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Pulmonary Embolism in Pregnancy

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minutes, immediate caesarean delivery of the fetus may result in potentially avoidable maternal mortality. In some cases, this means not waiting for theatre to be set up before you proceed. This may be unachievable in our setting, because wards are not equipped to handle an operative delivery, and getting a patient to theatre for emergency caesarean section still takes far too long in many of our institutions.

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INTRODUCTION

Maternal death is a particularly tragic event because pregnant women are usually young and healthy. Despite therapeutic advances during this century, death of pregnant women remains an important public health problem. The maternal mortality rate is used to evaluate the quality of maternal care. But in most developed countries maternal death has become an extremely rare event with rates between 5-10 per 100 000 maternities, which has weakened its value as a quality assurance indicator. There is growing interest in the use of major morbidity, so called "near miss" as an indicator of quality of hospital based obstetric care.

Since the criteria for major morbidity differs amongst institutions, the need to transfer to the Intensive care unit is an indicator of illness severity. In developing countries, and South Africa in particular, the maternal mortality rate has lost ground as a quality assurance indicator for other reasons- the overwhelming burden of HIV/AIDS has meant that more mothers are now dying during pregnancy from indirect causes, making the Maternal mortality rate a difficult tool to use in assessing the impact of obstetric related illnesses and interventions.

According to the 2007 Perinatal Education Policy document, when all indirect and direct causes of maternal death in South Africa are considered together, the following are the commonest in order of frequency:

1. nonpregnancy related infection especially AIDS
2. complications of hypertension in pregnancy
3. obstetric haemorrhage
4. pregnancy related infection especially septic abortion and puerperal sepsis
5. non pregnancy related diseases i.e. pre-existing medical conditions especially heart disease.

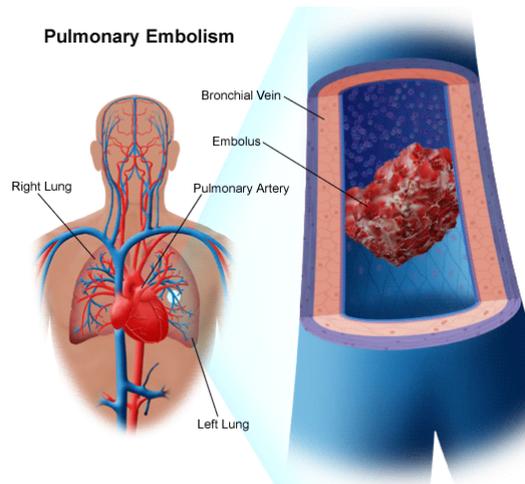
That report places the maternal mortality rate in South Africa at around 150 deaths per 100 000 maternities. As you would have noticed, in a country like ours, death from pulmonary embolism is quite rare, even placed behind anaesthesia related deaths from general and spinal anaesthetics.

This is in sharp contrast to the developed world, where death from pulmonary embolism is now considered to be one of the leading causes, if not the most common cause, of death during pregnancy and the puerperal period.

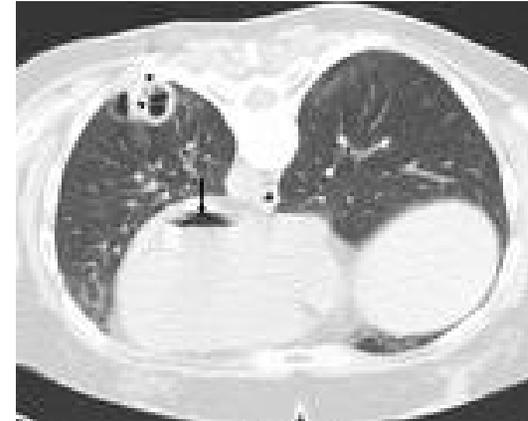
Pulmonary embolism occurs in many forms, but the scope of my talk for today will cover the following: venous thrombo-embolic disease, amniotic fluid embolism, air embolism and trophoblastic embolism.

VENOUS THROMBOEMBOLIC DISEASE

This is by far the most common type of embolic phenomena occurring in pregnancy and the postpartum period. Venous thromboembolism affects pregnant women five times more frequently than non-pregnant women of a similar age. It has been reported to complicate 1 in 1000 to 1 in 2000 pregnancies, and is reported to occur with 2-3 times this frequency in the puerperal period. Pulmonary Embolism (PE) and Deep Vein Thrombosis (DVT) represent the spectrum of one disease. Thrombi form in the deep veins of the calf and propagate into the proximal veins from which they are more likely to embolize.



If venous thrombosis remains untreated, 15- 24% of these patients will develop PE. PE during pregnancy is fatal in almost 15% of patients, and 66% of those who die, do so within the first 30 minutes of the event. Pulmonary embolism ranges from asymptomatic incidentally discovered emboli, to massive embolisation causing immediate death. Treatment of DVT can reduce the risk of death and appropriate primary prophylaxis is usually effective.



Hyperbaric oxygenation should be considered early in severe cases or when paradoxical arterial embolism is suspected. Increasing the pressure of a gas reduces its volume, which relieves obstruction and allows restoration of normal tissue oxygenation.

TROPHOBLASTIC EMBOLISM

This is a rare but life threatening complication of a hydatidiform mole. Embolization usually occurs during evacuation of the mole but can occur during the first trimester before the diagnosis of the mole has been established. Signs and symptoms are similar to an amniotic fluid embolus and treatment is supportive.

CONCLUSION

Acute collapse in pregnancy is really a diagnostic dilemma as you can see. Pulmonary embolism of varying aetiologies should be high on your differential list for pregnant patients who present with sudden cardiorespiratory or neurological symptoms during labour, delivery or any invasive procedures.

Aggressive cardiopulmonary resuscitation with left uterine displacement is imperative. It is also recognized, that when appropriately performed advanced cardiac life support has failed to restore circulation within 4-5

again to a catastrophic event. Nevertheless, cases are reported in which patients who survived an episode of AFE have gone on to have an uncomplicated next pregnancy.

Diagnosis

A pathognomonic marker for AFE is still lacking. It is still a clinical diagnosis of exclusion. The finding of fetal squamous cells or other amniotic fluid material in the maternal circulation is neither specific nor sensitive for the diagnosis of AFE. Indeed squamous cells have been retrieved from the pulmonary vasculature of patients being monitored for conditions other than AFE.

The finding of fetal material in broncho-alveolar lavage fluid may support the diagnosis of AFE especially if the patient developed pulmonary edema. Because there are fewer types of cells in broncho-alveolar fluid than venous blood, fetal cells could be found more easily.

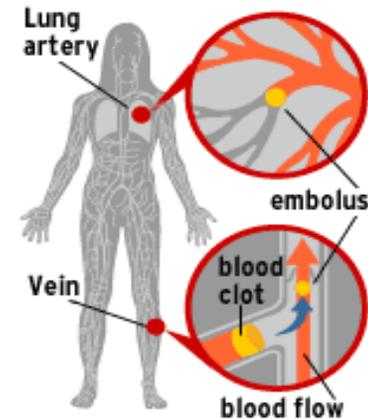
Treatment of amniotic fluid embolism consists of resuscitative measures with 3 specific aims- oxygenation, maintaining cardiac output and controlling the coagulopathy. Early aggressive CPR and support, administration of replacement blood products and prompt surgical intervention can produce improvement.

AIR EMBOLISM

This may result in cardiorespiratory collapse or the acute onset of neurologic symptoms and may be rapidly fatal. It is a rare cause of maternal mortality and is most likely underdiagnosed in patients with sudden collapse. It can occur during delivery by air entry into the subplacental venous sinuses.

The embolus travels to the right heart where it may break into microemboli and activate the immune system leading to ARDS or remain intact and block blood flow to the pulmonary outflow tract. These patients present with sudden dyspnoea, hypotension and tachycardia. Supportive care and mechanical ventilation are the only treatments.

In acute PE, anatomical obstruction is undoubtedly the most important cause of compromised physiology, but the release of vasoactive and bronchoactive agents from platelets may lead to ventilation-perfusion mismatching. As right ventricular afterload increases, tension in the right ventricular wall rises and may lead to dilatation, dysfunction and ischaemia of the right ventricle. Death results from right ventricular failure.



Recent studies have shown that the risk for DVT formation is highest in the antenatal period with up to 1/3 occurring in the first trimester. Despite the distribution of DVT throughout pregnancy however, the immediate post partum period continues to be a high risk period for pulmonary embolism. In fact, the immediate postpartum period after a caesarean section is the period of greatest risk for pulmonary embolism.

There is a clear left sided predominance of antepartum DVT. Although the exact mechanism is unknown, increased venous stasis in the left deep venous system could be the cause. During pregnancy the right iliac artery has an exaggerated compressive effect on the left common iliac vein which lies between it and the lumbar vertebrae. The enlarging gravid uterus could also selectively induce a compressive effect on the common iliac vein.

Risk factors in pregnancy

A normal pregnancy induces a hypercoagulable state. This hypercoagulable state is multifactorial and thought to be due to a combination of physical and hormonal factors as well as haematological

changes. Firstly, from early on in the first trimester progesterone mediates increased venous distensibility and capacitance which results in increased venous stasis.

The haematological changes of pregnancy are also important in the pathophysiology of thromboembolism. These include increased circulating levels of clotting factors as well as changes in fibrin generation and fibrinolysis. Circulating levels of multiple factors including factors I, II, VII, VIII, IX and X have been shown to be elevated in pregnancy and the puerperium. Protein S levels have been shown to decline with increasing gestation, although protein C activity appears to be unaffected. Platelet activation and fibrin generation is increased, whereas fibrinolytic activity is decreased. It is easy to see how the combination of the above results in a hypercoagulable state.

Other risk factors in the antenatal period include:

1. maternal age over 35 yrs
2. parity of 3 or greater
3. weight over 165lbs [75kg]
4. a personal or family history of DVT or PE
5. varicose veins
6. smoking
7. known antiphospholipid syndrome or other hypercoagulable state
8. oral contraceptive use

Several obstetric complications have also been associated with increased risk of thromboembolic disease including prolonged bed rest, instrument assisted delivery, surgical delivery, haemorrhage and sepsis, hyperemesis and disorders of fluid, electrolyte and acid-base balance.

Medical conditions that increase the risk of venous thromboembolism are heart disease, sickle cell disease, lupus, anaemia, diabetes and hypertension.

Diagnosis

The classic symptoms of thromboembolism are less specific in pregnancy, and unless a patient presents with a catastrophic collapse, the subtle signs and symptoms of leg swelling, pain, dyspnoea, tachypnoea, tachycardia and palpitations may be attributed to normal pregnancy niggles which increase towards the end of gestation. Pleuritic chest pain and haemoptysis occur more frequently in patients with pulmonary infarction. The extent of

Who gets AFE?

Amniotic fluid embolism typically occurs in the older multiparous patient in the third trimester, often in a tumultuous labour. In the midtrimester AFE is uncommon and cases are usually associated with induced abortion and following dilatation and curettage for missed abortion. Risk factors also include women with polyhydramnios and evidence of fetal aspiration.

Pathophysiology

Entry of amniotic fluid into the maternal circulation can occur through any break in the uteroplacental membranes. Such breaks can occur during normal delivery, C/S, or following placental abruption, placenta praevia or uterine rupture. There are a number of theories as to how amniotic fluid exerts its influence on the circulation.

First it can cause a mechanical obstruction leading to pulmonary hypertension, decreased left sided filling and consequently systemic hypotension. A mechanical obstruction would also cause ventilation/perfusion mismatching with resultant hypoxaemia. But numerous authors have suggested that this syndrome has little to do with mechanical obstruction but rather reflects an immunologic reaction to circulating amniotic debris.

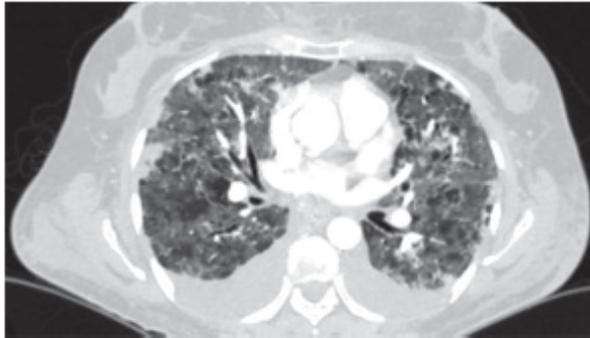
Another possibility could be an idiosyncratic massive inflammatory response to a number of different priming conditions. Clark et al have suggested the term "anaphylactoid syndrome of pregnancy" to shift emphasis away from the obsession with amniotic fluid. There are many vasoactive components in amniotic fluid which cause intense pulmonary vasoconstriction.

The alveolar capillary leak causing pulmonary oedema may be the result of extensive micro-embolic insult or following a more generalized anaphylactoid reaction mediated by leukotrienes in the amniotic fluid. Arachidonic acid metabolites are found in increased concentration in amniotic fluid of labouring parturients compared to those not in labour.

These metabolites produce most of the haemodynamic and haematological effects characterized by AFE. It is possible that an anaphylactoid reaction is precipitated by histamine or arachidonic acid metabolites in a relatively small volume embolism in atopic individuals. If this were true, repeated contact with amniotic fluid during a subsequent pregnancy should lead

AMNIOTIC FLUID EMBOLISM [AFE]

This is an extremely rare and often fatal form of embolism in pregnancy. Incidence varies in the literature from 1 in 8000 to 1 in 80 000 with a reported mortality rate of 86%. It was first described in 1926 and became a clinical entity in 1941 when Steiner and Luschbaugh published a maternal mortality case series that included eight women who had squamous cells and mucin, presumably of fetal origin, within their pulmonary vasculature.



High-resolution computed tomography scan of the chest, slice 2: ground-glass infiltrate and septal thickening predominantly in the upper thirds, as well as bilateral pleural effusion (atypical finding).

Presentation

The classical description is sudden onset of dyspnea, cyanosis and hypotension out of proportion to the blood loss, followed quickly by cardiorespiratory arrest. The US national registry for AFE has strict diagnostic criteria which includes onset during labour or 30 minutes post partum and the absence of confounding conditions that could provide an alternate explanation for signs and symptoms. Unless death is immediate, between 40% to 80% of victims will develop life threatening Disseminated Intravascular Coagulopathy. In the cerebral circulation this could account for neurological features, while in the pulmonary vascular bed it could lead to raised central venous pressure, respiratory distress, pulmonary edema and cyanosis.

symptoms depends on the thromboembolic burden. The possibility of massive pulmonary embolus should be considered in patients who have a sudden onset of near syncope or syncope, hypotension, extreme hypoxaemia or cardiac arrest.



The obstetrician faced with a pregnant patient who exhibits symptoms suggestive of a pulmonary embolus must also consider the consequences of an incorrect or false positive diagnosis and the hazards of inappropriate anticoagulation such as haemorrhage, osteoporosis and heparin induced thrombocytopenia. Contemporary approaches to the diagnosis of DVT and PE in pregnancy continue to be extrapolated from data provided by studies in the nonpregnant population.

For the diagnosis of DVT venography remains the gold standard but has a number of limitations. The risks associated with venography include pain at the time of injection of contrast, hypersensitivity to the medium and extravasation of the medium- which results in damage to the skin of the foot. Also, DVT occurring in the iliofemoral segment may not be visualized due to dilution of the contrast.

Compression ultrasound is now the most widely applied technique for investigation of DVT in pregnancy. It is non invasive, involves no radiation exposure and is without any known risks to mother or fetus. The presence of intraluminal thrombus is confirmed by gently compressing the vessel with the ultrasound transducer. In pregnancy however, it is also complicated by the difficulty in assessing the iliofemoral veins as they pass behind the gravid uterus. Indirect methods of assessing proximal venous patency are therefore required.

Impedance plethysmography is a non invasive test which works by applying a high frequency continuous current to the limb and measuring increased venous outflow resistance, or a reduction in electrical impedance in the deep veins of the proximal lower extremities. Since the basis of this test is the impedance of blood flow, it is insensitive for nonobstructive thrombi which includes the majority of isolated calf DVTs.

Previously, the diagnosis of thromboembolic disease during pregnancy was delayed or impaired by a reluctance to expose a pregnant patient and her fetus to ionizing radiation. Epidemiological studies have demonstrated that while exposure to radiation doses of less than 5 rad has not been associated with significant risk of fetal injury or abortion, there is however an increase in risk of some childhood cancers. There is an increase of one additional cancer death per 1700 1rad exposures. It should be stated that the pregnant state is not a contraindication to chest x-ray in an unwell mother. A chest x-ray is associated with fetal exposure of 0.02-0.07 mrad, while CT scan to the chest exposes the fetus to <1 rad.

The diagnosis of pulmonary embolus frequently begins with the clinical presentation and routine tests such as ECG, chest x-ray and arterial blood gas. These are however insufficient for a diagnosis or to guide management. ECG abnormalities include tachycardia or manifestations of acute cor pulmonale such as S1Q3T3 pattern, right bundle branch block, p-wave pulmonale or right axis deviation- this is more common with massive embolism than with smaller emboli. The chest x-ray is generally non diagnostic, though it may uncover an alternative diagnosis.

D-dimer assay probably has a role in the diagnosis of DVT and PE in the nonpregnant population, although its usefulness in pregnancy is controversial. The plasma D-dimer level measures the degradation products of cross linked fibrin in the circulation. These values increase throughout pregnancy with increasing gestational age, and are significantly elevated in patients with pre-term labour, pre-eclampsia and placental abruption. It should only be considered following assessment of clinical probability, and should not be performed in those with a high clinical probability of PE.

In terms of imaging for pulmonary embolism, ventilation-perfusion scanning is an appropriate first step in diagnosis as it is considered safe in pregnancy with the amount of radiation exposure within the safe range for use during pregnancy but it is not always available on site. Also, the chest x-ray should be normal and the patient should not have any co-existing cardiorespiratory disease. Standardized reporting criteria should be used and if a non-

pregnancy. Case series and reports also suggest that this may be true for the patient with inherited thrombophilia.

Caesarean delivery at least doubles the risk of venous thromboembolism, but in the otherwise normal patient the risk remains low. Randomized trials of thromboprophylaxis at the time of C/S have been small and not adequately powered to assess a decrease in the risk of DVT or PE with anticoagulation.

In the setting of unstable PE, anticoagulation alone may be insufficient. Haemodynamic instability and right heart strain may lead quickly to hypotension and death. In the case of massive PE supportive care and IV anticoagulation should be undertaken without delay.

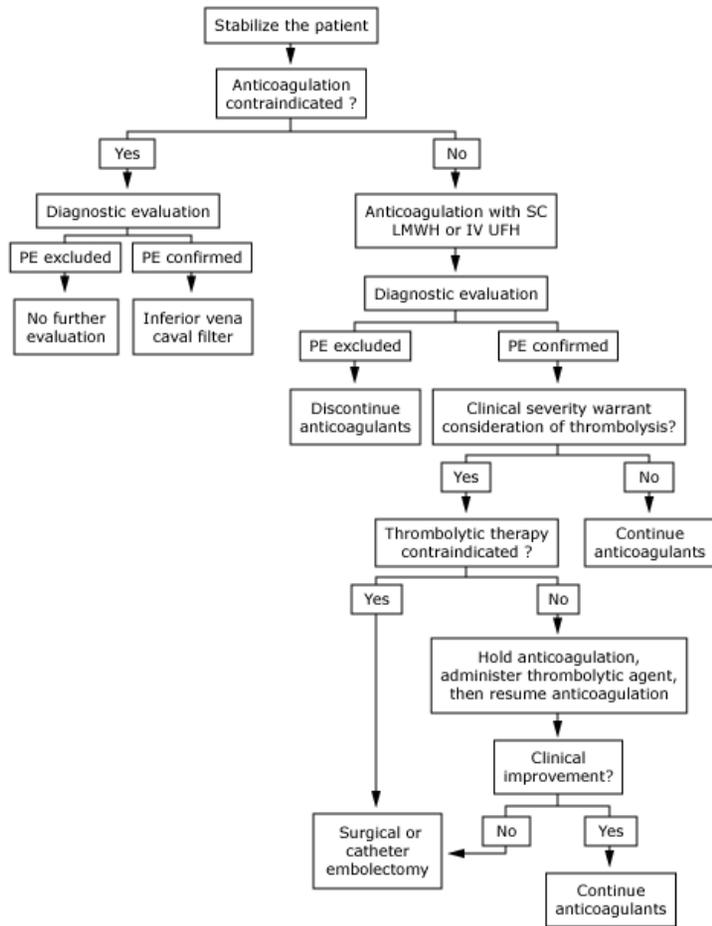
Subsequent treatment options include thrombolysis, inferior vena cava filter placement and embolectomy. Thrombolysis and embolectomy are treatments of last resort in the pregnant patient, with the only indication being pressor unresponsiveness in the setting of massive embolus.

Thrombolysis is relatively contra-indicated in pregnancy because of the presumed risk of maternal bleeding, placental abruption and fetal loss. The teratogenic effects of systemic thrombolysis in humans is uncertain. Systemic thrombolysis with tissue plasminogen activator is still considered an experimental treatment in pregnancy. Few case reports exist about its use, but it is preferred over streptokinase.

Also catheter directed mechanical fragmentation and local thrombolysis is a treatment option for PE in pregnancy. Advantages are rapid clot lysis with return to normal haemodynamics with the avoidance of systemic thrombolysis.

There are few survivors of embolectomy for massive postcaesarean PE. There are only a handful of reports in the literature. Neurological damage is a common complication, as is prolonged hospitalization. A few reports of continuous CPR during embolectomy have appeared in the literature, but these too have pretty dismal outcomes. These patients had severe liver lacerations as the swollen liver that results from massive PE –induced venous congestion is injured early on.

Acute thromboembolism in pregnancy can present in many ways, from a mild disturbance in maternal physiology to catastrophic maternal collapse, and the key in its prevention is to recognize the mother who is at risk.



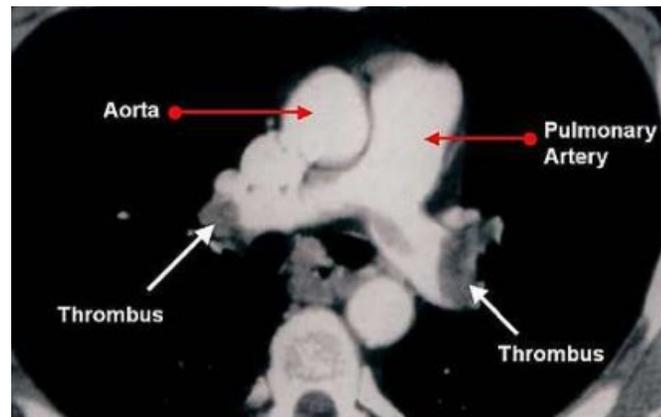
Sometimes it may be necessary to counsel against pregnancy. These conditions include mechanical heart valves, chronic thromboembolic pulmonary hypertension, a history of recurrent thrombosis while fully anticoagulated and a history of myocardial infarction.

In the antiphospholipid syndrome, an acquired thrombophilia, several studies have shown that anticoagulation improves the outcome of

diagnostic result is obtained, this should always be followed by further imaging. A normal scan however, reliably excludes PE.

Pulmonary angiography was once considered the gold standard for diagnosis of PE, but its clinical use continues to decline. It has largely been replaced by CT pulmonary angiography which has led to a revolution in diagnostic strategies. Pulmonary angiography is invasive and requires expertise to perform and interpret. Its use therefore is reserved for those patients in whom pulmonary embolism cannot be reasonably excluded. The contrast load of pulmonary angiography is similar to CT scan. The exposure to ionizing radiation depends on the number of films, but on average is less than that of a helical CT scan.

CT scanners provide newer technology, faster scanning times, increased sensitivity and better resolution. The sensitivities of spiral CT reported in the literature vary from 57% to 100% with reported specificities of between 64% to 100%. A CT scan that is negative for pulmonary embolus will reliably diagnose other abnormalities that are responsible for the patients symptoms.



Radiation exposure is the single major drawback of CT. As utilization has increased, CT has become the largest source of diagnostic medical radiation. Multidetector CT, which has revolutionized the diagnoses of so many illnesses including PE, is currently the one of highest sources of ionizing radiation patients are exposed to as part of diagnosing their disease. To put it in perspective, these doses are in the range of the atomic bomb victims with the lowest dose exposures who have shown a slightly

increased cancer mortality. The increased utilization of CT is simply because of its increased availability.

Also, the question of fetal exposure to iodinated contrast used during scanning is raised. The concern was that the free iodide in the contrast materials could induce fetal hypothyroidism and interfere with normal central nervous system development. The current consensus is that fetal exposure is likely minimal and shortlived, thus iodinated contrast is safe in pregnancy. MRI has been suggested as a replacement for CT in patients who are unable to receive contrast, but it only appears to be accurate for larger emboli and is of limited use for the ones at subsegmental level.

Echocardiography is diagnostic in massive PE but allows a firm diagnosis in only a minority of cases. Transthoracic echo can be performed at the bedside in the emergency situations. Although it can give prognostic information, it is of less value in predicting mortality than clinical features or presence of acidosis. The use of transoesophageal echo improves diagnostic accuracy by more reliably demonstrating intracardiac and intrapulmonary thrombus but availability and expertise are limited.

Ideally, imaging should be performed within 1 hour of suspected massive PE and within 24hrs in nonmassive PE.

Treatment

When pulmonary embolism is diagnosed, inpatient therapy with initial bed rest is often recommended. Parenteral anticoagulation with low molecular weight heparin or standard unfractionated heparin should be started unless contraindicated. Although they are not thrombolytic, these drugs allow the fibrinolytic system to function unopposed, ultimately decreasing the thromboembolic burden. There are currently no large trials of anticoagulants in pregnancy and recommendations for their use are based on case series and expert opinion.

Unique aspects of anticoagulation in pregnancy include both maternal and fetal issues. During pregnancy both unfractionated heparin and LMWH have shorter half-lives and lower peak plasma concentrations, necessitating higher doses and more frequent administration. Neither heparin nor LMWH crosses the placenta and both are considered safe in pregnancy.

Disadvantages of unfractionated heparin include necessity of parenteral administration, a risk of major bleeding, risk of reduced bone density, vertebral fracture and the risk of heparin induced thrombocytopenia.

Potential advantages of LMWH are less bleeding, more predictable response, a lower risk of HIT, a longer half life and less bone loss. There is also less bruising at injection sites. A disadvantage of LMWH is that it is more expensive, and its long half life may be problematic at delivery.

Monitoring of unfractionated heparin is achieved with the activated partial thromboplastin time, but LMWH requires monitoring with anti-Factor Xa activity, usually performed monthly in women who are fully anticoagulated.

Heparin should be given to patients with intermediate or high clinical probability before imaging. Although LMWH is sometimes used for the initial treatment of PE, it has not been well studied in the situation involving the pregnant patient. An advantage of intravenous unfractionated heparin over LMWH in the initial treatment of PE is that infusion can be turned off allowing the heparin to clear in a few hours. This is important in the setting of delivery, surgery or thrombolysis.

At the time of delivery, the purpose of converting to shorter acting unfractionated heparin has less to do with the risk of bleeding at the time of delivery but rather the rare possibility of an epidural or spinal haematoma with regional anaesthesia. Most anaesthetists are reluctant to place a regional if a woman has received LMWH within the previous 12-24 hrs. Depending on the risk of thrombosis, unfractionated heparin should be withheld for 6-24 hrs prior to delivery. Low dose aspirin however, may be continued.

To minimize bleeding complications, resumption of anticoagulation should be postponed until 12hr after vaginal delivery, 12 hrs after epidural placement or 24 hrs after caesarean section. After the risk of postpartum haemorrhage has decreased, women who require more than 6 weeks of anticoagulation may be bridged to warfarin. Although warfarin is contraindicated in pregnancy it is not contraindicated in breastfeeding.

Despite the increased risk of thrombosis in pregnancy and the postpartum period, most women do not require prophylactic anticoagulation. In most cases the risks of anticoagulants outweigh their benefits. The risk of bleeding from heparin or LMWH has been reported to be as high as 2%. Ideally evaluation of the woman at risk for thrombosis should be done preconceptually, or at least early in pregnancy.