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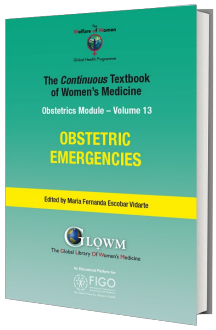

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Volume Editor: Dr María Fernanda Escobar Vidarte*, Fundación Valle del Lili, Cali, Colombia*

Chapter

Pulmonary Embolism during Pregnancy

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AUTHORS

Jose Rojas-Suarez , MD, MSc
Intensive Care and Obstetric Research Group (GRICIO), Universidad de Cartagena, Corporación Universitaria Rafael Nuñez (CURN), Colombia

Camilo Bello-Muñoz, MD, MSc
Intensive Care and Obstetric Research Group (GRICIO)

INTRODUCTION

Venous thromboembolism (VTE) disease is one of the most important causes of pregnancy-related death in developed countries and a common indirect cause of maternal mortality worldwide.[1] VTE disease has two common clinical forms: deep venous thrombosis (DVT) and pulmonary embolism (PE). The incidence of VTE during pregnancy increases in cases of intrauterine growth restriction (IUGR), fetal loss, gestational hypertension (GH), placental abruptio and intrauterine death. Pregnancy involves an increase in procoagulant factors, vascular stasis, and endothelial lesion, but also a decrease in fibrinolysis.[2] A typical distribution of DVT is on the left side and near to the iliofemoral vein junction, mainly secondary to the anatomical relation of the right iliac artery and the left iliac vein.[3]

Thrombotic events can occur at any time, increasing with the progress of the pregnancy, with a peak in the immediate postpartum period up to 7 days postpartum. Mortality associated with a thromboembolic disease is reported as high as 15% depending on the severity. However, implementing timely management of deep vein thrombosis, can decrease this mortality to less than 1%.[4]

Thromboembolic disease is preventable in most cases. Early mobilization, graduated compression stockings, and low molecular weight heparins for prevention of DVT are considered as cost-effective strategies.[5]

PREDISPOSING FACTORS

Predisposing factors increase the risk of VTE during pregnancy, some of which are related to pregnancy and others are not.

Factors not related to pregnancy

Previous thrombotic events

A previous history of an embolic event is the most critical risk factor, considering 15–25% of cases are recurrences. This recurrence is three times higher in pregnant women compared with the general population (10.9% versus 3.7%). However, this risk does not increase when the previous thrombotic event is generated by a transient factor.[6]

Obesity

Obesity increases the likelihood of thrombotic events by two mechanisms. First, a direct mechanism in which venous stasis, hypercoagulability, and fibrinolysis are altered.[7] The second, due to an increase in the rate of emergency cesarean section and the probability of postpartum hemorrhage, a well-known risk factor for thrombotic issues.[8,9]

Age

In the general population, the incidence of DVT doubles after 50 years. During pregnancy, the risk increases under 15 and over 35 years, this is not well explained and is observed mainly during puerperium.[10]

Multiparity

Multiparity is an independent and relevant risk factor, with up to 47% of embolic events occurring in these patients. [10]

Hospitalization

Hospital admission increases the risk of VTE by 18 times, compared to patients managed as outpatients. This risk persists after discharge and is higher if hospitalization was higher than 3 days.[5]

Immobilization

Immobilization and long-distance trips, defined as a trip longer than 4 hours, or immobilization, defined as a bed rest longer than 3 days, increase the risk of developing thrombotic events up to 62 times.[11]

Factors related to pregnancy

In vitro fertilization (IVF)

This technique increases the risk 10 times compared to spontaneous pregnancies. *In vitro* fertilization (IVF) is a technique increases the risk of VTE by ten times compared to in spontaneous pregnancies. The ovarian hyperstimulation syndrome is a potential complication of IVF, associated with a high risk of VTE disease during the first trimester. This situation may increase the risk of VTE events to up to 100 times. This risk disappears after the first 12 weeks of pregnancy.[12]

Cesarean section

Many patients today request delivery by cesarean section without understanding that this is major surgery that involves many risks, so the doctor provide the woman with awareness of the risks. This surgery is an independent risk factor for death from a pulmonary embolism, when compared with vaginal delivery, the elective cesarean section has a risk of thrombus embolism 2 times greater, which can be 4 times greater when that cesarean section is performed as an emergency.[8]

Obstetric hemorrhage

This factor is critical since, for many, it is a contradiction to recommend thromboprophylaxis to a patient who has had an obstetric hemorrhage. Patients with obstetric hemorrhage with blood losses higher than 1,000 ml are more likely to develop embolism and, therefore, should receive thromboprophylaxis.[13,9]

Pre-eclampsia

This is a disease that affects more than 7% of pregnant women in the world, in which there is a generalized endotheliosis with disorders of the endothelial and platelet activation that favor the formation of thrombi. This diagnosis increases the risk five times compared to healthy pregnancies.[13]

PATHOPHYSIOLOGY AND DETERMINANTS OF OUTCOME

Acute pulmonary embolism (PE) hits both circulation and gas exchange. However, respiratory failure in PE is predominantly a consequence of hemodynamic disturbances. Right ventricular (RV) failure due to acute pressure overload is considered the primary cause of death in severe PE.[14] Pulmonary artery pressure (PAP) increases if >30–50% of the total cross-sectional area of the pulmonary arterial area is occluded by an embolus. This abrupt increase in pulmonary vascular resistance (PVR) results in RV dilation, which impairs the contractile properties of the RV myocardium, including prolongation of the RV contraction time. This persists into early diastole in the left ventricle (LV) leading to a leftward shift of the interventricular septum. Finally, this forces to a reduction in the cardiac output (CO) and systemic hypotension, inducing hemodynamic instability.[15]

After PE, the imbalance between oxygen supply and demand can result in damage to cardiomyocytes and a further reduction in contractile strengths. Systemic hypotension is a critical element in this process, leading to an impairment of the coronary driving pressure to the RV, with a subsequent increase in biomarkers such as troponin and N-terminal pro B-type natriuretic peptide.[16,17]

There are three major clinical pictures of PE:

1. Cardiac arrest: as sudden cardiac death episode.
2. Obstructive shock: defined as systolic BP <90 mmHg or vasopressors required to achieve a BP ≥90 mmHg despite adequate filling status and end-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate).
3. Persistent hypotension: defined as systolic BP <90 mmHg or systolic BP drop ≥40 mmHg, lasting longer than 15 min.

DIAGNOSIS

Clinical presentation

Diagnosis of PE during pregnancy can be challenging as many symptoms overlap with those of normal pregnancy. A workup for pulmonary embolism (PE) is complex, with multiple clinical decision rules. A practical scheme based on the ***PQRsTU*** mnemonic,[18] is easy to remember and straightforward for the workup of PE, and considers five phases:

1. ***P***ERC (PE rule-out criteria);
2. ***Q***uantify gestalt phase (to determine the proper use of D-dimer or direct to imaging);
3. ***R***isk ***S***tratification phase (once PE has been diagnosed);
4. ***T***reatment phase;
5. ***U***nit or floor phase (patient disposition).

PERC phase (PE rule-out criteria)

During this first step, a clinical assessment of probability may help to rule out PE.[19] The most commonly used are the GENEVA and the pregnancy-adapted YEARS clinical prediction rules (Tables 1 and 2).[20,21] For patients with clinical signs of DVT the **LEFT** test allows to identify patients at risk as follows**: L** (**L**eft: symptoms in the left leg), **E (E**dema: calf circumference difference of ≥2 cm), and **FT** (**F**irst **T**rimester presentation). According to this clinical prediction rule, there is a probability of deep venous thrombosis of 12% in women with at least one LEFT criterion and 0 percent when there is none.[22]

Table 1 The revised Geneva clinical prediction rule for pulmonary embolism.

Items	Clinical decision rule points
1. Previous PE or DVT	1
2. Heart rate	1

Items	Clinical decision rule points
75–94 bpm	2
≥95 bpm	1
3. Surgery or fracture within the past month	1
4. Hemoptysis	1
5. Active cancer	1
6. Unilateral lower-limb pain	1
7. Pain on lower-limb deep venous palpation and unilateral edema	1
8. Age >65 years	
Clinical probability	
Three-level score	
• Low	0–1
• Intermediate	2–4
• High	≥5
Two-level score	
• PE-unlikely	0–2
• PE-likely	≥3

bpm, beats per minute; DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 2 The YEARS clinical prediction rule for pulmonary embolism.

1. Clinical signs of deep-vein thrombosis
2. Hemoptysis
3. Pulmonary embolism as the most likely diagnosis

Quantify gestalt phase

Based on the above described clinical prediction rules, the current approach for a pregnant or postpartum woman presenting to the emergency department with clinically suspected PE, involves a diagnostic strategy based on the assessment of clinical probability plus some complimentary analysis such as D-dimer measurement, compressive ultrasonography (CUS), and CT pulmonary angiogram (CTPA). Using this assessment, PE can safely be excluded during pregnancy.[21,23] Physiological changes of pregnancy rise the D-Dimer, and therefore, a positive value not undoubtedly confirm the diagnosis.[24] However, more recently, a practical algorithm based on specific cut-off values of D-Dimer allows better discrimination and classification.[23]

Based on clinical symptoms, CUS of lower limbs is useful test, with a good positive predictive value, suggesting the presence of PE.[23]

In cases with inconclusive or uncertain results, CTPA and ventilation–perfusion scintigraphy are the next steps for PE confirmation. In terms of performance, including sensitivity and specificity, both tests are similar.[25] Focusing on maternal radiation exposure, both the CTPA and ventilation–perfusion scintigraphy expose the pregnant mother to radiation much below the threshold level reported as being a risk of inducing fetal malformations, childhood cancer, or breast cancer. Finally, centered on fetal radiation, CTPA might be safer during the first two trimesters of pregnancy (see Table 3).[25,26,27]

Table 3 Estimated amounts of radiation absorbed in procedures used to diagnose pulmonary embolism (adapted from reference 27).

Test	Estimated fetal radiation exposure (mGy)	Estimated maternal radiation exposure to breast tissue (mGy)

Test	Estimated fetal radiation exposure (mGy)	Estimated maternal radiation exposure to breast tissue (mGy)
Chest X-ray	<0.01	<0.1
Perfusion lung scan with technetium-99m		
Low dose: ~40 MBq	0.02–0.20	0.16–0.5
High dose: ~200 MBq	0.20–0.60	1.2
Ventilation lung scan	0.10–0.30	<0.01
CTPA	0.05–0.5	3–10

Risk stratification phase

At the time of diagnosis, the next step is to determine the patient's risk of death. For this, four parameters are generally used:

1. Presence of shock or hypotension;
2. Presence of a simplified pulmonary embolism severity index (sPESI) greater than 2;
3. Evidence of right ventricular dysfunction in echocardiography or N-terminal pro B-type natriuretic peptide;
4. Troponin elevation.[28,29,30]

If these four elements are positive, the patient is considered as high risk, those patients who have one to three criteria are on intermediate risk and when all the criteria are negative, the patient is at a low risk patient.[31]

Treatment phase

Pulmonary embolism treatment is based on the **risk stratification** phase. However, for all patients no matter the risk, full anticoagulation is recommended to reduce the risk of early death and recurrent symptomatic or fatal PE;[32] low molecular weight heparin (LMWH) is the treatment of choice for PE during pregnancy, in a similar dosing to non-pregnant patients, based on early pregnancy weight (1 mg/kg every 12 hours).[32] Patients with high-risk PE prior to reperfusion or during the perioperative period, should receive prompt intravenous anticoagulation with unfractionated heparin (UFH), at a suggested bolus dose of 80 units/kg, and an initial infusion of 18 units/kg/h.[33] This dose is adjusted based on activated partial thromboplastin time (aPTT) controls every 6 hours (see Table 4).[34]

Table 4 Dose adjustment of unfractionated weight heparin (UFH). Adapted on reference 31.

Activated partial thromboplastin time (aPTT)	Change of dosage
<35 s (>1.2 times control)	Bolus dose of 80 units/kg and increase infusion rate by 4 units/kg/h
35–45 s (1.2–1.5 times control)	Bolus dose of 40 units/kg and increase infusion rate by 2 units/kg/h
46–70 s (1.5–2.3 times control)	No change
71–90 s (2.3–3.0 times control)	Reduce infusion rate by 2 units/kg/h
>90 s (>3.0 times control)	Stop infusion by 1 hour and reduce the infusion rate by 3 units/kg/h

For those patients at high-risk of PE, no guidelines currently exist to define the role of thrombolytic therapy in pregnant patients with PE. However, in non-obstetric patients with acute PE associated with hypotension (systolic blood pressure <90 mmHg) who do not have a high bleeding risk, systemically administered thrombolytic therapy is recommended.[33] However, despite limited experience with thrombolytics in pregnancy, this therapy may be lifesaving in pregnant patients with massive PE and severe hemodynamic compromise. There are several regimens recommended by the FDA (see Table 5).

Table 5 Schemes of thrombolytic therapy for the management of PE approved by the FDA.

Medication	Protocol
Streptokinase	250,000 IU as a loading dose over 30 min, followed by 100,000 IU/h over 12–24 h
Urokinase	4,400 IU/kg as a loading dose over 10 min, followed by 4,400 IU/kg/h over 12–24 h
rtPA	100 mg IV for 2 h

During the postpartum period a substantial risk of maternal major bleeding has been reported (58.3%). Therefore, during the days following delivery, other therapies, such as percutaneous (or surgical) thrombectomy or extracorporeal membrane oxygenation, may perhaps be preferable.[28]

As an important non-pharmacological alternative, the inferior vena cava filter should be considered in some specific situations: contraindications or complications associated with anticoagulation, recurrence of thrombotic episodes despite anticoagulation.[29] Due to the observation of a considerably high related complication rate, with a substantial removal failure rate and radiation exposure, inferior vena cava placement should be performed in limited circumstances and extreme caution.[30]

PRACTICAL RECOMMENDATIONS

- **Thromboembolic disease has a higher prevalence during pregnancy, with high mortality if adequate treatment is not started.**
- **It is necessary to establish a systematic approach to organize the teamwork and interventions.**
- **In all pregnant patients, risk stratification should be performed to determine those with a higher need for thromboprophylaxis.**
- **Heparins (LMWH or UFH) are the choice for prevention and treatment of VTE disease during pregnancy.**
- **Diagnostic images to confirm PE during pregnancy are safe, and radiation exposure poses a low risk of producing fetal variations.**
- **Obstetric patients diagnosed with high-risk thromboembolism should receive thrombolysis. However, those during the early postpartum period are at higher risk of major complications.**

CONFLICTS OF INTEREST

Author statement awaited.

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