and intrauterine death. The perinatal mortality is about 22% and is caused by placental abruption, intrauterine asphyxia, and prematurity. Approximately 60% of babies die in utero. Thirty percent of the infants (average gestational age 32 weeks) are small for gestational age, and thrombocytopenia is present in 25% of these.

The management of pre-eclampsia and HELLP is focussed on stabilising the mother until fetal maturity is more favourable. Fetal monitoring is mandatory, and will help to decide whether early delivery of the fetus is warranted. Early delivery of the fetus is warranted if there are threats to fetal or maternal life or if the syndrome develops beyond 34 weeks of gestation. Caesarean section is required in 60% of cases [42]. Platelet transfusions increase the platelet count prior to Caesarean section. However, the lifespan of the transfused platelets is shortened. Coagulopathy associated with PIH-related disseminated intravascular coagulation should be treated with fresh frozen plasma or cryoprecipitate if fibrinogen levels are low. If pre-eclamptic patients deteriorate or remain thrombocytopenic after delivery, plasma exchange and/or corticosteroids should be considered to reverse the abnormalities [6, 45].

Thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS)

Thrombotic thrombocytopenic purpura is characterised by microangiopathic haemolytic anaemia, thrombocytopenia, central neurological abnormalities, fever and renal dysfunction. In some series, up to 10% of all cases of TTP occurred in pregnant patients, and pregnancy is considered to be a predisposing factor for this disease [47]. A deficiency of a VWF-cleaving protease, ADAMTS 13, has been identified as a causative factor in the pathogenesis of TTP [48]. This deficiency may be caused by mutations in ADAMTS 13 gene in the congenital variant [49] or may result from antibodies against the protease in the acquired form of the disease. TTP usually occurs in the second trimester, with a mean onset of 23 weeks [50]. The clinical manifestations of haemolytic uraemic syndrome are similar to that of TTP except that renal
**Other causes of thrombocytopenia in pregnancy**

Disseminated intravascular coagulation can be associated with obstetric disorders such as placental abruption, amniotic fluid embolism, uterine rupture and intrauterine fetal death and may cause thrombocytopenia. In systemic lupus erythematosus (SLE) about 14–25% of patients develop thrombocytopenia caused by antiplatelet autoantibodies or circulating immune complexes [51]. Maternal autoantibodies can cross the placenta and cause fetal thrombocytopenia, especially in the presence of Ro- and La-antibodies [52].

Pregnant women suffering from antiphospholipid syndrome may have thrombocytopenia secondary to thrombosis, fetal loss or associated pre-eclampsia [53]. Approximately 28–42% of SLE patients have antiphospholipid and/or lupus anticoagulant, and have an increased risk of thromboembolism compared with those who lack these antibodies. The high fetal loss associated with the antiphospholipid syndrome is caused by recurrent thrombosis of the placental and decidual blood vessels.

Drug-induced thrombocytopenia occurs in pregnant as well as non-pregnant women. Quinidine and sulphonamides are among the most common drugs associated with acute thrombocytopenia [54].

Pregnant women with Type IIb von Willebrand disease may develop thrombocytopenia, which is caused by the enhanced clearance of platelets that bind to abnormal von Willebrand Factor molecule. HIV infection should be considered in any thrombocytopenic patient with risk factor [55].

**Anaesthetic considerations**

The choice of anaesthetic technique in the pregnant women with thrombocytopenia largely depends on the proposed method of delivery, gestational age of the fetus, coagulation status, associated obstetric complications, history of recent or current bleeding and other significant medical history. The risk of epidural haematoma in the general population is estimated to be 1 in 150 000 after epidural analgesia [56]. There are eight reports of spinal haematomas following obstetric epidural analgesia/anaesthesia in the literature but some of these are questionable [9, 57]. The incidence of epidural haematoma is 0.2–3.7 in 100 000 obstetric epidural blocks [59].

Circulating platelet numbers and their function determine the safety of regional anaesthesia. A lower limit of $100 \times 10^9 \text{L}^{-1}$ for platelet count is suggested as ‘safe’ for performing an epidural blockade, although there are no supporting data [60]. Several studies have attempted to address the issue of the risk of epidural haematoma when the platelet count is between 50 and $100 \times 10^9 \text{L}^{-1}$. Two
retrospective studies have suggested that epidural anaesthesia may be safely undertaken when the platelet count is $<100 \times 10^9 \cdot \text{l}^{-1}$ [2, 61]. In a study of 2929 parturients, no complications associated with regional anaesthesia were recorded in the 24 women who had a platelet count $<100 \times 10^9 \cdot \text{l}^{-1}$ [62]. Beilin and colleagues reported that, over a 3-year period, 30 parturients who had platelet counts ranging from 69 to $98 \times 10^9 \cdot \text{l}^{-1}$ safely received epidural anaesthesia [63]. A survey of American anaesthetists reported that 66% in academic practice and 55% of those in private practice would place an epidural anaesthetic when the platelet count is between $80 \times 10^9 \cdot \text{l}^{-1}$ and $100 \times 10^9 \cdot \text{l}^{-1}$ [64]. Most haematologists suggest that a platelet count $>50 \times 10^9 \cdot \text{l}^{-1}$ is safe for surgery and neuraxial blockade, provided platelet function is normal [5, 24].

Before carrying out further investigations to determine the cause of thrombocytopenia, factitious platelet counts due to laboratory artefacts must be ruled out by reviewing the peripheral blood film using a citrated blood sample. This artefact, termed as pseudo-thrombocytopenia, is caused by in vitro platelet clumping when EDTA is used as the anticoagulant, and is due to adhesion of platelets to the periphery of neutrophils in the presence of platelet agglutinins (IgG or IgM) [65].

The bleeding time test, a simple bedside test that evaluates the quality and quantity of platelets, is not considered to be reliable to determine the safety of epidural catheter placement because of wide observer variation. It is affected by technical (length and size of cut, occlusion pressure) and patient (ethnicity, diabetes, hypercholesterolaemia, etc.) factors [66].

Coagulation tests performed several weeks before delivery are not reliable in predicting coagulation abnormalities during labour [67]. In a study of 797 women, prothrombin time and the activated partial thromboplastin time were normal in all patients including those with low platelets and plasma fibrinogen concentrations (<2.9 gl$^{-1}$) and it was concluded that these tests are unnecessary in clinically normal parturients. The authors also reported that the percentage of women with platelet count values $<100 \times 10^9 \cdot \text{l}^{-1}$ increased from 0.5% (3/797) to 1.4% (11/797) between blood sampled during the 9th month of pregnancy and that obtained in labour.

The thromboelastogram (TEG) measures whole blood clotting, and the interactions between the coagulation cascade, fibrinogen, and platelets. However, TEG does not measure initial platelet adhesion to exposed collagen in the damaged vessel wall. Orlikowski measured platelet count, TEG variables and bleeding time in 49 parturients with pre-eclampsia. The thromboelastography variables, k time and maximal amplitude (MA) have a strong correlation with platelet count ($k$ time – platelet count $<100 \times 10^9 \cdot \text{l}^{-1}$, $r = -0.84$, $p = 0.02$; MA – platelet count $<100 \times 10^9 \cdot \text{l}^{-1}$, $r = -0.78$, $p = 0.04$). An MA of 53 mm correlated with a platelet count of $54 \times 10^9 \cdot \text{l}^{-1}$ (95% confidence limits, 40–75 $\times 10^9 \cdot \text{l}^{-1}$) and was associated with adequate clot formation produced by thromboelastography. The authors suggested that patients with platelet counts greater than $75 \times 10^9 \cdot \text{l}^{-1}$ should not be denied regional anaesthesia [68]. In another study of TEG in normal pregnant women and in women with preeclampsia, all patients with a platelet count $>75 \times 10^9 \cdot \text{l}^{-1}$ had a normal MA, which indicated a normal clot [69]. It is difficult to draw firm conclusions about the reliability of TEG to predict which patients might develop epidural haematoma from these studies because few patients with platelet counts $<75 \times 10^9 \cdot \text{l}^{-1}$ received epidural anaesthesia.

Aggregometry (measures platelet aggregation in response to specific agonist such as ADP and epinephrine) and flow cytometry (measures platelet activation and aggregation) are not practical clinical tests because they are time-consuming and require technical expertise.

The Platelet Function Analyser (PFA-100) may offer a rapid, simple point of care assessment of platelet aggregation. The PFA-100 platelet function analyser evaluates primary coagulation under high shear stress by measuring the time required for whole blood to occlude an aperture in a membrane coated with collagen and the platelet agonists, epinephrine (PFA-EPI), or adenosine diphosphate (PFA-ADP), called ‘closure time’. A 800-$\mu$l sample of citrated blood, maintained at 37 °C, is aspirated into stainless steel capillaries, through which a central aperture is cut into the membrane covered with collagen and epinephrine or collagen-ADP. Platelet activation and aggregation occurs on the membrane, resulting in the occlusion of the aperture and interruption of blood flow [70]. The test takes approximately 7 min. In a study of platelet function during pregnancy using the PFA-100 in patients with thrombocytopenia associated with preeclampsia, there was a correlation between platelet numbers and PFA-ADP closure time (normal range 71–118 s) particularly when the platelet count was less than $50 \times 10^9 \cdot \text{l}^{-1}$ [71]. The PFA-ADP closure times were normal in healthy patients. However, the PFA-EPI closure times increased in six otherwise healthy patients, suggesting that PFA-EPI may give false positive values. Further evaluation of the PFA-100 in pregnant women with platelet counts of less than $50 \times 10^9 \cdot \text{l}^{-1}$ is required [71]. Haemostasis is initiated by platelet adhesion to damaged vessel wall and the main disadvantage of all laboratory platelet function tests is that they do not measure the interaction between platelet and the vascular endothelium.
Large prospective studies with an estimated sample size of >200,000 patients are required to definitively determine whether it is safe to place an epidural or spinal anaesthetic in patients with a platelet count <100 x 10^9/L [63]. The entire clinical presentation of the patient must be considered when deciding on the appropriate choice of anaesthesia. It is important to ensure that there is no clinical evidence of bleeding and that the platelet count is not decreasing when epidural catheter placement is contemplated. A decreasing platelet count is considered a contraindication to neuraxial blockade, especially in dynamic conditions such as pre-eclampsia and ITP [63]. Pseudo-thrombocytopenia must be excluded. A manual platelet count is more accurate in patients with recent thrombocytopenia because automated counters are not reliable at low platelet counts. Specific questions about medications that might interfere with platelet numbers and function should be asked. A physical examination of the patient should include looking for evidence of bruising and bleeding at venepuncture sites or petechiae at the blood pressure cuff site. Consumptive coagulopathy associated with placental abruption and other conditions must be ruled out. When considering regional anaesthesia in patients with thrombocytopenia, spinal anaesthesia may be safer. A soft flexible catheter that is less likely to puncture blood vessels is preferred if an epidural anaesthetic is undertaken [66]. Careful monitoring of the patient in the postpartum period to detect early signs and symptoms of an epidural haematoma should be undertaken. General anaesthesia for urgent Caesarean section becomes necessary if coagulation is abnormal or there is bleeding.

References


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