Suspected Pulmonary Embolism in Pregnancy

Clinical Presentation, Results of Lung Scanning, and Subsequent Maternal and Pediatric Outcomes

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Background: Ventilation-perfusion (VQ) scanning is used when pulmonary embolism (PE) is suspected during pregnancy; however, the distribution of lung scan results and safety of VQ scanning have never been studied.

Objective: To study the distribution of lung scan results as well as the safety of withholding anticoagulation therapy following a normal or nondiagnostic scan in pregnant women.

Methods: The study group comprised 120 consecutive pregnant women who presented with suspected PE. Clinical data were collected, and the lung scans were reinterpreted by 2 independent experts. Subsequent pregnancy and pediatric outcomes were determined by direct patient follow-up.

Results: During the study period, 120 pregnant women (mean age, 32 years) underwent 121 VQ scans. Eight cases (6.6%) were already receiving treatment for venous thromboembolism prior to VQ scanning. In the remaining 113 scans, 83 (73.5%) were interpreted as normal, 28 (24.8%) as nondiagnostic, and 2 (1.8%) as high probability. In the 104 women who did not receive anticoagulation therapy following lung scanning (80 normal and 24 nondiagnostic), no venous thromboembolic events were reported (mean [range] length of follow-up, 20.6 [0.5-108] months). Examination of pediatric data from 110 live births (90.2%) (mean [range] age, 20.5 [0.5-100] months) revealed no increase in the rates of congenital and developmental anomalies.

Conclusions: The prevalence of high-probability VQ scans in pregnant women with suspected PE is very low. Withholding anticoagulation in pregnant women with normal or nondiagnostic VQ scans is probably safe. In addition, pediatric risks from VQ scans are low. Large prospective studies are needed to evaluate diagnostic strategies for pregnant women with suspected PE.

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PULMONARY EMBOLISM (PE) is a major preventable cause of maternal mortality during pregnancy and the puerperium.1-3 As in nonpregnant patients, the diagnosis of PE during pregnancy is usually made by combining clinical probability and the results of objective testing.4,5 Ventilation-perfusion (VQ) scanning remains a widely used imaging technique for the investigation of PE in nonpregnant patients.1,5 Results from PE diagnostic studies have been extrapolated to pregnant women even though these patients have been systematically excluded from participation in these studies largely due to concerns (on behalf of physicians and patients) about the dangers of fetal radiation exposure. The assumption that the results of lung scans in nonpregnant patients are generalizable to the pregnant subject might be incorrect because, as a group, pregnant women are younger and less likely to have concomitant respiratory illnesses that could cause an abnormal scan, but they might have physiological changes such as compression of the lungs by the enlarging uterus that could cause an abnormal scan. These issues are further confounded by nonthrombotic symptoms that mimic PE, such as shortness of breath and chest pain, which are common during pregnancy.

In nonpregnant patients, a normal perfusion scan excludes PE and a high-probability scan is usually diagnostic of its presence,4 whereas all other scan results (ie, abnormal perfusion but not meeting the criteria for high probability) are nondiagnostic. Nonpregnant patients with nondiagnostic scans are problematic because they are common, and PE is present in up to 30%.4 To circumvent the need for pulmonary angiography (the
PATIENTS AND METHODS

STUDY POPULATION

The present study was approved by the institutional review boards of the Women’s College Campus, Sunnybrook and Women’s Health Sciences Centre, Toronto, Ontario (WWC), and the McMaster Division, Hamilton Health Sciences Corporation, Hamilton, Ontario (McMaster). Consecutive pregnant women who presented with suspected PE and underwent VQ scanning at 1 of the 2 hospitals were identified through their nuclear medicine departments. The inclusion periods were from January 1990 to April 2000 (WWC) and from January 1996 to April 2000 (McMaster); in the latter facility, earlier scans were not accessible. The hospital medical records of these patients were reviewed, and information on maternal demographics, stage of pregnancy, symptoms at presentation, and the most responsible physician’s probable diagnosis (when available) prior to obtaining the VQ scans was abstracted. We sought for the results of additional relevant tests that were performed (ie, chest radiography, CUS, impedance plethysmography, D-dimer testing, and pulmonary angiography) and abstracted information on anticoagulation treatment and pregnancy outcomes. Patients were contacted by telephone (2 weeks to 9 years after their presentation) to verify information on immediate medical management at the time of suspected PE, including use of anticoagulation therapy, and to confirm subsequent pregnancy outcomes. Maternal venous thromboembolic events (VTEs), as well as pediatric outcomes, were then obtained using a standardized data collection sheet. If the woman could not be contacted directly, this information was obtained from her family physician and/or hospital medical record.

VQ SCANS

Perfusion scans at both centers were performed using intravenous injections of technetium Tc 99m macroaggregated albumin (99mTc-MAA), and the ventilation scans were performed using technetium Tc 99m methylene diphosphonate aerosol (99mTc-MDA) and technetium Tc 99m sulfur colloid (99mTc-SC) at WCC and McMaster, respectively. Patients were managed according to local practice by the attending physician, which was usually based on a combination of clinical probability, lung scan results, and the results of other relevant tests.

For this study, 2 experts (J.S.G. and G.C.) reinterpreted each scan separately using the “McMaster criteria.” Scans were defined as normal (ie, no perfusion defects), nondiagnostic (ie, 1 or more perfusion defects associated with a corresponding ventilation defect or a subsegmental perfusion defect with normal ventilation), or high probability (ie, large (>75%) subsegmental or greater perfusion defects with normal ventilation). Both experts were blinded to the original interpretation of the VQ scan, as well as all patient characteristics and outcomes. In cases in which disagreements occurred, the final interpretation was based on consensus between the 2 experts.

ANALYSES AND STATISTICS

For the distribution of lung scan results, the prevalence (and its corresponding 95% confidence interval [CI]) of patients with normal, nondiagnostic, and high-probability scans was calculated for (1) all patients who presented for VQ scan investigation and (2) the subgroup of patients whose primary presentation was suspected PE (and not DVT) and had not received full-dose unfractionated heparin or low-molecular-weight heparin for more than 2 weeks. The safety of withholding anticoagulants in patients with normal and nondiagnostic scans was assessed by determining the percentage (and 95% CI) of patients whose scans were independently adjudicated as nondiagnostic or normal, who were not anticoagulated, and who remained event free on follow-up.

The safety of VQ scanning during pregnancy was assessed by determining the prevalence of the following adverse pregnancy outcomes: preterm labor, preeclampsia, spontaneous loss, and stillbirths. The safety of fetal in utero VQ scan exposure was further assessed by determining the prevalence of congenital and developmental anomalies in the offspring and comparing these results with the observed national rates (Canada) and that seen at one of the hospitals (WWC). A weighted k statistic (and the corresponding 95% CI) was calculated for interobserver agreement between the 2 experts interpreting these scans.
The presenting symptoms of women with suspected PE who underwent VQ scanning were available for 97 (80.2%) of the 121 cases. The most common complaints, either alone or in combination, were dyspnea (60 [61.9%]), pleuritic chest pain (45 [46.4%]), and non-pleuritic chest pain (18 [18.6%]). Alternate clinical diagnoses thought to be more likely than PE were documented in 49 (40.5%) of the 121 cases. The most common alternate diagnoses were pneumonia or bronchitis (20 [40.8%] of 49) and exacerbation of asthma (7 [14.3%] of 49).

TESTS PERFORMED IN ADDITION TO VQ SCANS

A chest radiograph was obtained in 60 cases (49.6%) prior to lung scanning, and 24 (40.0%) were abnormal. Ten demonstrated consolidation consistent with clinical findings of pneumonia, 4 demonstrated atelectasis, and another 10 indicated pulmonary vascular congestion or effusion.

Bilateral CUS or impedance plethysmography was performed in 67 cases (55.4%) (not diagnosed with recent acute DVT), and all results were negative. Serial ultrasonography (multiple testing over 7 days) was performed in 7 women; all results remained normal. Pulmonary angiography was performed in 2 women; 1 test result was positive for PE in a woman with a nondiagnostic scan.

DISTRIBUTION OF VQ SCAN RESULTS, MANAGEMENT, AND SUBSEQUENT OUTCOMES OF THE STUDY POPULATION

Although 121 women underwent VQ scanning for suspected PE, 1 woman experienced a cardiopulmonary arrest during the lung scan and died before her lung scan was completed; therefore, reinterpretation was not performed in this patient. The reinterpretation of the remaining 120 scans by the 2 independent readers is summarized in Table 2. There was agreement in 112 of 120 scans; the weighted k score was excellent at 0.86 (95% CI, 0.76-0.96). The readers interpreted 83 scans (69.2%) as normal, 25 (20.8%) as nondiagnostic, and 4 (3.3%) as high probability. In the 8 cases in which there was disagreement, 4 scans were read as nondiagnostic by one and normal by the other; in the other 4 cases, the converse occurred. The discrepant scans were reviewed by the 2 readers, and consensus was achieved, yielding the following results: 87 (72.5%) were normal; 29 (24.2%), nondiagnostic; and 4 (3.3%), high probability.

In the subgroup of 113 women who presented with suspected PE during pregnancy and who were not receiving therapeutic anticoagulation, the lung scans were normal in 83 (73.5%), nondiagnostic in 28 (24.8%), and high probability in 2 (1.8%) (Figure). Based on initial on-site investigations, 8 of these 113 women were given full-dose anticoagulation after VQ scanning. Of these 8 scans, 2 were adjudicated as high probability, 4 as nondiagnostic, and 2 as normal. One of the women with a normal scan was given anticoagulation therapy because her scan had been interpreted locally as nondiagnostic, and she refused further definitive testing. The other

### Table 1. Characteristics of the Study Population*

<table>
<thead>
<tr>
<th>Total No. of women</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of pregnancies</td>
<td>121</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>60 (50.0)</td>
</tr>
<tr>
<td>Singleton</td>
<td>113 (93.4)</td>
</tr>
<tr>
<td>Twin</td>
<td>7 (5.8)</td>
</tr>
<tr>
<td>Triplet</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Weeks of gestation at presentation</td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>12 (9.9)</td>
</tr>
<tr>
<td>12-28</td>
<td>51 (42.5)</td>
</tr>
<tr>
<td>&gt;28</td>
<td>58 (47.6)</td>
</tr>
<tr>
<td>Receiving therapeutic doses of anticoagulation prior to ventilation-perfusion scanning</td>
<td>8 (6.6)</td>
</tr>
</tbody>
</table>

*Data are number (percentage) of pregnancies unless specified otherwise.

### Table 2. Distribution of the Lung Scan Results Based on Independent Interpretation of 120 Ventilation-Perfusion Lung Scans Performed in Pregnancy

<table>
<thead>
<tr>
<th>Reader 1 (J.S.C.)</th>
<th>Reader 2 (G.C.)</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>83 (69.2)</td>
</tr>
<tr>
<td>Nondiagnostic</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>High probability</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>87 (72.5)</td>
</tr>
</tbody>
</table>

*Data are number (percentage) of scans.

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MATERNAL DEMOGRAPHICS AND PRESENTATION

Approximately 30,000 deliveries took place at WCC between January 1990 and April 2000, whereas approximately 12,750 deliveries occurred at McMaster between January 1996 and April 2000. Both centers are high-risk obstetrical referral centers in Ontario. At WCC, 57 women presented with suspected PE and underwent lung scan testing. At McMaster there were 64 suspected episodes of suspected PE, and lung scans were performed in 63 women (1 woman presented twice in 2 different pregnancies and was included in the analyses both times).

Therefore, when pooling the results, 120 pregnant women presenting with 121 episodes of suspected PE underwent lung scans. Of these 120 women, 60 (50.0%) were nulliparous and presented for investigations after the first trimester of pregnancy (Table 1). In the 9 women previously diagnosed as having remote venous thromboembolism (8 women) or arterial thrombosis (1 woman) prior to the pregnancy of interest, 7 women were not receiving any anticoagulants, 1 was taking aspirin (81 mg/d), and 1 was taking dalteparin (low-molecular-weight heparin) at a “prophylaxis” dose of 5000 U/d; 8 other women were receiving full-dose anticoagulation therapy prior to their presentation for VQ scan testing because of previously diagnosed acute venous thromboembolism (PE or DVT).

The mean (range) maternal age at the time of presentation was 32 (17-41) years. Half of the women were nulliparous and presented for investigations after the first trimester of pregnancy (Table 1). In the 9 women previously diagnosed as having remote venous thromboembolism (8 women) or arterial thrombosis (1 woman) prior to the pregnancy of interest, 7 women were not receiving any anticoagulants, 1 was taking aspirin (81 mg/d), and 1 was taking dalteparin (low-molecular-weight heparin) at a “prophylaxis” dose of 5000 U/d; 8 other women were receiving full-dose anticoagulation therapy prior to their presentation for VQ scan testing because of previously diagnosed acute venous thromboembolism (PE or DVT).
woman received anticoagulation despite having a normal scan because of acute myocardial infarction.

Of the 105 women who received no anticoagulation, a second maternal death occurred 2 days after she had a normal lung scan. The cause of death was the result of complications of primary pulmonary hypertension.

In the remaining 104 cases (80 normal and 24 nondiagnostic scans), no anticoagulation was given. Follow-up was undertaken by phone contact in 88 (85%) of 104 cases and through family physicians or hospital medical records in the rest. The mean (range) follow-up period was 20.6 (0.5-108) months. No VTE was reported.

**OBSTETRICAL AND PEDIATRIC OUTCOMES**

Obstetrical and pediatric outcomes for all 121 pregnancies are presented in Table 3. Two maternal deaths occurred, one from massive PE and DVT at 19 weeks of gestation (incomplete lung scan) and the other from previous diagnosis of primary pulmonary hypertension (normal lung scan).

Of the remaining 119 pregnancies, 3 women experienced spontaneous pregnancy losses (<20 weeks). In the first case, miscarriage occurred 2 days after presentation with suspected PE during the first trimester, and in the remaining 2 cases, spontaneous loss occurred 3 to 4 weeks after the women presented with suspected PE in the first trimester of pregnancy. Another woman had an elective termination of pregnancy for unrelated reasons. Two women experienced neonatal deaths after premature delivery of twins at 24 to 25 weeks of gestation. In the first case (twin neonatal deaths), a lung scan was done 5 days earlier, and in the second case (1 of the twins died), 2 weeks earlier. In both cases, threatened premature labor was already present prior to investigation for suspected PE. The rate of spontaneous abortions was 2.5% (3 of 119 pregnancies; 95% CI, 0.5%-6.1%), and the rate of infant death was 1.7% (2 of 119 pregnancies; 95% CI, 0.2%-4.8%).

Information on the mode of delivery was available for 110 of 113 pregnancies: 79 (71.8%) were delivered vaginally and 31 (28.2%) were delivered by cesarean section. Nineteen pregnancies (16.8%) were complicated by preeclampsia. The mean (range) gestational age at delivery for these pregnancies was 37 (25-42) weeks; 27 (23.8%) were preterm (<37 weeks).

The mean birth weight for 112 newborns, which included 6 sets of twins and 1 set of triplets, was 2914 g (95% CI, 2724-3104 g). We were able to obtain follow-up pediatric data on the health of 110 children (90.2% of the total 122 live births, excluding the 3 neonatal deaths). The mean (range) age of these offspring was 20.5 (0.5-100) months.

Of 110 women, 4 (3.6%; 95% CI, 0.9%-7.8%) reported congenital anomalies in their offspring. The first was a child delivered at term who had hypoplastic lungs and short stature and was diagnosed as having a rare autosomal recessive genetic disorder. The VQ scan had been performed in the mother at 22 weeks of gestation, who had received low-dose subcutaneous heparin until delivery. The second case was a child diagnosed as having duplication of ureters born to a woman who underwent VQ scanning at 11 weeks of gestation. The third case was an infant with transposition of the great vessels; the anomaly was diagnosed in utero prior to maternal VQ scanning. The fourth woman reported that her child has a small hemangioma; VQ scanning had been performed at 28 weeks of gestation (normal), and the child delivered at term.

Of 106 women, 4 (3.8%; 95% CI, 1.0%-8.2%) further reported developmental abnormalities in their offspring. In 3 pregnancies, the children were born severely premature. The first occurred in 1 of 2 twins, who was delivered at 25 weeks of gestation because of premature labor and now has mild cerebral palsy. In this case, the maternal VQ scan was performed 4 days prior to delivery, and no anticoagulation was administered. The second child was delivered at 26 weeks because of maternal preeclampsia and now has cerebral palsy and blindness; her mother had been investigated with VQ scanning in the first trimester when she presented with pneumonia. The third developmental abnormality was reported in a child delivered at 26 weeks because of maternal acute appendicitis (several days after VQ scanning), and who now has respiratory and hearing problems and retinopathy as a result of being born prematurely. The fourth child, who was delivered at term and reported to have developmental abnormalities, had seizures at age 2 years. The maternal VQ scanning was performed at 25 weeks of gestation, and no anticoagulation was given.
No childhood cancers or leukemias were reported (0%; 95% CI, 0.0%-1.0%). These rates of pregnancy and pediatric outcomes as well as the corresponding rates observed at our hospitals and in Canada over the last 10 years are given in Table 3.

<table>
<thead>
<tr>
<th>Table 3. Rates of Various Pregnancy and Pediatric Outcomes*</th>
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<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Maternal death</td>
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<tr>
<td>Spontaneous abortion</td>
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<tr>
<td>Therapeutic abortion</td>
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<tr>
<td>Infant death</td>
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<tr>
<td>Preeclampsia</td>
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<tr>
<td>Cesarean section</td>
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<tr>
<td>Preterm delivery</td>
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<tr>
<td>Congenital anomaly</td>
</tr>
<tr>
<td>Developmental abnormality</td>
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</tbody>
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* Indicates confidence interval; NA, not available.
† Based on medical records data from Women's College Campus, Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario (1997-1999).

From this study, the VQ scan results in pregnant women with suspected PE clearly differ from those performed in nonpregnant patients with suspected PE. The prevalence of high-probability VQ scans in pregnant women is very low (1.8%) compared with that reported in nonpregnant patients (about 10%); the prevalence of normal VQ scans is much higher (73.5%) in pregnant women than in nonpregnant subjects (about one third). Finally, nondiagnostic scans were found in one quarter of pregnant patients compared with one half or more in nonpregnant patients. Intuitively, these results make sense; since the mean age of the women in our study is only 32 years, they would be expected to have fewer comorbid lung conditions that would cause abnormal perfusion scans. On the other hand, the low rates of high-probability scans among pregnant women highlight the common occurrence of nonthrombotic causes of chest pain and dyspnea seen in pregnancy, particularly during the second and third trimesters.

Perhaps the decision to withhold anticoagulant therapy in pregnant patients with a nondiagnostic VQ scan (which represented about a quarter of the women in our cohort) is still of great concern for clinicians. From a study of nonpregnant patients, the use of bilateral normal leg ultrasound to rule out the presence of DVT has been validated. If DVT is diagnosed, PE is assumed to be present. If DVT is not diagnosed, withholding anticoagulant therapy is a safe strategy. The safety of adopting such an approach in pregnancy is uncertain because ultrasound diagnosis of DVT in pregnancy has never been formally evaluated. This approach might also not be safe in pregnancy because the source of the embolus during pregnancy might be in the pelvic veins, which are not readily accessible by ultrasound. Although pulmonary angiography is the criterion standard and has been advocated as a test that can be safely performed in pregnancy, the invasive nature, use of contrast, and absorption of radiation by the fetus will always remain a concern. In our review, only 2 pulmonary angiograms were actually performed.

From our study, a normal scan safely excludes PE during pregnancy (0 of 80 women; 95% CI, 0.0%-1.2%), although 2 women with normal lung scans received anticoagulation (1 for myocardial infarction and 1 was empirically treated following a scan that was lo-

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cally interpreted as nondiagnostic). Drawing conclusions from the pregnant women with nondiagnostic scans might be difficult because of the small sample size and because of the 28 women who had received therapeutic anticoagulation (all with normal leg ultrasound findings). However, in the remaining 24 women (85.7%), no subsequent VTE was reported (95% CI, 67.3%-96.0%). Therefore, in this specific cohort of women, bilateral leg ultrasound testing should be performed; if the result is positive for DVT, then treatment should be given. If negative, the need for further testing should be based on the clinician’s pretest probability. Such an approach is justifiable because in this group of women, PE is likely absent (85.7%). This strategy, however, should be further validated.

The present study is also the first to determine fetal outcomes after VQ imaging during pregnancy. In a survey published in 1998, Boiselle and coworkers reported that although most (81%) of the physicians in the United States who responded to their survey performed VQ scanning in pregnant women, 19% avoided the use of this test “to avoid fetal radiation exposure.” In addition, 52% of facilities routinely obtained written consent prior to the test. From our study, no increased risk in spontaneous conception loss or adverse pregnancy events was observed. In addition, in the follow-up of more than 90% of these offspring after a mean age of 20 months, no increase in developmental abnormalities or malignancies were reported.

In conclusion, the distribution of lung scan results in pregnant women with suspected PE differs from that in nonpregnant patients, and a high-probability scan (and presumably PE) is rare. Future prospective studies are definitely needed to confirm our findings and to optimize the therapeutic approach for pregnant women with nondiagnostic lung scans.

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