

# Pulmonary thromboembolism and pregnancy: an updated approach for Emergency Departments

## *Tromboembolia de pulmón y gestación: una aproximación actualizada para urgencias*

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Pulmonary thromboembolism (PTE) constitutes a challenge for emergency physicians,<sup>1</sup> but it is even more so in pregnant women. If symptoms and signs are already nonspecific in the general population, tachycardia, dyspnea, and even chest pain can be physiological during pregnancy.<sup>2</sup> Moreover, if clinical diagnosis is difficult, the decision to request thoracic imaging—accompanied by the anxiety over possible radiation exposure and the hesitation to initiate anticoagulation in a young woman—makes the pregnant patient with suspected or confirmed PTE in the emergency department a truly complex clinical situation.

Pregnancy and the postpartum period (between 6 and 12 weeks, depending on the study) can be considered a prothrombotic state,<sup>3</sup> as all components of Virchow's triad are present. There is a physiological hypercoagulability, which is an adaptive evolutionary mechanism intended to protect the mother from hemorrhage during childbirth. In addition, several phenomena of venous stasis occur, such as compression of the gravid uterus over the left iliac vein, which promotes the formation of deep vein thrombosis (DVT)—one of the most frequent sites of DVT during pregnancy.<sup>4</sup> The risk of venous thromboembolic disease (VTE) increases during pregnancy and the puerperium up to 6-fold compared to non-pregnant women of the same age.<sup>4,5</sup>

This risk is not homogeneous throughout pregnancy, being higher during the puerperium and 3<sup>rd</sup> trimester (about nine times higher) vs the 1<sup>st</sup> and 2<sup>nd</sup> trimesters (2-fold increase).<sup>6</sup> Despite this elevated risk, the absolute incidence rate can be considered low (approximately 1 event per 1,000 deliveries), with a mortality rate accounting for 10% of all maternal deaths.<sup>7</sup>

Risk factors for the development of VTE during pregnancy are similar to those in the general population but include specific factors such as C-section delivery (particularly if

emergent rather than elective), in vitro fertilization, multiple pregnancy, preeclampsia, primiparity, infections, and gestational diabetes.<sup>4</sup>

As mentioned earlier, the symptoms and signs of PTE in pregnant women are nonspecific, and both tachycardia and dyspnea are physiological. Diagnostic strategies and algorithms for PTE based on clinical prediction rules (CPRs), D-dimer determination, and imaging modalities are not endorsed by current clinical practice guidelines (CPGs) for pregnant women with suspected PTE.<sup>8,9</sup> There are 2 main reasons: first, the widely recommended CPRs (Wells score and Geneva score) did not include pregnant women in their derivation or validation phases.<sup>10</sup> Second, D-dimer levels increase physiologically during pregnancy, reducing its specificity (more false positives) and its usefulness in obtaining negative results—its main diagnostic value.<sup>11</sup>

### Imaging modalities

Therefore, if no CPRs exist for this population and D-dimer testing is unreliable, the only way to confirm or exclude PTE in a pregnant woman is via imaging modalities, such as CT pulmonary angiography (CTPA) or ventilation/perfusion (V/Q) scintigraphy.<sup>12</sup> However, this direct approach has drawbacks. The actual prevalence of confirmed PTE in pregnant women undergoing imaging is 2–7% vs 10–20% in the non-pregnant population.<sup>5</sup> Although rare, false positives can occur—especially with CTPA—since the anatomical changes of pregnancy may complicate image interpretation. These cases not only lead to unnecessary months of anticoagulation but may also result in prophylactic anticoagulation in future pregnancies. Furthermore, the radiation emitted by these imaging techniques may raise concerns regarding fetal and maternal safety.

The question, then, is which imaging modality should we choose. A recent me-

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**Table 1.** Recommendations from the main clinical practice guidelines on the diagnostic management of suspected pulmonary thromboembolism in pregnant patients

	ESC (ERS)	ASH	RCOG	ASTR	ACCP
Use of D-dimer and CPRs	D-dimer and clinical prediction rules should be considered for the exclusion of PTE during pregnancy.	The role of D-dimer and clinical prediction rules in limiting radiological testing in pregnant women with suspected PTE needs to be evaluated and requires well-designed studies.	Clinicians should be aware that there is currently no evidence supporting the use of clinical prediction rules for VTE during pregnancy. D-dimer should not be used in the investigation of VTE during pregnancy.	NR	NR
Diagnostic imaging modality	V/Q scintigraphy or CTPA using a low-radiation protocol. CTPA should be considered the first option if the chest X-ray is abnormal. *If DVT symptoms are present, venous ultrasound should be the first option.	V/Q scintigraphy preferred over CTPA.	In the absence of DVT symptoms: V/Q scintigraphy or CTPA (low-radiation protocol). CTPA should be considered the first option if the chest X-ray is abnormal.	NR	V/Q CTPA or CTPA (low-radiation protocol). CTPA should be considered the first option if the chest X-ray is abnormal.

CPR: clinical prediction rules; PTE: pulmonary thromboembolism; VTE: venous thromboembolic disease; ESC: European Society of Cardiology and European Respiratory Society; ASH: American Society of Hematology; RCOG: Royal College of Obstetricians and Gynaecologists; ASTR: American Society of Thoracic Radiology; ACCP: American College of Chest Physicians; NR: no recommendation.

ta-analysis found that both imaging modalities have a negative predictive value of nearly 100% in pregnant women with suspected PTE, though CTPA appears slightly less sensitive (83% vs 100% for V/Q scintigraphy). The specificity of both imaging modalities is probably 100% in this population, but this has not been conclusively demonstrated—especially for CTPA—leaving room for possible false positives. In addition, non-diagnostic results have been reported in 12% and 14% of cases for CTPA and scintigraphy, respectively; this is particularly relevant in the case of CTPA, since to definitively rule out PTE, it will be necessary to perform a V/Q scintigraphy.<sup>13</sup>

One of the greatest concerns is radiation exposure to the fetus and maternal breast tissue. Neither technique emits radiation levels capable of causing fetal death, malformations, or neurodevelopmental impairment.<sup>2</sup> For the mother, breast tissue absorption increases as pregnancy advances, and exposure is somewhat higher with CTPA. However, newer techniques and protocols have substantially reduced radiation, making both imaging modalities now comparable in this regard.<sup>14</sup> The European Society of Cardiology recommends performing either study (if the chest X-ray is abnormal, CTPA is preferred). If the pregnant woman shows DVT symptoms, lower-limb venous ultrasound should be the first diagnostic test; if positive, PTE can be presumed and anticoagulation initiated.<sup>2</sup> The American Society of Thoracic Radiology<sup>15</sup> and the Royal College of Obstetricians and Gynaecologists<sup>9</sup> recommend either modality, whereas the American Society of Hematology<sup>8</sup> prefers the V/Q scintigraphy. The American College of Chest Physicians provides no specific recommendations.<sup>16</sup> Table 1 illustrates the current guideline recommendations for the diagnostic management of pregnant women with suspected PTE. Ultimately, the choice between V/Q scintigraphy and CTPA depends on the technical resources and logistics available in each center.

### Diagnostic strategies

However, the aim is to reduce the number of thoracic diagnostic tests given the previously mentioned low prevalence, which sits at around 5%. To this end, in recent years, 2 diagnostic strategies for PTE have emerged, designed for pregnant patients, although they are essentially adaptations of strategies originally developed for non-pregnant populations. In the ARTEMIS study,<sup>17</sup> the YEARS strategy was adopted (which uses 3 items from the Wells score and higher D-dimer cut-off limits). In this approach, if the patient exhibited clinical signs of DVT, a venous ultrasound was performed directly, assuming the pregnant woman had PTE if the result was positive. In the CT-PE trial, the Geneva score<sup>18</sup> was used; however, if the patient had a high probability or a positive D-dimer (cut-off 500) with moderate or low probability, instead of performing a thoracic imaging test, a lower-limb venous ultrasound (LLVU) was performed. These were 2 prospective trials, including 498 and 395 patients, respectively, recruited from emergency departments and obstetric services, with a mean age of 30 years. The overall prevalence of PTE was 4% and 7.1%, respectively, with a reduction in CTPAs of 39% in the ARTEMIS trial (greater within the 1<sup>st</sup> trimester) and 14.2% in the CT-PE trial. In these derivation trials, the number of patients who developed VTEs within 3 months among those in whom PTE had initially been ruled out was only 1 (0.51%; 95% CI, 0.09–2.9) and 0 (0%; 95% CI, 0–8), respectively. Despite these promising results, a retrospective validation study involving 219 pregnant patients with suspected PTE<sup>19</sup> showed that, when applying the YEARS-pregnancy strategy, 5 out of 12 confirmed PTEs were missed, and when applying the Geneva-pregnancy strategy, 3 were missed, which yielded an unacceptable sensitivity (58.3%; 95% CI, 28.6–83.5 and 75.0; 95% CI, 47.8–93.3, respectively) and specificity (44.0%; 95% CI, 37.1–51.0 and 20.8; 95% CI, 15.6–27.1).

## Treatment and prognosis

Anticoagulant treatment of PTE in pregnancy should consist of heparin throughout all phases, since vitamin K antagonists and direct oral anticoagulants (DOACs) cross the placental barrier.<sup>20</sup> Low-molecular-weight heparins (LMWH) are preferred over unfractionated heparin (UFH) due to the possibility of outpatient management. Based on extrapolation from general population studies, once- or twice-daily administration yields similar recurrence and bleeding rates, so a single daily dose is preferable. Toward the end of pregnancy, switching to twice-daily dosing, and to UFH near delivery, allows for easier and safer discontinuation and resumption of anticoagulation. The LMWH dose—always weight-adjusted—must be updated as maternal weight increases. Fondaparinux may be considered as an alternative in cases of LMWH allergy or heparin-induced thrombocytopenia, though its placental transfer is uncertain and it should be avoided in the 1<sup>st</sup> trimester.<sup>21</sup>

No specific prognostic stratification tools exist for this population, so general principles apply, focusing first on hemodynamic status.<sup>2</sup> In cases of high-risk PTE (cardiac arrest, cardiogenic shock, or sustained hypotension), systemic thrombolysis is indicated. While no clinical trials have been conducted specifically in pregnant patients, systematic reviews of

case reports and series exist. A recent review included 47 cases of PTE treated with systemic thrombolysis—mostly high-risk cases. The most frequently used thrombolytic was rt-PA, often at non-standard doses. The review reported 7 major bleeds (18%), all obstetric; no intracranial hemorrhages; 1 maternal death from cardiogenic shock; and 8 fetal deaths due to maternal shock-related hypoxia.<sup>22</sup>

In conclusion, pregnancy represents a prothrombotic state that confers a high risk of VTE and PTE to pregnant women, making it a significant cause of maternal mortality. There are no specific cCPRs for this population, and D-dimer testing has low specificity (with a high rate of false positives), although it may retain some sensitivity. Therefore, no validated diagnostic strategies exist for this group of patients, meaning that diagnosis relies directly on thoracic imaging modalities. These tests are safe for both the fetus and the mother and are diagnostically accurate. LLVU may be considered a first diagnostic approach, which is especially relevant for emergency physicians. The anticoagulant treatment of choice is LMWH during all phases, and systemic fibrinolysis is indicated in cases of high-risk PTE in pregnancy. At present, cCPGs provide inconsistent recommendations regarding key aspects of the diagnostic management of pregnant women with suspected PTE.

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