REVIEW ARTICLE

Pulmonary thromboembolism in pregnancy: Diagnostic imaging and related consideration

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Pulmonary thromboembolism (PTE) in pregnancy as a common cause of maternal death has been a challenge for both clinicians and radiologists. Choosing the appropriate modality in each case has been under question and there are also related imaging pitfalls and hesitancy about radiation exposure and using contrast media for a pregnant mother. The aim of this article is to review the imaging modalities used to investigate PTE in pregnancy, related pitfalls, and recommendations for optimizing them.

Keywords: pulmonary, thromboembolism, pregnancy

INTRODUCTION

Pulmonary thromboembolism (PTE) is among the most common causes of maternal death during pregnancy and puerperium worldwide and is the leading cause of maternal mortality in developed countries.[1] Pregnancy could be considered as an example of Virchow's triad: Hypercoagulability, Venous stasis, and vascular damage.[2] This is the reason that prevalence of thromboembolism in pregnant women is about two,[3] four,[4,5] or even five[6] times greater than for non-pregnant women of same age group. The greatest risk is in postpartum period, which is increased as approximately 30-fold in comparison to age-matched group.[3] The clinical diagnosis of PTE in normal population is usually difficult, but it is more complicated in pregnant patients, because physiologic changes of pregnancy can mimic signs and symptoms of pulmonary embolism confusing clinicians to make decision that in which situation they must pursue a diagnosis of pulmonary embolism and request imaging modalities. Apart from this, the Wells' criteria[7] and Genova score[8] used for predicting clinical probability of pulmonary embolism could not be used for pregnant population. To compound this problem, D-dimer which is the most frequent laboratory test in normal population with suspected PTE has not acceptable efficacy during pregnancy, because in normal pregnancy D-dimer is usually increased.[9] Even though, normal D-dimer levels seems to be rarely expected, especially in late pregnancy, European guidelines asserted that normal D-dimer levels can rule out PTE in pregnancy;[3] however, this is not essentially supported by American thoracic society (ATS), concerning a retrospective study[10] and two case reports[11,12] which found negative D-dimer in confirmed cases of PTE which were pregnant. In the same way, although some studies showed 100% sensitivity for D-dimer in the diagnosis of deep venous thrombosis (DVT) in pregnancy,[8,13,14] there is one case report of negative D-dimer in acute DVT during pregnancy.[15] Moreover, the most important challenge in the PTE of pregnancy is that both false-negative and false-positive diagnosis, which are not uncommon, have serious consequences for both mother and fetus. Missing the diagnosis of PTE carries high mortality rate. As Mallick and Petkova reported, undiagnosed PTE has a mortality rate of 30% which decreased to 2-8% in diagnosed and properly treated patients.[16] On the other hand, false-positive diagnosis carries potentially side effects and consequences. A diagnosis of PTE for a pregnant mother posses some important implications including need for long-term anticoagulation, avoidance of breast feeding if an oral anticoagulants is used, the potential need for prophylaxis during future pregnancies, and concern about future oral contraceptive use.[17] Anticoagulation with heparin is the mainstay of treatment in pregnancy; however, it is not devoid of any side effect.[18] CT pulmonary angiography (CTPA) and lung scintigraphy which are the most frequently used imaging modalities have also some related deficit because they expose mother and fetus to potentially risks of radiation and on the other hand diagnostic adequacy of them is lower than in non-pregnant population. The best imaging protocol is also in question. These two major problems with imaging modalities are more highlighted concerning the high mortality rate of undiagnosed cases in one hand and serious consequences of false-positive diagnosis of PTE for a pregnant woman on the other hand. Regarding to these introduced challenges, this article aim to review diagnostic adequacy, pitfalls, related radiation, routes of optimization and recommended

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Received: 29-05-2012; **Revised:** 22-07-2012; **Accepted:** 18-08-2012

protocols for these two modalities, and overall imaging modalities of PTE in pregnancy. So, PubMed search with key words of pulmonary, embolism, thromboembolism, pregnancy, scintigraphy, CT angiography, and radiation was performed, with no any date limitation up to May 2012.

DIAGNOSTIC IMAGING MODALITIES

At present, there have been no randomized trials or prospective studies in detection of PTE in pregnancy; so, there is currently no specific diagnostic algorithm for suspected PTE in pregnant population;[19] however, different methods, related documents and recommended algorithm are discussed and reviewed as follows. Lower limb compression ultrasonography (CUS) has been proposed as the first-line imaging modality for pregnant women with suspected pulmonary symptoms, suggesting PTE.[20] Although the benefit of using CUS is potential avoidance of next step radiation-associated tests (in positive cases), only small proportion of CUS studies are positive,[21,22] and it is estimated that the number of women need to do test would likely be several-fold higher, due to lower prevalence of PTE.[23] In a study by Chan *et al.*,[24] 55% of pregnant women with suspected PTE underwent either CUS or impedance plethysmography, but all results were negative. Furthermore, CUS is problematic in pregnant women due to swollen legs in the absence of DVT.[25] According to evidence-based guidelines, using the Grade of Recommendation, Assessment, Development and Evaluation (GRADE) system, by multidisciplinary panel of ATS,[23,26] it is recommended that in pregnant women with suspected PTE, CUS is performed in the presence of signs and symptoms of DVT, and in absence of signs and symptoms of DVT, CUS would not be first imaging modality; however, European society of cardiology (ESC) advocate CUS for all pregnant women with suspected PTE and a positive D-dimer test.[3] Second-line radiation-associated imaging begins usually with chest X-ray (CXR), but choosing the next step is more debated. Both Fleischner society and British thoracic society guidelines agree that CTPA is the first imaging test of choice in general population who are suspected to have PTE; however, none of them indicate which technique is preferred in pregnancy.[27,28] Ridge *et al.* had noticed considerable number of CTPA in pregnant women which had poor quality resulted in inadequacy of test and repetition of examinations.[29] Similar findings were also noticed in other studies which dealt with the incidence of diagnostic inadequacy, related causes and modification of techniques.[4,30,31] The rate of technical inadequacy of CTPA ranges between 17 to 36% according to some studies,[29,30,32,33] which was higher than non-pregnant group, but Shahir *et al.* reported that only 5.6% of pregnant women had poor quality image[34] similar to non-pregnant group.[24,35,36] Cardiac output increases during pregnancy to about 50% above non-pregnant levels[37] and this leads to earlier arrival and stronger dilution of contrast material. Shortening of "start delay" against fixed "start delay "of 20 second, as used, and also bolus triggering will allow better quality of study and this could be highlighted by using contrast agents with higher iodine concentrations (350-400 mgI/ml) or increasing flow rate of injection from 4 to 6 ml/s.[31] Respiratory physiological changes of pregnancy is other point of notice, leading to more artifactual images in pregnant women and contribute to impairment in good arterial opacification, because deep inspiration in pregnant women may increase influx of non-opacified blood via inferior vena cava into the right heart. This effect can disappear by Valsalva maneuver or request the patient to do shallow respiration during exposure.[31] Finally, using low KVP (kilovoltage) technique has shown to substantially increase contrast enhancement and also the fastest available scanners are recommended to use for pregnant women. [31] Regarding to better results of CTPA in more recent studies, and considering modification protocols which could potentially improve the quality of images together with this reality that CT scan also detect other important parenchymal findings, explain patient's symptoms, CTPA remains the mainstay imaging modality in pregnant women suspected to have PTE. On the other hand, lung scintigraphy as another main diagnostic modality for PTE evaluation uses a radio pharmaceutical agent to assess pulmonary perfusion and also usually includes a ventilation scan.[38] Several studies have focused on value of scintigraphy for evaluation of PTE in pregnancy[39,40] or compared accuracy, diagnostic adequacy and radiation of CTPA, and lung scintigraphy. [29,32-34,38,41] Diagnostic inadequacy of lung scintigraphy reported by Ridge *et al.* [29] is significantly less than CTPA (2.1% *vs* 35.7%). Also, Cahil *et al.*[32] found that non-diagnostic study is less for scintigraphy compared to CTPA 13.2% *vs* 17 which is more highlighted in subgroup with normal CXR (5.6% *vs* 30%); however, Revel *et al.*[33] reported no significant difference in the rate of indeterminate findings between these two tests. Similarly, Shahir *et al.*[34] found equivalent image quality and negative predictive value for these two modalities, and noted that the choice of study should be based on other considerations such as radiation concern, CXR findings, equipment availability, or clinical suspicion for alternative thoracic diagnosis. According to these concepts and evidence-based guidelines,[23] it is recommended to take CXR as the first radiation-associated imaging in the pregnant women with suspected PTE; then, in the patients who have normal CXR, lung scintigraphy is recommended as the next imaging test rather than CTPA; reversely, in the presence of abnormal CXR, CTPA should be next test rather than scintigraphy.

RADIATION EXPOSURE

A very important cause of hesitancy about using these radiation-associated modalities and challenge in choosing one of them is the potential risk of radiation and comparison between radiation dosages of both tests. The biological effect of radiation could be dose dependent (deterministic), has a threshold which above it severity is increased, or be non-deterministic (stochastic), which has no threshold. On the whole, in medical imaging like CTPA and lung scintigraphy, deterministic effect is unlikely and the major worry is about stochastic effects including teratogenicity and oncogenicity.[42] Fetal radiation by diagnostic imaging modalities causes no measurably increased prenatal death, malformation, or impaired mental development,[43] but carcinogenesis induced by low-level radiation is more considered, despite no direct evidence supporting it. Leukemia is the most common malignancy to develop in childhood after in utero radiation.[44] Valentine reported that in utero exposure of fetus to 0.01 Gy increases the probability of cancer risk in first and second decades of life from 0.03% to 0.04%,[45] but radiation exposure by both CTPA and scintigraphy are much lower than this value. On the other hand, the minimum dose required to produce teratogenicity is not known in human being; however, according to animal and few human studies, 0.1Gy is considered as a level beyond which teratogenic effect could be expected,[43] but similarly mean fetal radiation from CTPA and from scintigraphy are much lower than this value. Fetal dose by CTPA is about 0.03-0.66 mGy and for lung scintigraphy is more (about 0.32-0.74 mGy). This wide range of values is due to variable protocols, different equipments, and size and age of fetus. CTPA has the intrinsic advantage that fetus is not exposed directly, but in lung scintigraphy, radiotracer is injected intravenously and lead to direct fetal exposure, this is the cause that radiation exposure of fetus by lung scan is more than CTPA. Other important consideration is mother radiation which is important due to direct radiation to radiosensitive breast tissue which is more serious because the risk of breast cancer is inversely related to woman's age at the time of exposure,[46] and breast dose is higher by a factor of 2, more than defined effective dose of each test,[47] because breast tissue is very close to skin. Whole body effective dose of a woman who underwent CTPA is 4-18 mSv and for lung Scintigraphy is 1-2.5 mSv;[23] however, estimated breast dose from CTPA is 150 times more than scintigraphy.[48] Use of breast shields could reduce this dose to about 40 to 55%[49-51] or even up to 73%[52] and may be more considered in future. Also, technologist must consider other options which can reduce the amount of radiation such as reducing Z axis or manipulating milliampere, KVP, pitch, and rotation time.[53]

FETAL EXPOSURE TO CONTRAST MEDIA

The risk of fetal exposure to iodinated contrast media has not been fully investigated; however, there is no report of their teratogenicity in the literature.[6] Also, in animal studies, there is no teratogenic effect, so they are classified as category B by Federal Drug Administration (FDA).[54] The main potential risk might be due to free iodine and possible secondary neonatal hypothyroidism, which leads to this recommendation that these neonates must be evaluated for thyroid function tests in first week after birth;[6] however, in a study by Bourjeily *et al*. on 344 pregnant women underwent CTPA, there was no abnormal thyroxin level among their neonates.[55] The more important risk is for gadolinium, which has had teratogenic effect in animal studies,[56] but not approved by few human studies,[57] so it is classified as group C by FDA.[54]

ROLE OF MAGNETIC RESONANCE IMAGING

In general population, there are no sufficient studies to evaluate the role of non-contrast magnetic resonance pulmonary angiography (MRPA) for detection of PTE, and consequently, in pregnant women, its performance is not yet studied. On the other hand, gadolinium is contraindicated during pregnancy, so contrast-enhanced MRPA which is used in general population with sensitivities ranging from 31% to 92% and specificities ranging from 85% to 100% to detect PTE,[58-60] is contraindicated in pregnancy.

CONCLUSION

Clinical and paraclinical diagnosis of PTE in pregnant women is a challenge. Serious consequences of positive or negative false diagnosis in one hand, against potential risk of radiation and also increased rate of test inadequacy, on the other hand, highlight this challenge. In each case, the risks and benefits must compare to make decision, but if clinician is suspicious, the risk of mortality is far overweight the potential radiation exposure risk. If patient has leg symptoms, CUS will be the next step, otherwise CXR must be taken. In patients with normal CXR, the next recommended modality would be scintigraphy, but if CXR is abnormal, CTPA is preferred. Recommended protocols for improving diagnostic adequacy of these modalities and reducing mother and fetus radiation exposure should also be considered.

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How to cite this article: Moradi M. Pulmonary thromboembolism in pregnancy: Diagnostic imaging and related consideration. J Res Med Sci 2013;18:255-9.

Source of Support: Nil, **Conflict of Interest:** None declared.