The diagnostic management of acute venous thromboembolism during pregnancy: recent advancements and unresolved issues

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**ABSTRACT**

Adequate diagnostic management of suspected venous thromboembolism (VTE) in pregnant women is of great importance. The diagnostic performance of clinical decision rules and D-dimer testing is influenced by physiological changes during pregnancy and is understudied. Recent studies have addressed these issues by developing a new clinical decision rule and raising the D-dimer level cut-off points.

With imaging of suspected pulmonary embolism (PE) the radiation exposure remains a concern. Recent studies have adjusted CT settings and scan length to minimize this exposure without loss of image quality. Furthermore the first choice imaging modality of suspected PE in pregnant women remains a matter of debate in view of studies showing high inadequacy rates for both CT scanning and VQ scanning.

Issues concerning the diagnostic management of VTE in pregnant women and advancements made in recent years will be discussed.

**Introduction**

Pregnant women have an increased risk for developing venous thromboembolism (VTE). Venous stasis, vascular damage and changes in coagulation are the main causes of this higher risk[1].

The clinical assessment of VTE in pregnant women is difficult. Physiological changes during pregnancy often lead to symptoms of the legs and dyspnea. These complaints could mimic the symptoms of a VTE. Distinguishing these physiological changes and the diagnosis VTE is very important, because of the high morbidity and mortality of (mis) diagnosing a VTE. Pulmonary embolism (PE) is still considered one of the major causes of maternal mortality[1]. Therefore accurate diagnostic management is of great importance. However, the reliability of widely implemented clinical decision rules, D-dimer testing and imaging for the diagnostic management of VTE in pregnant women is not well known.

In recent years new studies have been performed to enhance the knowledge of the diagnostic management of VTE in pregnancy, however uncertainties still exist. This review will discuss the recent advancements of diagnosing acute VTE during pregnancy.

**Clinical decision rule**

The Wells rule, the most validated clinical decision rule in the diagnosis of deep vein thrombosis (DVT) has not been validated in pregnant patients with clinically suspected DVT[2]. Complaints of edema and pain in the legs, both of which are items of the Wells rule, occur often in pregnancy.

A recent study aimed to identify prediction variables which could be used in pretest management of pregnant women with suspected DVT[3]. Three clinical variables were demonstrated to be highly predictive for DVT in pregnant patients; left leg symptoms (L), ≥ 2 cm calf circumference difference (E) and presentation in the first trimester (Ft), altogether named LEFT[3]. If all of these items are absent in a pregnant woman with a suspected DVT, the clinical probability of DVT was considered low. In case one or more items are present, the clinical probability is high. The sensitivity and negative predictive value of the LEFT rule were high, respectively 100% (95% CI, 81–100 and 95% CI, 96–100). This LEFT clinical decision rule seems promising and is potentially a step forward in the clinical management of pregnant women with a suspected DVT, however this rule has to be prospectively validated before it can be implemented in daily practice.

The Wells rule for a suspected PE has also not been validated in pregnant women. Dyspnea is a common complaint during pregnancy, especially in the third trimester when the diaphragm is raised and breathing is often more difficult. Unlike the diagnostic management of a DVT, a new clinical decision rule has not yet been developed for pregnant women with a suspected PE.

In conclusion, the Wells rule for both suspected DVT and PE has not been validated in pregnant patients. The use of clinical decision rules for both DVT and PE during pregnancy awaits further investigation.
**D-dimer testing**

The role of D-dimer testing in VTE diagnosis is to exclude VTE in a proportion of patients in whom (invasive, radiation) imaging could be withheld. This issue is especially important for pregnant women, because of the potential harm of radiation for the fetus in case of imaging for a suspected PE. However the D-dimer levels of pregnant women are raised compared to non-pregnant controls, influencing the specificity of the D-dimer test. This rise in D-dimer level already starts in the first trimester and increases during the pregnancy period, reaching the highest levels in the third trimester. From a gestational age of 35 weeks all D-dimer levels are raised above the cut-off level of 500 μg/L [4]. Therefore the use of D-dimer testing is limited during pregnancy.

A low D-dimer level in combination with the clinicians pretest assessment indicating DVT unlikely can safely exclude a DVT in pregnant women. The SimpliRed assay had a sensitivity of 100% (CI, 77–100%) and the negative predictive value was 100% (CI, 95–100%) [5]. Nevertheless the decreased specificity of D-dimer testing remains an issue and whether a low D-dimer level in combination with low clinical probability estimation could safely rule out PE is still uncertain. A recent study has assessed whether elevating the cut-off level of the D-dimer test in pregnant women with suspected DVT would raise the specificity of the test without jeopardizing the sensitivity. This study has been performed with five different D-dimer assays. All assays had a sensitivity of 100% (95% CI, 74.7–100%) with the use of the assay specific cut-off point for non-pregnant D-dimer assays. The slow venous flow associated with pregnancy could cause false-negative results on ultrasonography. The slow venous flow associated with pregnancy could cause false-positive results on ultrasonography [1]. Despite these limitations, CUS remains the first choice imaging modality in the diagnosis of DVT in pregnant women.

In conclusion D-dimer levels rise physiologically during pregnancy. Therefore the role of D-dimer testing is limited for the diagnostic management of VTE during pregnancy. Elevating the D-dimer cut off level could potentially overcome this issue, however this has to be further evaluated before implemented in daily practice.

**Imaging**

**DVT**

Compression ultrasonography (CUS) is a widely implemented and accurate imaging method for a suspected first episode of acute proximal DVT, with a sensitivity of 94% and specificity of 98% in non-pregnant patients [7,8]. Compression ultrasonography could also be used for the diagnosis of DVT in the popliteal and femoral vein during pregnancy. However, iliac veins deserve special attention. Isolated iliac venous thrombosis is a more common finding in pregnant women and diagnosis of this entity is difficult [9]. The size of the uterus and change in flow during pregnancy, especially in the third trimester complicate the diagnosis by ultrasonography. The slow venous flow associated with pregnancy could cause false-positive results on ultrasonography [1]. Despite these limitations, CUS remains the first choice imaging modality in the diagnosis of DVT in pregnant women.

Figure 1 shows a proposed diagnostic algorithm for a suspected DVT during pregnancy. If CUS of the popliteal and/or femoral veins shows a DVT, no further examination is necessary. In case of a normal CUS, one should always consider the likelihood of the presence of isolated iliac thrombosis. If a suspicion of iliac thrombosis is high on the basis of symptoms (pain in the back or buttocks, massive swelling of the upper part of the leg), duplex Doppler examination should be performed; if flow is absent the diagnosis iliac thrombosis is strongly suspected. As an alternative CT venography or MRI examination should be considered [10]. MRI examination has to be a non-gadolinium technique, because gadolinium is contraindicated during pregnancy [11].

**Pulmonary embolism**

The most widely implemented imaging methods for diagnosing a PE in non-pregnant patients are computed tomography scanning (CT scanning) and ventilation/perfusion scanning (VQ scanning). Both techniques are accurate imaging techniques for a suspected PE, but both modalities involve the use of radiation. Radiation damage should be divided into maternal and fetal radiation damage. The radiation dose per maternal breast has been reported to be 0.11–0.31 mSv in perfusion scanning and 10–70 mSv for CT scanning for
A result of fetal radiation damage could be teratogeneity and carcinogenicity. Malformations in a fetus occur from a radiation threshold of 100–200 mSv. For leukaemia and cancer the relative risk is 1.4 due to fetal radiation dose of 10 mSv[14]. To keep these numbers in perspective, perfusion scintigraphy exposes the fetus to around 0.2 mSv and multi detector row helical CT to 0.013 mSv[10]. These numbers are thus considerably lower than the thresholds for damage to the fetus and imaging with radiation should therefore not be restrained, because the risk of a potential fatal pulmonary embolism outweighs the radiation damage risk.

Compression US should always be considered in pregnant women presenting with a suspected PE and leg complaints suggestive of DVT. The advantage of CUS is the noninvasive nature and absence of radiation. In case a DVT has been diagnosed by CUS, no further imaging is needed. In case of a normal CUS, a CT scan or VQ scan should be performed.

For CT examination several studies showed that, by either reducing the kilovoltage or milliamper second settings or excluding the apices and bases of the lungs, radiation exposure could be limited without loss of image quality[15–18]. Another advantage of CT scanning is the possibility to establish an alternative diagnosis in case of an excluded PE. However, recent studies have questioned the reliability of the CT scan for diagnosing PE during pregnancy[19–21]. During pregnancy the hyperdynamic state, hemodilution and interruption of contrast agent by unopacified blood from the inferior vena cava could be potentially reasons of the diminished reliability of the CT scan. In a retrospective study of Ridge et al. CT scanning had higher diagnostic inadequacy in pregnant patients (35.7%) than in non-pregnant patients (2.1%) and furthermore CT scanning performed less than VQ scanning (inadequacy rate of 35.7% vs. 4%)[21].

In a small retrospective study the percentage of non-conclusive VQ scans was 24.8% with a low percentage of high probability scans (1.8%)[22].

A recent study showed equivalent negative predictive values for both CT scanning (99%) and VQ scanning (100%) with a 3.7% prevalence of PE[12].

Other studies suggest to use VQ scanning in pregnant patients with a normal X-ray result without a medical history of lung disease and to use CT scanning for patients with an abnormal X-ray or history of lung disease[23–25]. However this has never been prospectively evaluated.

The choice between CT scanning and VQ scanning as first choice diagnostic modality remains a dilemma.

Figure 2 shows a proposed diagnostic algorithm for the diagnostic management of suspected PE in pregnant patients. All pregnant patients with a suspected PE with symptoms of the leg should undergo CUS. If CUS diagnoses a DVT, anticoagulant treatment should be started and no further diagnostic imaging need to be performed. In case of the absence of leg symptoms or a negative CUS, CT scanning or VQ scanning should be performed. In case of an inconclusive VQ scan result, CT scanning should be performed (Figure 2).

In conclusion the choice between CT and VQ scanning is difficult. Both imaging modalities have advantages and disadvantages. An appropriate advice in this matter is complex, because of the lack of prospective studies. Furthermore the choice of the proper modality is also dependent on local availability and expertise.
Conclusion

Accurate diagnostic management of VTE is of great importance during pregnancy. In recent years several advancements have been made in this area.

The LEFT rule has been developed to categorize pregnant women with a suspected DVT in a low or high pretest probability. This rule has to be further evaluated and a clinical decision rule for suspected PE during pregnancy has still to be developed.

D-dimer testing with non-pregnant cut-off points is problematic in pregnant patients, because of the physiological rise of D-dimer levels during pregnancy. Elevating the D-dimer cut-off points for pregnant women seems promising, but has still to be validated in management studies.

Finally radiation is still an issue in imaging a suspected PE in pregnant women. Recent studies have adjusted CT settings and the length of the scan to lower radiation dose without loss of imaging quality. Whether VQ scanning or CT scanning should be the first choice in pregnant patients with a suspected PE remains a matter of debate.

Furthermore studies have shown a low prevalence of diagnosed PE (respectively 1.8% and 3.7%) with imaging of pregnant patients, indicating a need of a structured diagnostic algorithm for the diagnostic management of suspected PE during pregnancy [12,22].

Although the advancements are all promising, an urgent need still exists for prospective studies to resolve the current issues in the diagnostic management of pregnant patients with a suspected VTE.

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Conflict of Interest Statement

The authors have no conflicts of interest to report.

References

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