Anesthetic management of patients with placenta accreta and resuscitation strategies for associated massive hemorrhage

Denis Snegovskikh[a], Anna Clebone[a] and Errol Norwitz[b]

[a]Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut and [b]Department of Obstetrics and Gynecology, Tufts University School of Medicine, Boston, Massachusetts, USA

Correspondence to Denis Snegovskikh, MD, Department of Anesthesiology, Yale University School of Medicine, New Haven, CT, USA
Tel: +1 203 785 2802;
e-mail: Denis.Snegovskikh@yale.edu

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Purpose of review

Placenta accreta is one of the leading causes of peripartum hemorrhage. The goal of this article is to review anesthetic management of parturients with placenta accreta and to examine a modern approach to massive peripartum hemorrhage.

Recent findings

The incidence of placenta accreta is rising in parallel with the increased rate of cesarean delivery. If accreta is diagnosed or suspected preoperatively, anesthetic management can be optimized. Even with the best possible management, the blood loss associated with placenta accreta can resemble that of a major trauma. The use of Damage Control Resuscitation strategies to guide transfusion may improve morbidity and mortality.

Summary

Careful planning and close communication are essential between anesthesiology, obstetric, interventional radiology, gynecologic oncology, blood bank, and specialized surgical teams when taking care of a patient with placenta accreta.

Keywords

blood transfusion, obstetric hemorrhage, placenta accreta

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Introduction

Hemorrhage following cesarean delivery is one of the most common preventable causes of maternal mortality in the USA [1]. According to a recent review, 90% of all hemorrhage-associated maternal deaths in North Carolina potentially could have been avoided [2]. Major pitfalls included failure to make the correct diagnosis and provide adequate medical and surgical treatment in timely fashion. Absence of teamwork was another important contributor [3]. Placenta accreta is one of the two leading causes of peripartum hemorrhage and the most common indication for peripartum hysterectomy [4]. The deeper the placental invasion, the more serious the sequelae. For example, in cases involving placenta percreta, maternal mortality may be as high as 7% and fetal mortality 9% [5].

Definitions

Placenta accreta is defined as the abnormal adherence of the placenta to the uterine wall with invasion of the placental villi through the decidua. Depending on the depth of invasion, abnormal placentation can be divided into three categories: placenta accreta, which is when the villi are embedded directly into the myometrium in the absence of a well defined decidual layer; placenta increta when the villi invade through the full depth of the myometrium; and placenta percreta in which the villi penetrate through the uterine serosa [6].

Epidemiology

Over the last 30 years, the incidence of placenta accreta has increased 10-fold. In developed countries, reported rates range from 1 : 530 to 1 : 2500 deliveries [7•]. In Utah, the incidence rose from 5.4/10 000 deliveries in 1996–2002 to 11.9/10 000 in 2002–2006 [8]. This parallels the increasing rate of cesarean deliveries in the USA, which reached an all-time high of 32.8% of all births in 2008 [9].

Risk factors

The majority of women with placenta accreta have no symptoms during pregnancy. As such, identification of known risk factors is essential to early diagnosis [10]. A history of a prior cesarean delivery is a major risk factor, especially in the presence of placenta previa [11]. The greater the number of prior cesarean deliveries, the higher the risk of placenta accreta (see Table 1) [11]. Additional risk factors include other uterine procedures [12], a short cesarean-to-conception interval [13], advanced maternal age [12] and smoking [14]. Unfortunately, 20% of all cases of placenta accreta have no identifiable risk factors [10].

Table 1 Cesarean delivery, placenta previa and accreta

Cesarean delivery	No previa (%)	Previa present (%)
1	0.03	3.3
2	0.2	11.0
3	0.1	40.0
4	0.8	61.0
5	0.8	67.0
6	4.7	67.0

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Pathophysiology

Two possible mechanisms of accreta formation have been proposed: abnormal decidualization and pathological over-invasiveness of the trophoblast. In the former, a localized defect in the natural barrier allows the trophoblast to break through the decidua and invade the uterine wall. A scar from a previous cesarean delivery or other uterine surgeries, pelvic radiation [15,16], or localization of the placenta in an area deficient of decidua around the cervical os (placenta previa) [11] may allow for abnormal decidualization. However, many cases of placenta accreta occur in the absence of a decidualization defect [17]. In such cases, the abnormal placentation may be due to excessive invasion of the trophoblast. For example, some cases of placenta accreta have been associated with overexpression of a specific isoform of CD44 receptors also seen in highly metastatic choriocarcinomas [18], changes in the activity of growth-related, angiogenesis-related and invasion-related factors in trophoblast [19], alteration in adrenomedullin gene expression [20], and specific mitochondrial DNA mutations [21], all of which support the over-invasiveness theory. Indeed, a placenta percreta invading the adjacent pelvic organs looks very similar both pathologically and histologically to a malignant tumor. In practice, it is likely that both theories play a role in the development of placenta accreta.

Diagnosis

For those patients who present for routine prenatal care, placenta accreta is often detected at the time of routine imaging. Perinatal ultrasound has a sensitivity of 77–93% and specificity of 71–96% for detecting placenta accreta [7•]. Whether magnetic resonance (MR) imaging is of any additional benefit is unclear. Overall, MR imaging has a sensitivity of 80–88% and a specificity of 65–100% in diagnosing accreta [7•], which is no better than that of ultrasound, although it may be superior in detecting the depth of trophoblast invasion.

Management

The management of placenta accreta requires close coordination amongst anesthesiologists, obstetricians, interventional radiologists, gynecologic oncologists, blood bank providers, and specialized surgical teams. Thorough planning has been shown to decrease blood loss, requirements for blood products, and perioperative morbidity and mortality [8,22]. For all these reasons and to avoid an unanticipated emergent delivery, an elective cesarean delivery prior to the onset of labor is generally recommended once a favorable gestational age has been reached, which is commonly regarded as approximately 34 weeks [23].

An elective cesarean delivery and planned puerperal hysterectomy is the traditional approach to the management of placenta accreta with a hysterectomy rate of 98% according to one retrospective cohort study [8]. Nowadays, with recent advances in endovascular procedures, uterine sparing management can be offered to selected patients. During this 'conservative' approach, the placenta may be left in place followed by selective uterine artery embolization or inflation of angioballoons [24]. Resorption of the retained poorly perfused placenta can be augmented by concurrent treatment with methotrexate [24].

Key points

- Despite the fact that peripartum hemorrhage is one of the leading causes of maternal mortality in the world, it is frequently managed suboptimally.
- The incidence of placenta accreta, one of the two main causes of peripartum hemorrhage, significantly increased during the last decades.
- Early diagnosis and comprehensive planning by a multidisciplinary team may result in the reduction of intraoperative blood loss and decreased maternal morbidity and mortality.
- Application of the principals of 'Damage Control Resuscitation' to massive peripartum hemorrhage may improve outcome.
- Use of a 'point-of-care device' (thromboelastography or thromboelastometry) and antifibrinolytics may optimize management of massive peripartum hemorrhage.

Endovascular interventions

In the last 30 years, interventional radiologists have developed and refined percutaneous techniques to occlude specific uterine arteries. One preoperative strategy is to endovascularly embolize the internal iliac arteries or to occlude these arteries with temporary balloons [25]. Alternatively, the collateral pelvic vessels can be embolized percutaneously, with ligation of the internal iliac arteries performed by the surgical team (along with surgical control of any bleeding from delivery-associated injuries to the genital tract) [25]. Anticipated arterial bleeding from pathologic placentation

can also be managed endovascularly before surgery [25]. Prophylactic pelvic artery catheterization and embolization in women with placenta accreta can decrease perioperative blood loss and potentially allow for the avoidance of hysterectomy, preserving the uterus [26]. Many institutions throughout the world have developed protocols for the use of interventional radiology techniques for the management of postpartum hemorrhage. At some centers, high-risk cesarean deliveries are performed in interventional radiology suites in an attempt to increase the success of the arterial occlusion and avoid migration of the angioballoons [27]. One systematic review reported a high rate of success for endovascular procedures for the treatment of postpartum hemorrhage [28].

In the absence of data from large randomized controlled trials, controversy still exists about the safety and efficacy of endovascular interventions [26]. Indeed, some authors were unable to find evidence that this technique reduces the need for cesarean hysterectomy or the amount of perioperative blood loss [29]. Such procedures may also be associated with significant complications. In a recent review of 14 parturients who underwent prophylactic iliac artery occlusion, four patients required interventions to manage complications related to the balloon catheters, one patient suffered a massive hemorrhage leading to three perioperative cardiac arrests, and in four other cases surgical conditions did not improve after inflation of the balloons [30]. In our own experience, a patient with placenta percreta had massive hemorrhage and required transfusion of 25 units of fresh frozen plasma (FFP), 20 units of red blood cells (RBCs), 30 units of platelets, and 20 units of cryoprecipitate following iliac artery rupture during balloon inflation by an experienced interventional radiologist (D. Snegovskikh, unpublished data).

Preoperative blood bank communication

As soon as it is known that a patient with suspected accreta will be undergoing surgical delivery, the anesthesiologist should call the blood bank to request blood products and provide information about the possibility of massive transfusion. The amount and type of requested products depends on the predicted severity of bleeding (i.e., accreta vs. percreta), baseline patient condition (i.e., presence of severe anemia or thrombocytopenia) and expected limitations in supply (rare blood group or difficult match due to the presence of antibodies). In routine accreta cases, we have four units of matched RBCs and four units of FFP in the operating room before the beginning of surgery. In complicated cases, we have 10 units of matched RBCs, 10 units of FFP, 10 units of platelets, and sometimes 10 units of cryoprecipitate.

In emergency cases, when the diagnosis of placenta accreta is made intraoperatively, the anesthesiologist calls the blood bank to initiate the massive transfusion protocol. At our institution, the blood bank will immediately release six units of O negative RBCs and four units of AB FFP. Twenty minutes later, the blood bank will be ready to release an additional 10 units of O negative RBCs, 10 units of AB FFP, 10 units of platelets, and 10 units of cryoprecipitate, with the option of having recombinant factor VIIa sent. It is recommended that a massive transfusion protocol be present at any institution that provides obstetric care.

Anesthetic technique

Compared with general anesthesia, regional anesthesia for cesarean delivery is associated with a 17-fold decrease in the overall rate of complications, including failed endotracheal intubation, aspiration of gastric contents, hypoxia [31], intraoperative recall [32], and a 1.7-fold decreased risk of maternal death [33]. Regional anesthesia also gives both parents the opportunity to be present during the birth of their child. Neuraxial anesthesia for peripartum intervention is now considered a standard of practice in developed countries.

Hypotension due to sympathectomy and an inability to quickly titrate down the level of anesthesia after establishment of neuraxial block make spinal and epidural anesthesia a less favorable choice in cases in which hemodynamic instability is likely. Coagulation abnormalities, which frequently follow hemorrhage and transfusion, substantially increase the risk of spinal or epidural hematoma formation, especially during manipulation of the catheter [34]. Due to the significant risk of massive bleeding complicated by profound hypotension and coagulopathy and a high likelihood of hysterectomy during cesarean delivery, general anesthesia is generally regarded as the anesthetic of choice for patients with placenta accreta. Lately, some authors have suggested that regional anesthesia may be an acceptable alternative for otherwise healthy patients with a minimal degree of invasion of placenta accreta [35]. Patients selected for conservative management would also benefit from avoidance of general anesthesia. For such patients, epidural [35] or combined spinal–epidural [36] anesthesia would be preferable. Some authors have advocated a combination of regional and general anesthesia. In this way, delivery of the baby can be performed under regional anesthesia which would allow the mother to be awake during that critical time, followed by conversion to general anesthesia for performance of the hysterectomy [37].

If preoperatively the estimated risk of coagulopathy secondary to massive bleeding is high, we avoid neuraxial techniques. In rare cases, when a patient unexpectedly develops massive bleeding and coagulopathy, we stop

any manipulations of the epidural catheter until normalization of hemostasis.

Conversion of regional to general anesthesia is likely in high-risk situations, even when it was not initially planned. Chestnut *et al.* [35] reported that, during cesarean hysterectomy, 28% of epidural anesthetics needed to be converted to general because of inadequate operating conditions and/or patient discomfort. We agree with authors who state that general anesthesia is preferred in cases with a high likelihood of massive bleeding and coagulopathy (such as placenta percreta or morbidly obese patients with placenta accreta) [36,38,39]. All such patients should also have two large-bore intravenous catheters and an arterial line placed before surgery [38].

Insertion of a central line catheter during the peripartum period carries a higher risk of overall complications compared with nonpregnant medical or surgical patients (15–20 vs. 25%, respectively), especially as regards infectious complications [40]. The internal jugular vein overlies the carotid artery to a greater extent in pregnant than in nonpregnant patients, thereby making the standard landmark approach more risky for carotid puncture (19 vs. 10% for landmark and 6 vs. 3% for palpatory technique, respectively) [41]. We reserve central line insertion only for patients with difficult intravenous access. We utilize full barrier precautions and practice only ultrasound guided insertion, should it become necessary.

Although bleeding or thrombosis after line placement may be a theoretical concern due to the alterations in coagulation in these patients, neither has occurred in our experience. This is consistent with the findings of one study in the general surgical population which showed that only a decreased platelet number ($>50 \times 10^9$/l) and not an increased international normalized ratio (INR) (>1.3) or partial thromboplastin time (PTT) (>37 s) is significantly associated with bleeding after central line placement [42]. In those few cases, however, resolution required only local suturing, and further intervention was not needed to achieve hemostasis.

We always have a rapid infuser available in the operating room. Whenever possible, we have at least one member of the anesthesia team dedicated to managing transfusion.

Blood loss

Blood flow through each uterine artery increases from 100 to 350 ml/min in pregnancy [43]. In the setting of placenta accreta, blood vessels may be even larger in diameter with increased blood flow. Such vessels do not have a thick elastic layer and lose most muscular tissue from their walls [17]. They are torn during delivery and become a source of uncontrolled hemorrhage [8] because of their inability to undergo vasospasm [17]. In one study, the estimated blood loss for patients with placenta accreta ranged from 2.5 to 5 liters, with an average blood loss of 3 liters [44]. The mean transfusion volume was 10 units of packed RBCs with a range of 3–29 units [44]. In a recent review of placenta percreta, 40% of patients received more than 10 units of RBCs [5]. Hemorrhagic shock occurs in over half of all cases of emergency postpartum hysterectomy, and coagulopathy or disseminated intravascular coagulation (DIC) occurs in more than 25% of patients [45].

Utility of cell saver technology

The use of autologous RBC salvage can decrease requirements for transfusion of allogenic blood products. The use of the 'cell saver' began in the 1970s in cases of nonobstetric hemorrhage. Unfortunately, there are as yet no prospective trials to confirm its safety in obstetric practice. Concerns include the risk of amniotic fluid embolism and maternal alloimmunization. Theoretically, the washing process and leukocyte-reducing filter should eliminate the risk of amniotic fluid contamination. Several studies have shown that the level of contamination of the maternal circulatory system by amniotic fluid is similar during cesarean delivery with or without the use of the cell saver [46]. Two articles have reported episodes of severe hypotension related to the use of the cell saver during cesarean delivery. It is unknown if this hypotension was related to the presence of amniotic fluid and fetal tissue or, alternatively, caused by an increase in bradykinin production by platelets after being exposed to the negatively charged leukodepletion filter [47]. Regardless of the mechanism, we recommend caution if cell salvage is used during cesarean delivery and awareness of the risk for severe hypotension.

Damage control resuscitation

In 2005, the US Army's Institute of Surgical Research proposed a new strategy for the transfusion of severely injured military patients, which included decreased use of crystalloids and colloids and the matching of RBC transfusion in a 1:1:1 ratio with FFP and platelets [48,49]. Results of this new strategy, called Damage Control Resuscitation, appear promising. With an increase in the FFP to RBC ratio from 1:8 to 1:1.4, mortality dropped from 65 to 19% and the number needed to treat to save one life was only two patients [50]. Results of a similar trial from a civilian trauma center published in 2006 showed a dramatic drop in mortality at 24h from 87.5 to 26% among massively transfused patients [51]. This study also showed an improvement in outcome among patients who received only 4 units of RBCs (mortality at 24h decreased from 21.2 to 11.8%)

Table 2 Effects of hypothermia and metabolic acidosis on coagulation

Effects of hypothermia	Effects of metabolic acidosis
Decreases the synthesis of acute phase proteins and clotting factors [53••]	Decreases thrombin generation [54•]
Reduces coagulation factor activity: every 1°C drop causes a 10% reduction in coagulation factor activity [55]	Decreases the activity of factor VIIa–tissue factor complex: a decrease in pH from 7.4 to 7.0 reduces the activity of factor VIIa–tissue factor complex by 55% [56]
Slows down the coagulation cascade (mainly via prolongation of the initiation phase of coagulation) [54•]	Impairs the coagulation cascade (main impact on the propagation phase) [54•]
Prolongs clotting time (at temperatures below 33°C) [57]	Decreases the activity of factor VIIa: a decrease in pH from 7.4 to 7.0 reduces the activity of factor VIIa by more than 90% [56]
Decreases citrate metabolism [53••]	Decreases the activity of Xa–Va: a decrease in pH from 7.4 to 7.0 reduces the activity of Xa–Va (prothrombinase) complex by 70% [56]

[51]. The largest retrospective study (466 patients from 16 level 1 trauma centers) showed a decrease in mortality at 6h (42–2%), 24 h (50–14%), and 30 days (57–27%) with an increase in the FFP and platelets to RBC ratio [52]. Moreover, there does not appear to be an increase in mortality from multiorgan failure among patients who received more FFP and platelets [52].

Extrapolation of data from nonpregnant patients managed in military and civilian trauma centers to massively bleeding parturients should be viewed with caution. The pathophysiologic mechanisms of dilutional and consumption coagulopathy, and the harmful effects of metabolic acidosis and hypothermia are present in both populations (see Table 2) [53••,54•,55–57].

Some physiologic mechanisms, however, are different in pregnant as opposed to nonpregnant patients, such as early activation of the thrombomodulin–protein C anticoagulation system in trauma patients in contrast with protein C resistance in parturients [58,59]. Here, we briefly review some normal physiological changes in the hemostatic system caused by pregnancy.

Physiological changes in hemostasis during pregnancy

Normal pregnancy is associated with substantial changes in hemostasis resulting in a relatively hypercoagulable state. The activity of the majority of coagulation factors is increased (I, VII, VIII, IX, X, XII) [35], whereas the activity of physiological anticoagulants is decreased, including a significant reduction in protein S activity and acquired activated protein C resistance [60]. Deep vein thrombosis occurs in 1 per 1000 deliveries, which is 5.5–6 times higher than in the general female population of childbearing age [61]. Procoagulant changes during normal pregnancy are counterbalanced by a significant activation of the fibrinolytic system [62] and deactivation of natural antifibrinolytics via a decrease in the activity of factors XI and XIII [35]. A relative deficiency of factors XI and XIII cause decreased polymerization of fibrin monomers into fibrin and diminishes the crosslinks of α2-antiplasmin to fibrin, which makes fibrin much less resistant to degradation [63]. The relatively low level of factors XI and XIII decreases the activation of thrombin-activatable fibrinolysis inhibitor resulting in a decrease in antifibrinolytic potential. Increased activity of the coagulation system and fibrinolytic system, and decreased activity of the anticoagulation and antifibrinolytic systems predispose pregnant patients the development of consumption coagulopathy (increased fibrin generation following its degradation). Indeed, levels of D-dimers and fibrin degradation products increase during normal pregnancy with rapid depletion of fibrinogen and factor XIII [64].

On the basis of the principles mentioned above, we utilize the following strategies in our approach to massively bleeding parturients:

(1) Minimize use of crystalloids and colloids. To avoid the development of a dilutional coagulopathy and further exacerbation of the discrepancy in activity of the coagulation factors, we try to minimize transfusion of colloids and crystalloids during massive resuscitation of bleeding parturients. Colloids may also impair platelet function, inhibit fibrin polymerization, and increase fibrinolytic activity [65].
(2) Optimize FFP to RBC ratio. We believe that a higher FFP and platelets to RBC ratio significantly decreases the risk of coagulation abnormalities during massive peripartum resuscitation. This recommendation is based on the literature on Damage Control Resuscitation (discussed above) and the fact that a mixture of 1 unit of RBCs, 1 unit of FFP and 1 unit of platelets has a hematocrit of 29%, platelets of 85 000 cells/ml and coagulation factor activity of 62% [53••].
(3) Appropriate use of cryoprecipitate and antifibrinolytic agents. A recent review of clinical data in the setting of postpartum hemorrhage suggests that higher than previously recommended levels of fibrinogen (2–3 vs. 1 g/l, respectively) are necessary for adequate hemostasis [66]. Factor XIII activity levels should be kept above 50–60% to minimize bleeding

Table 3 Electrolyte abnormlities associated with transfusion

Electrolyte abnormality	Causes	Problems	Prevention/Treatment
Hyperchloremia	Iatrogenic; massive transfusion of normal saline	Metabolic acidosis; kidney dysfunction; increased mortality in both critically ill [58] and postoperative patients [59]	Monitor level, avoid normal saline; Lasix
Hypocalcemia	Dilutional; citrate binding[a]	Tetany, laryngospasm, coagulopathy, decreased systemic vascular resistance myocardial contractility, elevation of central venous pressure, and end diastolic left ventricular pressure, long QT, arrhythmias [76]	Monitor level of ionized calcium; supplement with calcium chloride or calcium gluconate
Hypomagnesemia	Dilutional; citrate binding[a]	Seizures, tremor, nystagmus, arrhythmias	Monitor level; supplement with magnesium sulfate
Hyperkalemia	Overload due to the high concentration of potassium in stored packed RBCs (7–77 mEq/l) [62]	Small P waves, peaked T waves, widening of the QRS complex	Monitor level; albuterol, D5W+insulin, bicarbonate, Lasix; calcium chloride for myocardial stability

[a] Each unit of RBCs has approximately 3 g of citrate. This amount of citrate can be metabolized by a healthy, normally perfused liver in about 5 min [61]. Rapid transfusion (more than 1 unit of RBCs in 5 min), especially in the settings of hypoperfusion or liver damage could cause rapid accumulation of nonmetabolized citrate, resulting in citrate toxicity.

after major surgery [67]. As much as 30 ml/kg of FFP may be required to increase the fibrinogen level by 1 g/l [68]. Therefore, even when transfusing a high FFP to RBC ratio, we recommend early administration of cryoprecipitate to parturients. Cryoprecipitate is rich in fibrinogen as well as in factors XIII and VIII. Approximately 3 ml/kg of cryoprecipitate is sufficient to raise the fibrinogen level by 1 g/l [69]. The WOMAN trial is currently being conducted to study the utility of early administration of tranexamic acid, an antifibrinolytic agent, for the treatment of bleeding obstetric patients [70].

(4) Consider factor VII. Several case reports and case series have proposed the use of recombinant factor VIIa for the management of massive obstetric hemorrhage. A dose of 81.5–92 mcg/kg significantly reduced hemorrhage in 76–85% of women, without an increase in the incidence of thromboembolic events [71,72]. Failure to respond to recombinant factor VIIa may be caused by hypothermia, acidosis, or low fibrinogen levels [73].

Monitoring

In addition to baseline measurements, PTT, prothrombin time (PT), platelet count and fibrinogen levels should be checked every hour after the initiation of massive transfusion to guide therapy. The PT is more sensitive than PTT (88 vs. 50%) for indicating a nonhemostatic level of at least one clotting factor in trauma patients [74]. Unfortunately, none of these tests adequately assess platelet function, factor XIII levels, clot stability, or fibrinolytic activity, all of which are abnormalities specific to obstetric patients. Use of point-of-care devices such as thromboelastography and thromboelastometry may improve assessment of overall hemostasis and provide valuable information to direct hemostatic therapy [75].

Plasma electrolytes should also be checked at baseline and every hour after the initiation of massive transfusion, specifically assessing for hyperkalemia, hypomagnesemia, hypocalcemia and hyperchloremia (see Table 3) [58,59,61,62,76].

Postoperative management

In one review, admission to the ICU was required for 51.6% of women with placenta accreta; of these, 29% had intraoperative and 40% postoperative complications [44]. Infectious morbidity may complicate up to one-third of patients [5].

Conclusion

Future research is needed to evaluate the risks and benefits of Damage Control Resuscitation, point-of-care devices such as thromboelastography and the use of novel antifibrinolytic medications in massively bleeding parturients.

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