Chapter

Peripartum Pulmonary Embolism

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Abstract

Pregnancy and peripartum increase the risk of venous thromboembolism (VTE) by many folds. Interestingly, the VTE is more common during the pregnancy, whereas the pulmonary embolism is more frequent in postpartum period. There are various risk factors for the VTE and pulmonary embolism in these patients. The important risks are improper thromboprophylaxis, obesity, and multigravida. The clinical parameters and the d-dimer are not used for diagnosis of thromboembolism during pregnancy and in the postpartum period. The compression ultrasonography (CUSG) is commonly used for VTE diagnosis; for the pulmonary embolism diagnosis, one has to consider the radiation hazard to the fetus as well as to the mothers. Ventilation/perfusion scan is the imaging of choice for patient who has respiratory signs with normal chest radiograph. If chest X-ray is abnormal with suspicion of peripartum pulmonary embolism (PPE), the choice should be computed tomographic angiography. Heparin and its derivatives remained the anticoagulation of choice for the treatment of VTE as well as the PPE, as it is a shorter acting, easy to reverse with protamine sulfate. Proper thromboprophylaxis is the key for prevention of VTE and peripartum pulmonary embolism.

Keywords: computed tomography, heparin, low-molecular-weight heparin, pregnancy, peripartum, pulmonary embolism, thrombolysis, ultrasound, ventilation/perfusion scan and warfarin

1. Introduction

The first description of a case compatible with deep venous thrombosis (DVT) appears during the Middle Ages: Guillaume de Saint-Pathus in 1271 reported as "La vie et les miracles de Saint Louis." It was about a 20-year-old Norman cobbler who suffered unilateral pain and swelling of the right calf that subsequently extended up to the thigh, and his surgeon advised him to wait and see. Patient's symptoms worsened, and he developed a leg ulcer. He was advised to visit the tomb of King Saint Louis. He spent days praying near the tomb and then decides to collect the dust below the stone covering the tomb and applied it directly to the ulcer. He was miraculously healed after this direct application and reported to survive. On the basis of the writings from the New Testament, Brenner surmised that Jesus Christ himself may have suffered from a pulmonary embolism (PE), but this hypothesis

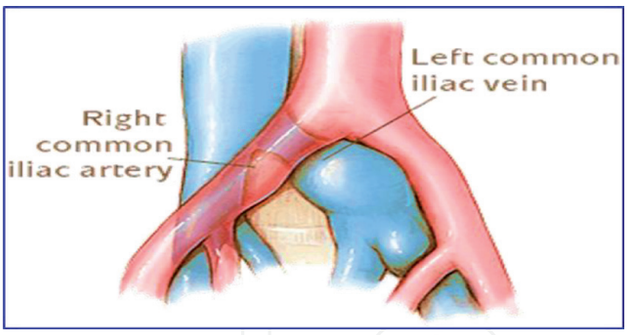

Figure 1.
May-Thurner Syndrome (narrowing of left iliac vein by crossing right iliac artery).

is debated. Avicenna warned against the risk of "particle migration" after the vein surgery: consistent with embolization of a DVT [1]. During the Renaissance physicians hypothesized that pregnancy-related DVT, which was the leading or even only cause of reported DVT at that time, was the consequence of retention of "evil humors." It was also thought that postpartum DVT was caused by retention of unconsumed milk in the legs ("milk leg"). Thus in the 1700s, breastfeeding was encouraged to prevent DVT, and bloodletting technique was used to treat DVT [1]. Virchow in 1856 demonstrated the relationship between DVT and fatal PE. The major pathologic mechanisms of venous thrombosis were first summarized in the famous Virchow's triad theorized by Andral in 1831, and in the 1920s, a consensus appeared regarding the three factors contributing to thrombosis: stasis, vessel wall alteration, and hypercoagulability: during this period a number of treatment breakthroughs were discovered by accident revolutionizing the DVT management [1].

Patients in pregnancy and postpartum are at the higher risk of thromboembolic phenomenon, particularly postpartum period. These risks are due to the normal or physiological changes of pregnancy to save the blood loss of parturition. These physiological changes will lead to the Virchow's triad. The peripartum pulmonary embolism (PPE) is 10 times more common than the nonpregnant females in the same age group. The risk of PPE increases by 20-fold in the postpartum period [2]. The incidence of pulmonary embolism during pregnancy and postpartum is 1.59 per 100,000 maternities. The venous thromboembolism (VTE) complicates 1–2/1000 pregnancies. Interestingly the VTE is common throughout all trimesters of pregnancies in contrast to pulmonary embolism which is most common in the postpartum period [3]. As described above, the VTE is equally distributed in all three trimesters of pregnancy; it is frequent in pelvic/iliofemoral veins and more common on the left side as there is compression on left iliac vein which is crossed by the right common iliac artery called May-Thurner syndrome (**Figure 1**). This is in contrast to the nonpregnant females where the VTE is common in the popliteal femoral venous system [4].

2. Risk factors

There are various risk factors for VTE and PPE in pregnancy and postpartum period. These risk factors are divided into three categories as follows (**Table 1**).

High-risk patients are mainly those patients with previous history of VTE, congenital, and acquired thrombophilia pregnant patients. The obstetric risk factors for VTE are multiple pregnancies, surgical delivery, and patients with the postpartum hemorrhage. The transient risk factors for the development of VTE and PPE are ovarian hyperstimulation syndrome, hyperemesis gravidarum, severe dehydration, surgical interventions, and immobility. There can be more than one risk factor for VTE in one patient. Obesity and multiple pregnancies were the risk factors for VTE in Middle East population [5].

Higher risk
Congenital or acquired thrombophilia
History of VTE
Obesity
Multigravida
Maternal smoking
Elderly parturient
Obstetric risk
Multiple pregnancies
Assisted reproduction
Cesarean section
Postpartum hemorrhage
Transient risk
Ovarian hyperstimulation syndrome
Hyperemesis gravidarum
Surgical intervention in the peripartum
Immobility
Systemic infections

Table 1.
Categories of risk for VTE in pregnancy.

3. Pathophysiology

The various physiological changes of pregnancy in combination with venous stasis and vascular injury (normal delivery as well as surgical deliveries) will form the Virchow's triad and a higher risk for thromboembolic phenomenon in pregnancy and postpartum period.

Venous stasis results from a hormonally induced decrease in venous tone and obstruction of venous flow by the enlarging uterus. A reduction of venous flow velocity of 50% occurs in the legs by 29 weeks of gestation and remains up to 6 weeks postpartum. In pregnant and postpartum women, the left lower extremity is the most common site of DVT. The anatomic reasons (compression of the left common iliac vein by the right common iliac artery which is accentuated by the enlarging uterus) have been attributed [6]. Endothelial damage in the pelvic veins occurs from the delivery or from venous hypertension. Normal pregnancy induces a hypercoagulable state. This hypercoagulable state is multifactorial and is thought to be due to a combination of physical and hormonal factors and hematologic changes. The physical and hormonal changes of pregnancy begin early in the first trimester. Progesterone-mediated increases in venous distensibility and capacity are apparent in the first trimester that result in increased venous stasis [6].

During pregnancy there will be increased in procoagulant factor concentration (factor VII, VIII, X, and vWF); there is a fivefold increase in the plasminogen activator inhibitor type 1 levels, whereas there is a decrease in natural anticoagulant particularly protein S and the fibrinogen levels. There is an increased resistance to protein C activity. These changes during pregnancy and parturition are for the protection from massive blood loss during delivery. The dark side of it is that it increases the risk for VTE and pulmonary embolism during pregnancy and in the peripartum period [7].

Pulmonary embolism (PE) can occur if venous thrombi detach and emblaze to the pulmonary circulation. It causes pulmonary vascular occlusion and impairs gas exchange and circulation. Larger emboli wedge in the main pulmonary artery, whereas smaller emboli occlude the peripheral arteries and peripheral PE can

cause pulmonary infarction. Obstruction of the pulmonary flow creates dead space ventilation due to alveolar ventilation exceeds pulmonary capillary blood flow. This contributes to ventilation-perfusion mismatch with increasing in pulmonary vascular resistance. As the pulmonary artery systolic pressure increases, the right ventricular afterload increases leading to a right ventricular impairment. When right ventricular failure progresses, the left ventricular filling may be impaired, and it may rapidly progress to myocardial ischemia which may occur secondary to inadequate coronary artery filling with potential for hypotension, syncope, electromechanical dissociation, or sudden death. The humoral mediator serotonin and thromboxane are released from activated platelets and trigger vasoconstriction in the healthy lungs [6].

4. Diagnosis

It is of vital importance to accurately diagnose the VTE and PPPE to avoid the misdiagnosis and increase the morbidity and mortality, whereas when falsely diagnosed, it will unnecessarily increase the risk of bleeding and increased morbidity and mortality.

The clinical manifestations such as tachypnea, dyspnea, and tachycardia may be considered as related to pregnancy. The d-dimer are not of help in pregnant and postpartum patients, as it raises changes of normal pregnancy and takes weeks in postpartum to return to the normal limits [8].

Arterial blood gas (ABG) may show respiratory alkalosis, and 12 lead ECG may be useful as it may show changes in right-sided leads. These tests are neither sensitive nor specific in the diagnosis of pulmonary embolism.

4.1 Echocardiography

Echocardiography is a noninvasive procedure and may show the indirect signs called “McConnell” sign that is the right ventricular hypokinesia and hypercontractility of the apical wall with raised pressures [9]. Echocardiograph also helps in rule of other possible etiologies such as peripartum cardiomyopathy.

Imaging studies are the corner stone for the diagnosis of the pulmonary embolism; it is of vital importance that while considering the selection of imaging studies, one has to be very careful in its effects not only on fetus but equally important for mothers as well.

4.2 Chest X-ray

All patients suspected of PE will have a chest X-ray; in pregnant patient we can cover the abdomen and do a chest X-ray. Normal chest X-ray with respiratory symptoms should raise the high index of suspicion for the pulmonary embolism. Presence of the wedge-shaped opacity with pleural base is considered as hallmark for the diagnosis of PE in chest X-ray, but this also found to be not sensitive or specific for the pulmonary embolism [10].

4.3 Bilateral compression sonography

Bilateral compression sonography of the lower limbs has an advantage of portability, noninvasive and no radiations; at the same time it diagnoses the VTE with accuracy. If it is positive and shows thromboembolic lesion, we have to start the anticoagulation therapy. But if it is negative, then we have to proceed with further diagnostic imaging studies [11].

4.4 Ventilation/perfusion (V/Q) scan

Those pregnant and postpartum patients with normal chest X-ray and suspected to have PPPE, the ventilation/perfusion (V/Q) scan is the imaging of choice. A positive V/Q scan will demonstrate a mismatch perfusion pattern. The low and high probability scans are diagnostic, as the low probability scan has up to 6% chances of having pulmonary embolism, whereas the high probability scan had up to 96% chances of PE. As most of the parturient are healthy with a normal chest X-ray, the V/Q scan has a higher diagnostic accuracy for the diagnosis of PE [12].

4.5 CT pulmonary angiography (CTPA)

CTPA is increasingly used, and it is a sensitive and specific imaging study for the diagnosis of the pulmonary embolism in both pregnant and nonpregnant patients (**Figure 2**). It is also an imaging study of choice in patients suspected of pulmonary embolism with an abnormal chest X-ray as it gives alternative diagnosis if there is no pulmonary embolism. In pregnant patients, there is an increase in cardiac output and blood volume; hence, there can be issues with quantification and time of intravenous contrast is difficult [13].

4.6 Magnetic resonance pulmonary angiography (MRPA)

It is not much evaluated in pregnancy, despite of MRI contrast (gadolinium) has no evidence of causing fetal teratogenicity. In contrast, it is highly sensitive and specific in diagnosis of PE in the general population (up to 92% and up to 100%) [14].

4.7 Digital subtraction angiography (DSA)

It is a historical gold standard for the diagnosis of PE. It is rarely performed nowadays and it also not evaluated in the pregnant population. In retrospective subpopulation evaluation, it was found that the DSA is less sensitive than CTPA with a higher reports of false negativity [15].

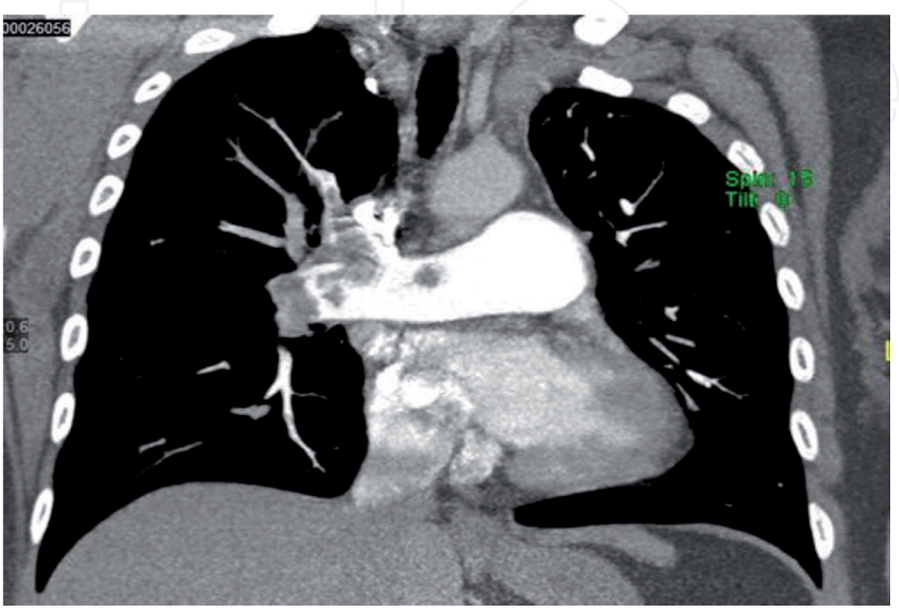

Figure 2.
CTPA showing pulmonary embolism.

In the concluding lines about the selection of imaging studies, the fear of fetal radiation exposure and adverse effects should not deprive the mother of timely and accurate diagnosis of PPE. Each of the imaging study has advantages and disadvantage (**Table 2**). Better approach is to follow the diagnostic algorithm (**Figure 3**) [16].

Imaging Study	**Benefit**	**Risk**
Computerized Tomographic Pulmonary Angiogram (CTPA)	Will show Thrombus, gives alternative diagnosis and lower fetal radiations	Higher breast radiations; use of contrast
Ventilation / perfusion Scan (V/Q Scan)	Lower maternal breast radiation	No Clinical Decisions or no alternative diagnosis
Compression Ultrasonography (CUS)	No radiations, Non Invasive; potential to detect deep venous thrombosis	Low sensitivity

Table 2.
Risk and benefits of various imaging studies.

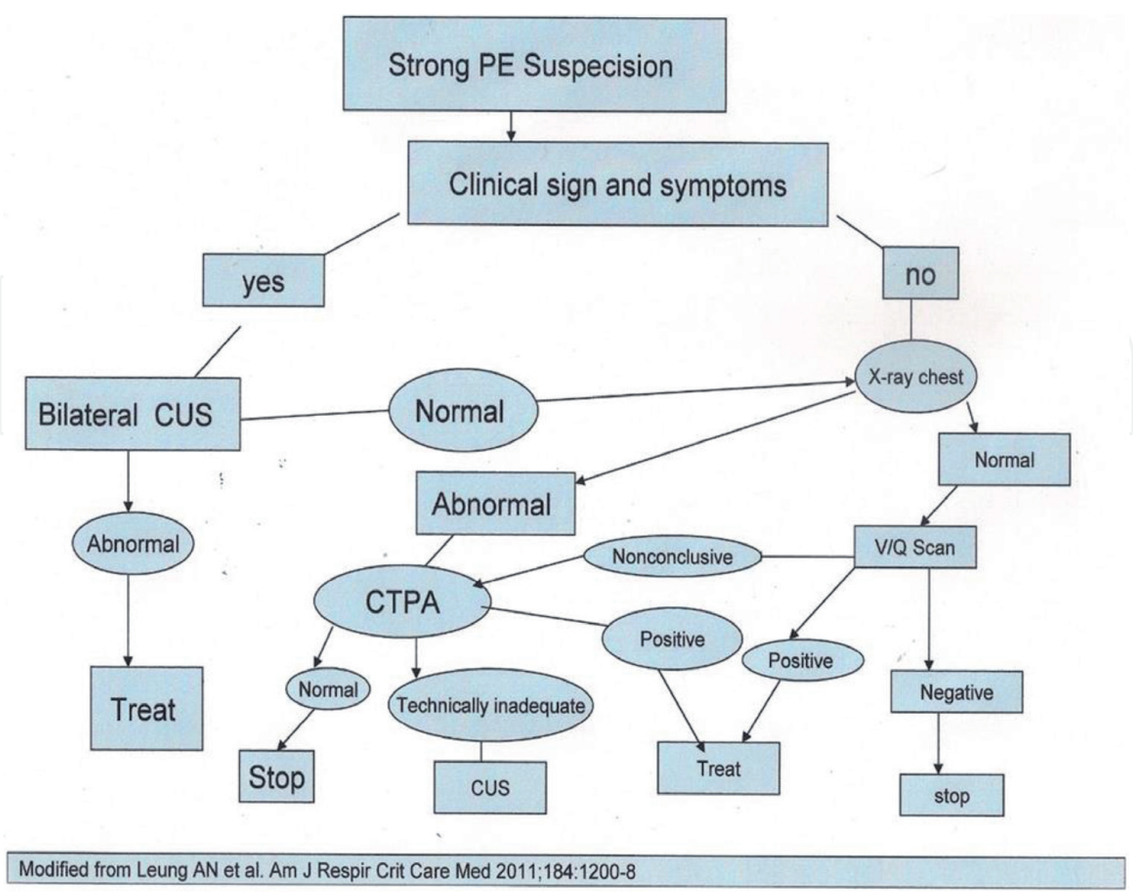

Figure 3.
Diagnostic algorithm for PPE.

The V/Q imaging is of choice when chest X-ray is normal; CTPA should have upper hand if chest X-ray is abnormal, but it had more radiation exposure to the maternal breast, with slightly increased risk of carcinoma, and it will increase the lifetime risk for breast cancer by 13.6% [17].

4.8 Single-photon emission CT ventilation/perfusion scan (SPECT V/Q)

The use of SPECT V/Q is superior to planar V/Q scintigraphy and CTPA. In nuclear medicine, the transition from planar techniques to SPECT has led to improvements in sensitivity and diagnostic accuracy. The published literature on SPECT V/Q has consistently shown improvements in sensitivity and specificity. The CTPA sensitivity in prospective multicenter PIOPED 2 study suggests that even with current-generation CT technology, CTPA fails to diagnose PE in approximately one in every six patients. If the limitations of CTPA in the detection of smaller emboli and larger emboli are missed, it is suggested that emboli not detected by CTPA are not clinically significant; it may not be true in patients with cardiorespiratory disease, and in these patients in particular, accurate detection is of vital importance. The PIOPED 2 study demonstrated that the CTPA accuracy falls further, if the scan results do not correlate with the clinical likelihood of disease, and in these circumstances, the incidence of false-positive and false-negative results is significant SPECT V/Q. Using Technegas also has the advantage of an extremely high-negative predictive value, reaching 98.5% in a large prospective series [18].

In PIOPED 2 study, over 40% of patients did not undergo CTPA because of renal impairment, contrast allergy, or too poor a state of health. This hardly endorses the notion that CTPA should be regarded as the primary screening test for the imaging of PE. Although CTPA has the advantage of being able to detect other lung diseases, it should be noted that V/Q scintigraphy can detect conditions other than PE [18].

V/Q scintigraphy in many countries continues to be done with planar imaging and using 133Xe as the ventilation agent. SPECT V/Q can be adequately performed with diethylenetriaminepentaacetic acid aerosols and in many in many countries. SPECT V/Q is clearly superior to planar imaging, and combined with recent developments in computing and camera hardware, V/Q SPECT also has the ability to quantify the extent of PE, and it is helpful in guiding treatment decisions [18]. Ventilation SPECT significantly increased the number of pregnant patients who could be classified as definitely positive or definitely negative. Only a minority of pregnant patients in the cohort had perfectly normal perfusion SPECT studies. A ventilation study is recommended as part of SPECT scintigraphy in pregnancy to improve diagnostic accuracy and reporter confidence. It also has a lower radiation dose to the mother [18].

5. Management

Heparin (indirect thrombin inhibitors) remained the commonly used anticoagulation medication in patients with thromboembolic phenomenon. It should be started when one suspected the diagnosis of pulmonary embolism. The advantages of unfractionated heparin (UFH) are shorter half-life, can be easily reversed, and have bigger molecular size; hence it cannot cross the placenta and no fetal adverse effects, and it is also not secreted into the breast milk. As there is increased blood volume during the pregnancy and peripartum period, increased heparin-binding proteins, and increased clearance of heparin through the renal system, the pregnant patient requires a higher dose of heparin to achieve the therapeutic levels. The dose of heparin may have to be increased to double to achieve the therapeutic effects [19]. The adverse effect of heparin, the fearsome, is the heparin-induced thrombocytopenia. It is divided into two types, the type 1 (also called heparin-associated thrombocytopenia or HAT) is

mainly benign condition and occurs due to negatively charged heparin that binds and destroys the positively charged platelets. HAT is a self-limiting clinical entity and does not require ant addition therapy. The HIT type 2 is immunologically mediated and can cause life-threatening thromboembolism, needs immunoassay or platelet aggregation test for diagnosis, and needs immediate stoppage of all forms of heparin to start direct thrombin inhibitors [20]. The osteopenia is another adverse effect of heparin use; it occurs due to inhibition of active metabolites of vitamin D. It increases the risk of fracture of the bones in pregnant patients [21].

5.1 Warfarin

Warfarin is a vitamin K antagonist commonly used anticoagulant in general population. It is a cost-effective medication. It is contraindicated in pregnancy as it crosses placenta and fetal teratogenic changes mainly the central nervous system defects. It also increases the risk of fetal miscarriages [22].

5.2 Thrombolysis and thrombectomy

In patients with massive pulmonary embolism causing hemodynamic deteriorations, hypoxia and right ventricular strain, immediate thrombolysis or thrombectomy is indicated (**Figure 4**) [16]. It may be associated with significant

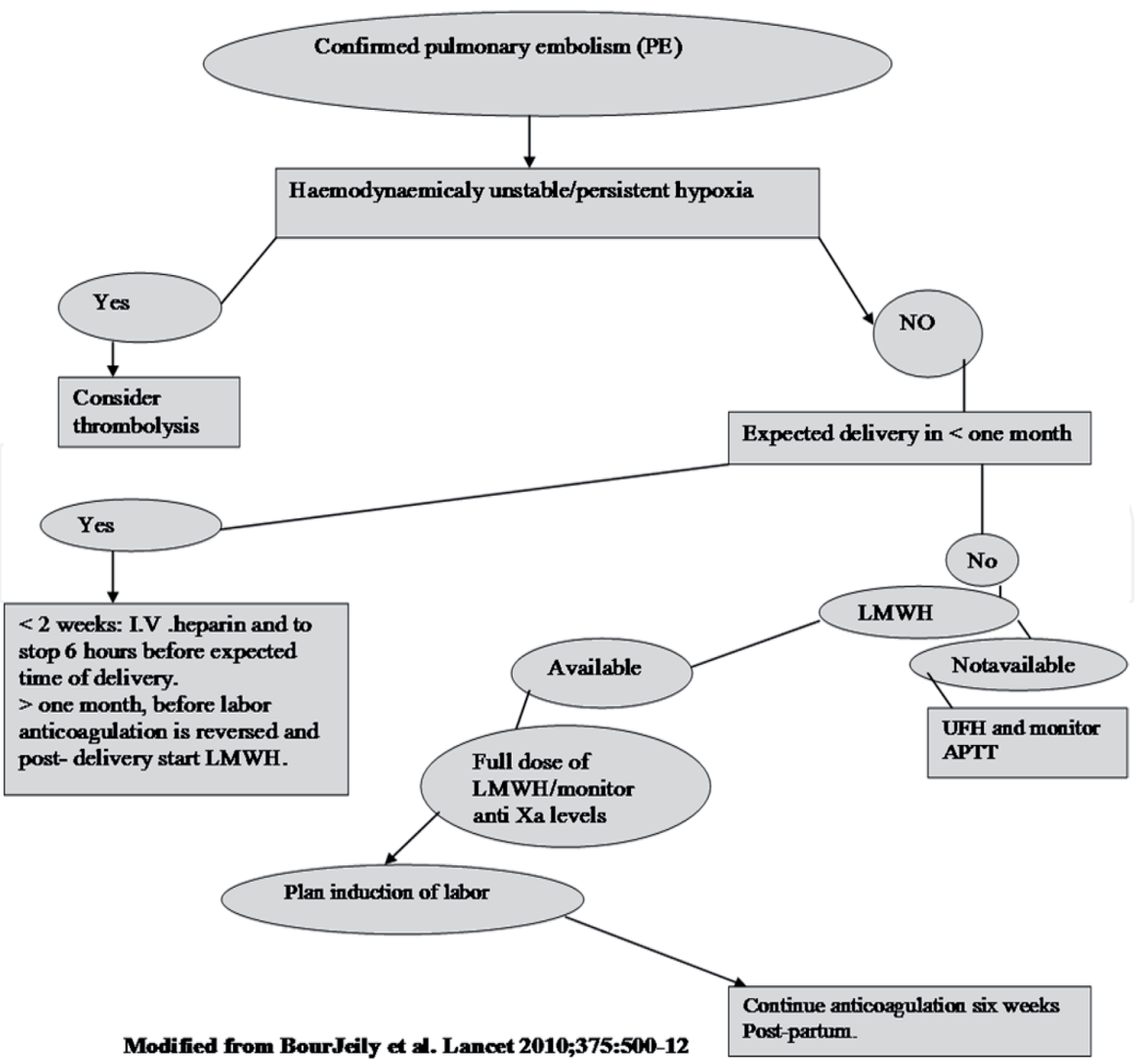

Figure 4.
Treatment of pulmonary embolism in pregnancy and postpartum.

bleeding risk in pregnant patients. A literature review found that the thrombolytic therapy in pregnancy is having a lower maternal mortality of around 1% and premature delivery and fetal loss of around 6%, which is significantly lower to the embolectomy where the fetal loss is reported up to 40%. Thrombolytic agent plasminogen activator is preferred as it does not cross placenta and does not generate antibodies [23].

Saeed et al. reviewed 13 patients with peripartum pulmonary embolism reported between 1970 and 2012, age was ranging from 21 to 39 years, and the clinical manifestations of PE were respiratory and cardiac dyspnea in nine patients, tachycardia in five, cyanosis in four, tachypnea in four, hypoxemia in two, acute respiratory distress in one, and palpitations in one patient. Heparin at therapeutic doses in nine patients was insufficient to resolve their unstable hemodynamic conditions. In all 13 patients, surgical pulmonary embolectomy was indicated because of rapidly worsening hemodynamics and cardiogenic shock. All patients underwent cardiopulmonary bypass. The thrombi were removed through an opening in the main PA in all patients. Two maternal deaths and three fetal deaths occurred leading to a 15.4% maternal mortality rate and 23% fetal mortality rate [24].

5.3 Inferior vena cava (IVC) filter

The IVC filter is indicated in patients with whom systemic anticoagulation is contraindicated or patients with recurrent embolization and patients developing recurrent embolization in spite of systemic anticoagulation. IVC filter is not free from complications, which includes perforation and migration to the surrounding structures [23].

5.4 Supportive care and vasopressors

Respiratory distress and hemodynamic instability in patients with peripartum pulmonary embolism may need invasive ventilation and hemodynamic support with vasopressors. Treating physician should be well aware of physiological changes in pregnancy. Normal blood pressure and partial pressure of carbon dioxide are lower in pregnancy. The position of the patient being nursed is again of vital importance; patient should be in lateral position to avoid IVC compression by the gravid uterus. The vasopressor should be used judiciously as they decrease the blood flow in uteroplacental circulation, whereas the persistent hypotension also poses a serious risk for the vital organ functions [25].

6. Differential diagnosis

The PPE should be differentiated from community-acquired pneumonia and peripartum cardiomyopathy. The echocardiogram will help in ruling out peripartum cardiomyopathy, and signs of sepsis will differentiate PPE from community-acquired pneumonia.

7. Prevention

Peripartum thromboembolism common, as still the prophylaxis, is adequately administered in high-risk patients [5]. Those patients with a higher risk of thromboembolism during pregnancy and peripartum should receive the thromboprophylaxis to prevent proper thromboembolisms (**Figure 5**).

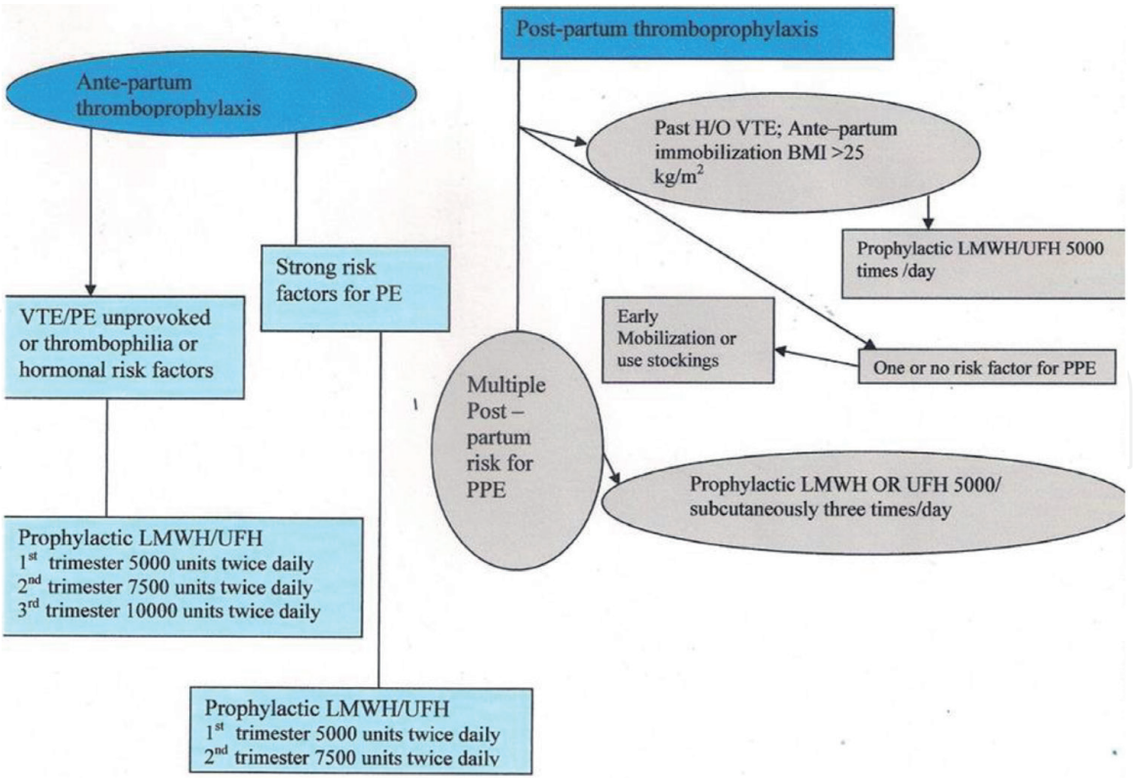

Figure 5.
Treatment of pulmonary embolism in the peripartum period (modified from Bourjeily et al. [26]).

8. Conclusion

The pregnant patients are at higher risk for VTE in all three trimester pregnancy, but in the postpartum period, they are at higher risk for the development of peripartum pulmonary embolism (PPE). The physiological changes of pregnancy and normal or surgical delivery will form Virchow's triad, hence increasing the risk of VTE by 20-folds. It is important to diagnose early and manage it properly to avoid increase in morbidity and mortality in these special groups of patients. The risk factors for VTE and pulmonary embolism in these patients are broadly categorized into high risk, obstetric risk, and transient risk factors. The diagnosis is an important aspect of the management of VTE and PPE. As the misdiagnosis will increase the morbidity and mortality, wrong diagnosis will expose these patients for unnecessary risk of hemorrhagic complications of the anticoagulant use. We have to consider the ration hazard to the fetus and mother, but at the same time, one should not deprive the mother of accurate and early diagnosis of PPE for the fear of radiations. Compression USG, V/Q scan, and CTPA can be used for the diagnosis of VTE and PPE depending on the chest conditions. PPE has to be differentiated from community-acquired pneumonia and peripartum cardiomyopathy. Heparin is the anticoagulation of choice in VTE and PPE; if patients develop heparin-induced thrombocytopenia (HIT), the choice is direct thrombin inhibitors. Warfarin has the teratogenic effect; it should not be used during the pregnancy. Risk evaluation and strict use of thromboprophylaxis will prevent or decrease the incidence of PPE and VTE.

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