Venous thromboembolism (VTE) remains a major cause of maternal death. Despite widespread thromboprophylaxis use, it was the third highest cause of direct maternal death in the recent UK Confidential Enquiries into Maternal Deaths (17% of direct maternal deaths). The diagnosis of pulmonary embolism (PE) in pregnancy is difficult; a balance of maternal and fetal radiation exposure against potentially fatal misdiagnosis is required. In pregnancy, prospective clinical predictive models have not been validated, and D-dimer assays are said not to be useful because of physiologically increasing levels throughout gestation with a resultant increased reliability on imaging to exclude PE. Validated clinical prediction models combined with biomarkers that are specific for pregnancy may (1) enable risk stratification, (2) reduce the number of patients whose condition requires imaging, and (3) reduce percentages of fetomaternal radiation exposure. If risk stratification is not possible, then imaging modalities with higher sensitivity and specificity and lower radiation risk are required. We will discuss the use of 3-dimensional nuclear medicine ventilation and perfusion single photon emission computed tomography (V/QSPECT), an exciting new imaging modality. In the past decade, new anticoagulants have been developed, and their potential role in pregnancy will be explored.

New directions in diagnosis
Clinical prediction models
In the nonpregnant population, validated clinical predictive models such as the modified Well’s score stratify “likely PE” from “unlikely PE” to exclude patients from potentially harmful diagnostic imaging (Table 1). Combined with a negative D-dimer, the negative predictive value is 99.5%. Pregnancy confers a 5-fold increased risk of VTE because of venous stasis, a prothrombotic state caused by increased levels of coagulation factors, reduced protein S, and fibrinolytic activity. When pregnant women have chest symptoms such as pain and shortness of breath, determination of “normal pregnant” from PE symptoms may be difficult. The number of mothers who are imaged to exclude PE as a result of those symptoms is high, which reflects clinicians’ fear of fatal misdiagnosis. The low incidence of high-probability V/Q scans in the pregnant, compared with nonpregnant, population (≤5% vs 15-20%) illustrates this.

Rodger et al showed that interobserver reliability was improved with the use of clinical prediction models vs clinical judgment alone. A retrospective assessment by O’Connor et al that studied the usefulness of the modified Well’s score of 125 mothers with suspected PE who had a helical computed axial tomographic pulmonary angiography (CTPA) found sensitivity and specificity levels of 100% and 90%, respectively, using a score of ≥6. However, this does not address how to differentiate low- from intermediate-risk pregnant women and who can be excluded from diagnostic imaging, perhaps because of the criterion within the Well’s score of an alternative diagnosis that is at least as likely as that of PE. This criterion contributes substantially to the final score, is open to interpretation, and is dependent on clinical expertise.

There have been no prospective trials that have validated clinical prediction models to exclude PE in pregnancy.

Biomarkers
D-dimers are plasma break-down products of cross-linked fibrin and therefore are used as markers of recent thrombus formation. Unfortunately, D-dimers are also elevated in malignancy or acute inflammatory states; therefore, they are used for their negative predictive value (ie, a normal value excludes VTE). They can be measured by a number of methods that enable rapid clinical turnaround. Highly sensitive D-dimer assays with a cutoff value of 0.5 μg/mL will ex-
clude acute PE in nonpregnant patients when combined with “unlikely PE” stratification with the use of modified Well’s score criteria. In pregnancy, D-dimers rise throughout gestation, drop rapidly after delivery, and return to normal 4–6 weeks after delivery. The standard cutoff value of 0.5 μg/mL for D-dimers shows their limited usefulness in pregnancy. Kline et al found that, of 50 pregnant women, none had a D-dimer concentration of <0.50 μg/mL by the third trimester. A case report of a negative D-dimer concentration in a pregnant woman with PE who was subsequently diagnosed on imaging also exists. Chan et al hypothesized that higher cut-off points for the diagnosis of deep vein thrombosis (DVT) may compensate for the higher baseline D-dimer values that are seen in pregnancy. Five D-dimer assays that diagnose DVT in symptomatic mothers were tested and, with the use of receiver operating curves, showed improved specificity (range, 61–79%) and a small reduction in sensitivity in 4 of the 5 assays (range, 93–100%). This approach has not been assessed to exclude PE in pregnancy.

Brain natriuretic peptide (BNP) is a natriuretic hormone that is released from cardiac ventricles. Pro-hormone cleavage produces N-terminal pro-BNP (NT-pro-BNP). Cardiac troponin I and T are cardiac-specific proteins. All become elevated in cardiac damage and failure. Recent metaanalyses show that death in nonpregnant patients with PE is predicted by raised serum troponin and NT-pro-BNP levels; predicted death from acute PE is 33% if both are elevated. BNP levels double during pregnancy but remain stable irrespective of gestation. Tanous et al showed that women with preexisting cardiac disease had further elevation of BNP levels in pregnancy and that rising BNP levels predicted events or decompensation in 88% of mothers. A level of <100 pg/mL had a negative predictive value of 100% for gestational cardiac events. The use of troponin I levels as a marker of right heart strain in pregnancy have not been studied and require validation. Serum BNP or NT-pro-BNP levels are an attractive option for clinical trials of risk-stratification models for PE in pregnancy.

**Imaging**

Various diagnostic algorithms to exclude PE in pregnancy exist (Figure 1); however, most mothers will require radiologic imaging. A correct diagnosis is essential because missing a PE can be fatal; a false-negative result has short- and long-term management implications for anticoagulation in current and subsequent pregnancies. The modalities that are used most frequently are V/Q scans and/or CTPA in conjunction with lower limb compression Doppler ultrasonography. V/Q scans take planar images of patient lungs after inhalation and injection with a radioactive isotope. Pulmonary arterial thrombus is identified by areas of mismatched perfusion compared with ventilation. Low-dose perfusion scans have comparable detection rates for PE in pregnancy, with no statistically significant difference between the number of positive, nondiagnostic, or normal scans compared with CTPA.

Unfortunately, approximately 20% of women who undergo imaging with CTPA require further imaging because of initial nondiagnostic scans; however, most centers have 24-hour accessibility, unlike nuclear medicine imaging, which depends on isotope supply. CTPA can also visualize emboli directly, diagnose alternative disease, and deliver a lower dose of fetal radiation. Its main drawbacks are poor vessel opacification because of physiologic higher cardiac outputs in pregnancy and high doses of radiation to maternal breast tissue. Compression Doppler ultrasonography is a safe and accessible modality, but imaging of pelvic DVT in pregnancy can be difficult because the uterus obscures imaging. If compression Doppler ultrasonography shows a DVT, then chest symptoms are assumed to be due to PE, and no further imaging is required. The fear that is associated with fetal radiation exposure has been overstated.

Low-dose radiation, defined as exposure of <50 mSv, does not increase fetal or infant death or cause mental defects or growth retardation at 8–15 weeks’ gestation; however, a small increase of childhood malignancy (1:5000), increased heterochromia, and a mild preponderance of male sex have been seen. Radiation exposure to the fetus with both V/Q scans and CTPA is 1.2 mSv. V/Q scanning has comparable exposure to CTPA, although perfusion-only scanning decreases this further (Table 2). During the consent procedure in the past, radiologists focused on fetal radiation exposure and neglected to inform mothers of radiation exposure to maternal breast tissue. Perfusion-only scanning delivers a dose of 0.28 mSv to maternal breast tissue, but CTPA gives a dose 35 times higher at 10–70 mSv. In the long-term, CTPA confers a 14% increased risk against the background for breast cancer in pregnant women who are <40 years old. This exposure can be halved with the use of bismuth shielding.

Disadvantages of current imaging modalities means other diagnostic procedures such as magnetic resonance imaging (MRI; which is noninvasive and does not require radiation exposure) are appealing in pregnancy. MRI direct thrombus imaging requires no contrast...
agent but depends on inherent thrombus qualities. Red cells that are trapped in venous clot become hypoxic and produce methemoglobin with resultant reduced T1 signaling. It has shown value in the detection of DVT but has not been validated for PE and requires an experienced interpreter. Magnetic resonance angiogram detects central and segmental emboli accurately but is less able to detect smaller subsegmental emboli. It also requires gadolinium contrast, which has not been verified as safe in human pregnancy, although it has been used to diagnose placenta accreta and leiomyoma with no fetal side-effects. High-dose gadolinium produced fetal growth retardation in mice, but clinically relevant doses showed no fetal teratogenic effects. Maternofetal pharmacokinetics of high-dose gadolinium in mice found the maximal gadolinium fetal concentration at 30 minutes after injection with undetectable level within 24 hours in the fetus and within 48 hours in amniotic fluid. Unfortunately, such studies in humans are unethical. Real-time MRI with fast imaging steady-state precession reduces artifact caused by motion by delivering rapid radiofrequency excitation pulses that minimize the usual signal decay time for T1 or T2 signals that causes magnetization to obtain a steady state. It does not require the use of gadolinium, and initial trials show promise but require further validation.

The European Association of Nuclear Medicine recently has published data on V/QSPECT imaging. In contrast to the 2-dimensional image from standard V/Q scanning, multiple 3-dimensional images are acquired because the scanner

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**FIGURE 1**

Diagnostic algorithm used for the management of possible PE in pregnancy at our institution

<table>
<thead>
<tr>
<th>Symptoms of PE</th>
<th>Doppler US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis present</td>
<td>Treat</td>
</tr>
<tr>
<td>Normal</td>
<td>CXR</td>
</tr>
<tr>
<td>Normal</td>
<td>Perfusion only Scan</td>
</tr>
<tr>
<td>Abnormal</td>
<td>CTPA</td>
</tr>
<tr>
<td>Thrombosis present</td>
<td>PE Excluded</td>
</tr>
<tr>
<td>Normal</td>
<td>PE Excluded</td>
</tr>
<tr>
<td>Non-Diagnostic</td>
<td></td>
</tr>
</tbody>
</table>

CTPA, computed axial tomographic pulmonary angiography; CXR, chest x-ray; PE, pulmonary embolism; US, ultrasound scanning.

rotates around the patient. This results in better image quality and fewer nondiagnostic scans and is faster than regular planar V/Q imaging (Figure 2). Two studies found V/QSPECT to have a higher sensitivity and specificity compared with planar V/Q: 97% and 91%, compared with 76% and 85%, respectively. Excitingly, V/QSPECT has higher rates of sensitivity (97% vs 68-86%) and comparative rates of specificity when compared with CTPA. The radiation dose with V/QSPECT is approximately 35-40% of the dose that is required for CTPA with a slightly lower radiation dose to the fetus and a significantly lower dose to maternal breast tissue (approximately 4% of CTPA). CTCA can be inconclusive in approximately 25% of women, whereas V/QSPECT was inconclusive in <1% of cases. Efficacy in the determination of differential diagnoses, which include pneumonia and heart failure, was also seen. Its main disadvantage is a limitation to the access of appropriate radioactive isotopes. The current recommendation by the European Association of Nuclear Medicine is that V/QSPECT become the gold standard for the diagnosis of PE in all patients (pregnant and nonpregnant) and should be used in preference to CTPA.

New directions in treatment

New anticoagulant agents

Clinical trials to establish best practice for treatment of VTE in pregnancy are lacking; thus, treatment with current anticoagulants has been extrapolated from trials in nonpregnant populations. Treating VTE with vitamin K antagonists in pregnancy is avoided preferably because warfarin embryopathy causes
nasal hypoplasia and epiphysis stippling during the first trimester.\(^{42}\) In the second and third trimester, there is increased risk of fetal intracranial hemorrhage, spontaneous abortion, stillbirth, ventricular septal defects, and growth retardation, especially with maternal warfarin doses of \(\geq 5\) mg.\(^{43}\) Warfarin’s transplacental passage results in a higher international normalized ratio in the fetus than in the mother because the fetal liver fails to metabolize vitamin K and warfarin as effectively as an adult liver.\(^{44}\)

Low molecular weight heparins (LMWHs) are the anticoagulants of choice in pregnancy because they do not cross the placenta.\(^{44}\) LMWHs act by potentiating antithrombin 10,000-fold; their main effect is through anti-Xa activity. Unlike unfractionated heparin, they have reliable pharmacokinetics (ie, dose has a linear relationship anti-Xa activity).\(^{45}\) LMWHs are cleared renally and so, in pregnancy, have a shorter half-life with improved creatinine clearance.\(^{46}\) This combined with the increased plasma volumes of pregnancy reduce peak drug concentrations and shorten the half-life.\(^{45,46}\) Unfortunately, existing twice daily dosing recommendations in the Royal College of Obstetricians and Gynaecologists guidelines (no. 37b) for treatment of VTE in pregnancy are extrapolated from thromboprophylactic data only.\(^{47}\) Knight et al\(^{44}\) reviewed the UK obstetric surveillance data and found that a variety of once- and twice-daily dosing regimens existed.

Because of the reliable pharmacokinetics of LMWH in nonpregnant patients, the monitoring of anti-Xa levels is reserved for the elderly, extremes of bodyweight, and impaired renal clearance.\(^{47}\) No published data exists to support recommendations in the Royal College of Obstetricians and Gynaecologists guidelines to test anti-Xa levels in pregnant women at extremes of bodyweight and renal impairment.\(^{45}\) A 3-hour post-dose peak level of 0.4–1.2 unit/mL is considered within the “therapeutic range” by 1 expert, but this is not supported by clinical trials because few studies of dosing and the monitoring of anti-Xa levels in the pregnant population exist.\(^{42}\) Those investigators who have studied thromboprophylactic doses show conflicting data about whether doses correlate with anti-Xa levels.\(^{48,49}\) Moreover, the UK quality program showed enormous variation between hospital laboratories when a sample spiked with LMWH was sent out for evaluation of anti-Xa activity.\(^{50}\) Whether the alteration of doses to maintain anti-Xa levels within a theoretic target window impacts clinical outcomes, which include recurrent VTE and hemorrhage, is unknown.

LMWH has a lower incidence of heparin-induced thrombosis compared with unfractionated heparin. Indeed in pregnancy, no cases of heparin-induced thrombosis because of LMWH have been published.\(^{46}\) The bleeding risk is also low; in a systematic review of 64 studies that involved 2777 pregnancies, the overall frequency of bleeding was 1.98% (95% confidence interval, 1.50–2.57%).\(^{51}\) Osteoporosis is a known complication of unfractionated heparin, but only a handful of cases have been described with the use of LMWH throughout pregnancy.\(^{52}\) Thus, despite the lack of clinical trials studying the efficacy of LMWH in thromboprophylaxis in pregnancy, it is used widely and perceived as to be safe. However, the use of LMWH for treatment of VTE in pregnancy has been studied inadequately and should not be considered so benvolently.\(^{46,47}\)

In the last 5 years, new anticoagulants have been developed; their usefulness of treating PE in pregnancy is discussed later.

**Fondaparinux**

Fondaparinux is a synthesized derivative of the natural pentasaccharide within heparin. It shows high-affinity reversible binding to antithrombin that causes conformational change with enhanced factor Xa inactivation. It has a longer half-life of 17 hours when compared with the half-life of approximately 12 hours for LMWH.\(^{53}\) There is limited experience with its use in pregnancy (mainly animal studies and a few human case reports), so it is used as an alternative anticoagulant. There is a lack of clarity of its ability to cross the placenta. Dempfle\(^{44}\) reported drug cord blood levels one-tenth of maternal levels using anti-Xa and activated partial thromboplastin time assays that indicated minor transplacental passage of the drug. However, Knol et al\(^{55}\) documented no fetal hemorrhages or anomalies in 12 pregnant women who received treatment doses of 7.5-mg fondaparinux daily; median delivery blood loss was 450 mL with 3 significant (>1000 mL) postpartum hemorrhages occurring, 2 within 12 hours of the last injection. From limited data fondaparinux appears efficacious in pregnancy, but bleeding risk is not absent, and care is required when used as second-line therapy.

**The new oral anticoagulants**

There are a number of new, exciting oral anticoagulants coming that have predictable pharmacokinetics so that, unlike vitamin K antagonists, they do not require monitoring. At the vanguard are rivaroxaban and dabigatran followed by apixiban and endoxaban, among others. Rivaroxaban is a direct factor Xa inhibitor, and dabigatran is a direct thrombin inhibitor. Worldwide both have been licensed for VTE prophylaxis after hip and knee replacement and are licensed or awaiting license for stroke prevention in atrial fibrillation and for secondary VTE prevention.\(^{56–60}\) However, there are no data for the use of either agent in human pregnancy. Animal studies with both drugs have found teratogenic effects, reduced fetal viability, hemorrhagic changes, and placental abnormalities. Rivaroxaban is secreted in breast milk, but no such data exists for dabigatran.\(^{61,62}\) For these reasons, dabigatran or rivaroxaban cannot be recommended for use in pregnancy, and women who take these drugs and wish to conceive are advised to change to a vitamin K antagonist and then LMWH, depending on their underlying problem.

**Thrombolysis, graduated compression stockings, and inferior venacaval filters**

Postthrombotic syndrome develops in 80% of pregnant women after DVT. Grade II graduated compression stockings (ankle pressure, 30–40 mm Hg) for 2 years after diagnosis reduces the incidence of postthrombotic syndrome.\(^{63}\) There is minimal experience of thrombolysis of PE in pregnancy. Case reports
show its use in women who are compromised hemodynamically from PE. Hemorrhagic complication rates are similar to nonpregnant patients with pregnancy-related complications that include placental abruption and documented preterm labor.43

A fresh DVT (ie, after 37 weeks’ gestation), especially in the pelvis or proximal veins, has a likelihood of embolization during labor, possibly made more so by anticoagulation withdrawal in labor. Temporary retrievable inferior vena caval filters are used most appropriately in this setting.2,65

**Future directions**

Clinical trials are needed to improve the management of PE in pregnancy. Existing clinical prediction models require prospective validation in pregnancy. Do biomarkers such as high cutoff D-dimers and BNP in conjunction with clinical prediction models exclude low-risk women and thus reduce the risk of maternofetal radiation exposure? Certainly V/QSPECT is a major advance, and the latest magnetic resonance imaging technology requires trials to investigate rates of sensitivity and specificity in pregnancy. Given the altered pharmacokinetics of LMWH in pregnancy, future trials that will identify optimal dosing regimens for the treatment of VTE and the study of maternal and fetal outcomes in women are needed. Finally, new oral anticoagulant agents cannot be recommended for use in pregnancy; any data obtained will be based on case reports.

**REFERENCES**


