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Coagulation abnormalities and bleeding in pregnancy: an anesthesiologist's perspective

Hea-Jo Yoon

Department of Anesthesiology and Pain Medicine, Ilsan Jeil Hospital, Goyang, Korea

Corresponding author
Hea-Jo Yoon, M.D., Ph.D.
Department of Anesthesiology and
Pain Medicine, Ilsan Jeil Hospital,
174 Jangbaek-ro, Ilsandong-gu,
Goyang 10414, Korea
Tel: 82-31-900-2000
Fax: 82-31-900-2014
E-mail: heajo7890@daum.net
ORCID
https://orcid.org/0000-0003-2180-4940

During pregnancy, the procoagulant activity increases (manifested by elevation in factor VII, factor VIII, factor X, and fibrinogen levels), while the anticoagulant activity decreases (characterized by reduction in fibrinolysis and protein S activity), resulting in hypercoagulation. Standard coagulation tests, such as prothrombin time or activated partial thromboplastin time, are still used despite the lack of evidence supporting its accuracy in evaluating the coagulation status of pregnant women. Thromboelastography and rotational thromboelastometry, which are used to assess the function of platelets, soluble coagulation factors, fibrinogen, and fibrinolysis, can replace standard coagulation tests. Platelet count and function and the effect of anticoagulant treatment should be assessed to determine the risk of hematoma associated with regional anesthesia. Moreover, anesthesiologists should monitor patients for postpartum hemorrhage (PPH), and attention should be paid when performing rapid coagulation tests, transfusions, and prohemostatic pharmacotherapy. Transfusion of a high ratio of plasma and platelets to red blood cells (RBCs) showed high hemostasis success and low bleeding-related mortality rates in patients with severe trauma. However, the effects of high ratios of plasma and platelets and the ratio of plasma to RBCs and platelets to RBCs in the treatment of massive PPH were not established. Intravenous tranexamic acid should be administered immediately after the onset of postpartum bleeding. Pre-emptive treatment with fibrinogen for PPH is not effective in reducing bleeding. If fibrinogen levels of less than 2 g/L are identified, 2–4 g of fibrinogen or 5–10 ml/kg cryoprecipitate should be administered.

Keywords: Blood transfusion; Conduction anesthesia; Fibrinogen; Postpartum hemorrhage; Tranexamic acid.

INTRODUCTION

The physiology of coagulation in pregnant women differs from that in men or in women who are not pregnant. Pregnant women frequently develop physiological anemia and experience changes in the levels of coagulation factors that alter the balance between coagulation and bleeding in preparation for bleeding during birth. Anesthesiologists should understand both physiological changes in the coagulation system and disease- and medication-induced pathophysiological changes during pregnancy and increase the safety of regional anesthesia for painless delivery and cesarean section. According to Vandermeulen et al. [1], spinal hematoma following the administration of regional anesthesia was associated with coagulation abnormalities in 68% of cases. In addition, obstetrical bleeding is the major cause of maternal mortality [2]. Although much progress has been made in the management of massive bleeding after conducting vigorous research, most study participants were trauma patients rather than pregnant women [3]. Massive bleeding caused by trauma and postpartum hemorrhage (PPH) differ in terms of the gender and coagulation mechanisms of the subjects;

therefore, PPH requires an evidence-based treatment from the perspective of internal medicine, which is different from that used for treating bleeding caused by trauma [4].

This study takes an anesthesiologist's perspective to examine the changes in coagulation-related factors. It also aims to determine the risk for coagulation during pregnancy, incidence of hereditary or acquired coagulation disorders in pregnant women, risk for regional anesthesia administration in pregnant women with coagulation abnormalities, rate of transfusion in women with PPH, and pharmacological treatment for pregnant women with coagulation disorders under special circumstances such as intrauterine fetal death.

CHANGES IN COAGULATION-RELATED FACTORS DURING PREGNANCY

During pregnancy, the levels of factor VII, factor VIII, and factor X increase along with fibrinogen, while fibrinolysis and the activity of protein S decrease, resulting in hypercoagulation [5]. The level of fibrinogen increases significantly from the 28th week of pregnancy and is two times higher (350–650 mg/dl) than that in non-pregnant women (200–400 mg/dl) at the end of pregnancy [4]. D-dimer level also increases throughout pregnancy; at the end of pregnancy, the level exceeds the level used to diagnose thromboembolism in non-pregnant population [4].

TESTS FOR COAGULATION STATUS

Standard (traditional) coagulation test

Prothrombin time/international normalized ratio or activated partial thromboplastin time has been used to diagnose coagulation disorders and to assess coagulation disorder correction or hemostasis. Haas et al. [6] reviewed 11 mass transfusion or perioperative bleeding management guidelines and 64 studies that examined the efficacy of standard coagulation tests. They could not identify well-founded and well-designed studies that demonstrated the usefulness of standard coagulation tests in the diagnosis of coagulation disorders and hemostasis [6].

Although the prothrombin time/international normalized ratio and activated partial thromboplastin time are suitable methods for evaluating the coagulation status in patients re-

ceiving warfarin and heparin treatment, respectively, it is difficult to properly evaluate the coagulation status in patients with clinical bleeding [7]. Moreover, the results of standard coagulation tests are usually obtained 1 h after [8]. Nevertheless, results of traditional standard coagulation tests are still used as a basis to determine the need for blood transfusions, as new standard tests to measure coagulation status are not yet established [9].

Fibrinogen

A few studies have reported fibrinogen as an important predictor of PPH [10,11]. Fibrinogen level less than 2 g/L can predict PPH with 100% positive predictability and 99.3% specificity and is an independent variable that predicts the need for invasive techniques such as artery ligation, embolization, and hysterectomy [10–12]. When fibrinogen level exceeded 4 g/L, the outcome of PPH was good, with 79% negative predictability [10].

Thromboelastography (TEG)/rotational thromboelastometry (ROTEM)

TEG or ROTEM can replace the standard coagulation test by measuring the overall process of hemostasis in whole blood [13]. These tests are used to measure platelet, soluble coagulation factor, and fibrinogen levels and determine the role of fibrinolysis [13]. As fibrinogen is recognized as a predictor of severe PPH, the need for rapid testing for hypofibrinogenemia is becoming apparent [10]. TEG and ROTEM are gaining attention because they can be used to diagnose hypofibrinogenemia and verify the effectiveness of fibrinogen supplement therapy while being the only test that can detect excessive fibrinolysis [13,14]. By measuring the amplitude of FIBTEM, which is a type of ROTEM that measures fibrinogen levels, the level of fibrinogen can be estimated within 5 min [14]. In addition, FIBTEM amplitude is an independent variable for predicting massive bleeding (> 2,500 ml), the need for transfusion of red blood cells, and the duration of ICU stay [15]. However, only a few studies have reported the accuracy of TEG and ROTEM in predicting the development of hematomas during regional anesthesia [16]. Hydroxyethyl starch (HES) can cause coagulation disorder and may have an effect on coagulation tests [17]. The use of HES in patients undergo-

ing cesarean section can extend the clot reaction time and kinetic time of TEG, although the values are still within the normal range [18].

The 2019 Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA) PPH guidelines recommend monitoring the coagulation status of PPH patients and using laboratory tests including traditional standard tests (platelets, prothrombin time, international normalized ratio, activated partial thromboplastin time, and fibrin level) or TEG/ROTEM to determine the need for goal-oriented transfusion strategies and administering hemostasis-inducing drugs [9].

HEREDITARY COAGULATION DISORDERS

Von Willebrand disease or hemophilia (carrier) is a representative hereditary disorder in pregnant women. Regional anesthesia and normal vaginal delivery are possible in patients with hereditary coagulation disorders [8]. In the case of a severe coagulation disorder, the blood coagulation factor levels should be maintained within normal range for 3–5 days following an uncomplicated vaginal delivery or 5–7 days following a cesarean section [19]. Moreover, tranexamic acid, 1-desamino-9-d-arginine vasopressin (DDAVP), recombinant protein, and plasma or cryoprecipitate can be used to treat coagulation disorders [8]. After treating the coagulation disorders, the use of anticoagulants should be considered to prevent deep thrombosis [8].

ACQUIRED COAGULATION DISORDERS

Platelet disease

Platelet abnormalities are the most common blood disorder during pregnancy and can be categorized into platelet count and platelet function disorders [8]. Platelet count of 150×10^9/L or less is used as a criterion for diagnosing thrombocytopenia during pregnancy [20]. Ninety-nine percent of thrombocytopenia cases during pregnancy are associated with hypertensive diseases such as preeclampsia, gestational thrombocytopenia, or idiopathic thrombocytopenic purpura [8]. In addition, platelet count should be evaluated to help in the diagnosis of premature placental detachment and deter-

mine if the patient recently received an anticoagulant therapy [21].

The platelet level in pregnant women with gestational thrombocytopenia or idiopathic thrombocytopenic purpura is usually stable and within normal range [8,22]. On the contrary, the platelet count in patients with preeclampsia changes rapidly, requiring continuous platelet measurement; and the platelet function in severe preeclampsia patients may be reduced [22]. Pregnant women with mild or moderate preeclampsia may receive regional anesthesia based on the platelet count and coagulation test results obtained within 6 h [21]. However, in patients with severe preeclampsia, preeclampsia, and HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, platelet counts and coagulation tests should be performed immediately prior to the administration of regional anesthesia, as the platelet count may decrease rapidly [21]. The incidence of spinal hematoma associated with the use of epidural anesthesia in preeclamptic pregnant women with thrombocytopenia is very low, and only one case was reported [23].

The plasma platelet levels that are associated with a high incidence of hematoma after the administration of regional anesthesia were not, even if agreed upon by experts, reported in clinical trials; hence, it is difficult to mention a specific value, but reference platelet levels have been suggested in several studies [8,21]. In healthy pregnant women, the risk for hematoma does not increase in patients with a platelet count of 100×10^9/L or above, and the level does not decrease at a platelet count of 75×10^9/L; hence, regional anesthesia can be administered in pregnant women with these values in the absence of other risk factors [21,24]. Thrombocytopenia occurring in pregnant women with preeclampsia can be accompanied by other coagulation disorders, and a coagulation disorder test should be performed when platelet count is below 100×10^9/L [21]. If the result of the coagulation disorder test is normal, regional anesthesia may be administered in pregnant women with a platelet count of 75×10^9/L, taking into account the rate at which platelet decreases [25]. In idiopathic thrombocytopenic purpura and gestational thrombocytopenia, regional anesthesia can be administered if the platelet count is greater than 50×10^9/L and stable [21]. Referring to the report that hematologists have performed lumbar puncture without sequelae using a needle that is thicker than the needle for spinal anesthesia used in obstetric anesthesia,

spinal anesthesia may be administered in pregnant women with a platelet count of 50×10^9/L or less [21]. In addition, spinal anesthesia can be safely administered, even if the platelet count is less than 40×10^9/L, in the absence of other coagulation disorders [21,26].

Pregnant women who use anticoagulants

Caution is required for pregnant women who use drugs that affect coagulation. Table 1 summarizes the time required after injection of regional anesthetics (basically neuraxial anesthesia in pregnant women with normal kidney function), drug injected during epidural catheterization, and anticoagulant injected after regional anesthesia or catheter removal in pregnant women who use anticoagulants.

RELATIVE RISK OF REGIONAL ANESTHESIA AND PERIPHERAL NERVE BLOCK

The likelihood of developing hematoma after administering regional anesthesia or peripheral nerve block decreases in the following order: the risk increases after epidural anesthesia with catheterization, while the risk decreases after administering epidural anesthesia without catheterization, spinal anesthesia, paravertebral block, deep block (celiac plexus block, stellate ganglion block, etc.), superficial perivascular blocks (popliteal sciatic block, femoral nerve block, etc.), fascia block (ilio-inguinal block, Ilio-hypogastric block, etc.), superficial block (brachial nerve block, Bier's block, etc.), and regional anesthesia [21]. Catheterization is more dangerous than one-time injection, and there is a risk for catheter removal [21]. Ultrasound-guided regional anesthesia can reduce vascular rupture, thereby reducing the risk of clavicle block in patients with coagulation disorders [21].

RISK ASSOCIATED WITH REGIONAL ANESTHESIA IN PREGNANT WOMEN WITH COAGULATION DISORDERS

The relative risks of spinal cord compression and permanent injury due to vertebral hematoma during the administration of neuraxial anesthesia in pregnant women with coagulation disorders are listed in Table 2.

Table 1. Recommendations related to Drug Use that Affect Coagulation

Drug	Acceptable time after drug for block performance	Administration of drug while spinal or epidural catheter in place	Acceptable time after block performance or catheter removal for next drug dose
Heparins			
UFH sc prophylaxis	4 h or normal aPTT	Caution	1 h
UFH iv treatment	4 h or normal aPTT	Caution	4 h
LMWH sc prophylaxis	12 h	Caution	4 h
LMWH sc treatment	24 h	Not recommended	4 h
Antiplatelet drugs			
NSAIDs	No additional precautions	No additional precautions	No additional precautions
Aspirin	No additional precautions	No additional precautions	No additional precautions
Clopidogrel	7 days	Not recommended	6 h
Prasugrel	7 days	Not recommended	6 h
Oral anticoagulants			
Warfarin	INR ≤ 1.4	Not recommended	After catheter removal
Rivaroxaban prophylaxis (CrCl > 30 ml/min)	18 h	Not recommended	6 h
Thrombolytic drugs			
Alteplase, anistreplase, reteplase, and streptokinase	10 days	Not recommended	10 days

UFH: unfractionated heparin, sc: subcutaneous, aPTT: activated partial thromboplastin time, iv: intravenous, LMWH: low molecular weight heparin, NSAIDs: non-steroidal anti-inflammatory drugs, INR: international normalized ratio, CrCl: creatinine clearance. Modified from the article of Harrop-Griffiths et al. Anaesthesia 2013;68:966-72 [21].

Table 2. Relative Risks associated with Neuraxial Blocks in Obstetric Patients with Coagulation Abnormalities

Risk factor	Normal risk	Increased risk	High risk	Very high risk
LMWH – prophylactic dose	> 12 h	6–12 h	< 6 h	< 6 h
LMWH – therapeutic dose	> 24 h	12–24 h	6–12 h	
UFH – infusion	Stopped > 4 h and APPT ≤ 1.4			APPT above normal range
UFH – prophylactic bolus dose	Last given > 4 h	Last given < 4 h		
NSAID + aspirin	Without LMWH	With LMWH dose 12–24 h	With LMWH dose < 12 h	
Warfarin	INR ≤ 1.4	INR 1.4–1.7	INR 1.7–2.0	INR > 2.0
General anesthesia	Starved, not in labor, antacids given		Full stomach or in labor	
Preeclampsia	Platelets > 100 × 10^9/L within 6 h of block	Platelets 75–100 × 10^9/L (stable) and normal coagulation tests	Platelets 75–100 × 10^9/L (decreasing) and normal coagulation tests	Platelets < 75 × 10^9/L or abnormal coagulation tests with indices ≥ 1.5 or HELLP syndrome
Idiopathic thrombocytopenia	Platelets > 75 × 10^9/L within 24 h of block	Platelets 50–75 × 10^9/L	Platelets 20–50 × 10^9/L	Platelets < 20 × 10^9/L
Intra-uterine fetal death	FBC and coagulation tests normal	No clinical problems but no investigation results available		With abruption or overt sepsis
Cholestasis	INR ≤ 1.4 within 24 h	No other clinical problems but no investigation results available		

LMWH: low molecular weight heparin, UFH: unfractionated heparin, aPTT: activated partial thromboplastin time, INR: international normalized ratio. Modified from the article of Harrop-Griffiths et al. Anaesthesia 2013;68:966-72 [21].

RISK OF REGIONAL ANESTHESIA IN PREGNANT WOMEN WITH COAGULATION DISORDERS UNDER SPECIAL CIRCUMSTANCES

After intrauterine fetal death (particularly 2 weeks after fetal death), there is a high likelihood of developing coagulation abnormalities and sepsis [27]. Coagulation abnormalities occur in 3% of patients who experienced uncomplicated intrauterine fetal death and in 13% of patients with placental detachment or uterine perforation [27]. The timing of onset for coagulation disorders varies and can progress rapidly; hence, it is important to know the patients' coagulation status to determine the risk for intrauterine fetal death [21].

Because trauma can cause coagulation disorders due to shock, hemodilution, hypothermia, acidemia, and inflammation, it is advisable to identify the coagulation status before administering regional anesthesia in patients with severe traumas [21]. Severe sepsis is a contraindication to regional anesthesia, as it can lead to coagulation disorders as well as consumptive coagulopathy and can increase the incidence of epidural abscess or meningitis [21]. In severe cases of uremia,

platelet count and function tests are required, and platelet function may be improved by administering DDAVP [21]. The residual effects of anticoagulants should be assessed in dialysis patients receiving heparin, and the heparin effect should be reversed, if necessary [21,28]. If heparin was administered in dialysis patients who received regional anesthesia, caution must be taken during catheter removal to prevent bleeding [21] As all coagulation factors except for coagulation factor VIII are synthesized in the liver, liver failure is associated with coagulation disorders and coagulation tests should be performed before administering regional anesthesia [21,28]. In addition, hypersplenism may result in platelet count decrease and platelet dysfunction [21,28]. In mass transfusions, coagulation disorders may occur due to dilution and consumption of coagulation factors, and platelet function should be assessed if the patient has a history of platelet transfusion as this can lead to platelet dysfunction [21,29]. Disseminated coagulation disorders are consumptive coagulopathies, contraindicated in regional anesthesia, and should be blocked where they can be compressed with peripheral nerve blocks [21].

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MEDICAL TREATMENT OF PPH

Obstetrical bleeding is a major cause of uterine atony, but it can also be caused by premature placenta detachment, placenta accrete, amniotic embolism, and consumptive coagulopathy [30]. Anesthesiologists and physicians are advised to actively intervene when there is massive bleeding or if early bleeding occurs in patients with severe PPH, even in the absence of cardiovascular instability [9]. The main components of the medical treatment of PPH are rapid testing of coagulation disorders, transfusion therapy, and prohemostatic pharmacotherapy as adjuvant therapies [17].

Transfusion

A large-scale cohort study conducted among patients with massive bleeding from trauma reported that a higher ratio of plasma and platelets to red blood cells during transfusion reduced the rate of mortality within 24 hours after hospitalization [31]. A four-year retrospective study of 142 patients reported a reduction in the incidence of interventional procedures when blood transfusions were performed with a serum to erythrocyte ratio of 1:2 or higher [32]. In addition, a randomized study of 680 patients with severe trauma published in JAMA in 2015 had the following conclusion. Patients with severe trauma and massive bleeding did not show a difference in the overall 24-h and 30-day mortalities when transfusion was performed with plasma, platelet, and erythrocyte ratio of 1:1:1 and 1:1:2. However, hemostasis success rate was higher in the patient group with 1:1:1 ratio and had a lower bleeding-related mortality rate within 24 h [33]. However, in the absence of a large, well-designed, randomized study of PPH patients, it is difficult to determine the appropriate plasma, platelet, and erythrocyte ratios for transfusions in pregnant women with PPH. The guidelines for the management of coagulation disorders related to PPH in the International Society of Thrombosis and Haemostasis are against the 1:1:1-ratio transfusions of plasma, platelet, and erythrocytes and recommended fibrinogen supplementation (cryoprecipitates or fibrinogen concentrate transfusion) and platelet transfusion if it is difficult to obtain coagulation test results after transfusing 8 units of red blood cells and fresh frozen plasma [34]. Some studies have shown that vascular endothelial glycocalyx, which protects the blood vessels, is damaged

in patients with traumatic bleeding, and that plasma transfusions have been reported to reduce glycocalyx degradation, autoheparinization, and bleeding [35,36]. These studies emphasize that blood transfusions not only replenish plasma components but also protect the blood vessels [36]. The vascular endothelium in pregnant women, especially those with HELLP syndrome, has damaged glycocalyx; therefore, the plasma components may be expected to play a protective role in pregnant women [37].

NATA guidelines recommend a restrictive erythrocyte transfusion policy that considers erythrocyte transfusion only if hemoglobin levels are less than 7 g/dl for PPH unless in cases of massive bleeding, and 15 to 20 ml/kg plasma transfusion for coagulation abnormality in pregnant women with severe PPH NATA [9].

Pharmacologic treatment of coagulation abnormalities caused by PPH

Antifibrinolytic therapy

Antifibrinolytic agents such as tranexamic acid inhibit fibrinase activity and stabilize fibrin clots [17]. Tranexamic acid reduces perioperative bleeding by interfering with fibrin degradation by plasmin without any special side effects [38]. In their meta-analysis, Ferrer et al. [39] reported that preadministration of tranexamic acid in patients who underwent cesarean sections or vaginal delivery can reduce bleeding.

A randomized study was conducted in 20,000 individuals to examine the effects of early administration of tranexamic acid [40]. This study was performed in patients with a clinical diagnosis of PPH after cesarean section or vaginal delivery. If postpartum bleeding occurred, 1 g of tranexamic acid was given as an intravenous (IV) injection; if postpartum bleeding continued for 30 min or if bleeding re-occurred within 24 h, an additional 1 g was injected intravenously. Tranexamic acid reduced PPH mortality. Previous studies suggested that tranexamic acid should be administered as soon as the bleeding begins (within 3 h after delivering the fetus). The incidence of thromboembolism was not correlated with the administration of tranexamic acid [40].

The NATA guidelines recommended the IV injection of 0.5 to 1.0 g of tranexamic acid along with oxytocin if there is a high likelihood of PPH upon cesarean section and the IV injection of 1 g of tranexamic acid as soon as postpartum bleed-

ing begins within 3 h, with an additional 1 g of tranexamic acid as via IV injection if postpartum bleeding continues after 30 min [9].

Fibrinogen supplementation

Low fibrinogen levels in the early stages of PPH have been associated with excessive bleeding and transfusion in several observational studies [10,11]. Cryoprecipitates and fibrinogen concentrates can be used to supplement fibrinogen, both of which contain more fibrinogen than plasma [17]. Fibrinogen concentrate differs from cryoprecipitates in that it contains less germs and can be used within 10 to 15 min (cryoprecipitates take more than 30 min to thaw) [41]. Cryoprecipitates, however, has von Willebrand factor, coagulation factor VIII, and coagulation factor XIII as well as fibrinogen [41]. Although fibrinogen concentrates are widely used to correct hypofibrinolysis, it remains unclear whether fibrinogen concentrates reduce bleeding [42,43].

In a randomized study conducted in patients with severe PPH (blood loss of at least 1 L after vaginal delivery or at least 0.5 L after placenta removal in vaginal delivery, and blood loss of at least 1 L during cesarean section) who had normal fibrinogen level prior to PPH but whose plasma fibrinogen level was not identified, the administration of 2 g of fibrinogen concentrate as a treatment for PPH could not reduce the frequency of transfusions although it did increase the level of plasma fibrinogen [44]. Therefore, it is advisable to assess the plasma level of fibrinogen and administer 2–4 g of fibrinogen or 5–10 ml/kg of cryoprecipitates only when fibrinogen level is 2 g/L (or ROTEM FIBTEM A5 < 12 mm or TEG FF MA < 14 mm) [9].

Prevention of thromboembolism

Correction of coagulation abnormality is important in severe PPH, but care must also be taken to prevent thromboembolism; the NATA guidelines recommend that prevention of thromboembolism be initiated if bleeding stabilizes after severe PPH and transfusion [9].

CONCLUSION

Regional anesthesia is often used in pregnant women. Therefore, when anesthesia is administered in pregnant women with coagulation disorders or in those using heparin and antiplatelet agents, the anesthesiologists should accurately identify the coagulation status of individual patients according to the procedure or the processes involved in the procedure (e.g., catheter removal after epidural anesthesia administration). Compared with traditional standard laboratory tests, field tests such as TEG and ROTEM can quickly diagnose a wider range of coagulation disorders [13]. In addition, anesthesiologists should be actively involved as part of a multidisciplinary team from the onset of PPH. In patients with severe PPH, the active use of plasma, platelets, and fibrinogen should be considered, and tranexamic acid, which is currently the most justified treatment, should be administered [9,40].

SUPPLEMENTARY MATERIALS

Supplementary data containing Korean version of this article is available at https://doi.org/10.17085/apm.2019.14.4.371.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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KSOA

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