

VENOUS THROMBOEMBOLISM & OBSTETRIC ANAESTHESIA

ANAESTHESIA TUTORIAL OF THE WEEK 207

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QUESTIONS

Before continuing, try to answer the following true/false questions. The answers can be found at the end of the article, together with an explanation.

1. Regarding deep vein thrombosis and pregnancy:
 - a. Of lower limb DVTs, 90% occur on the left side
 - b. The incidence is approximately 2% overall
 - c. Clinical signs are sufficient to make a definitive diagnosis
 - d. Warfarin is commonly used for management prior to delivery
 - e. Risk assessment should commence after delivery

2. Regarding pulmonary embolism in pregnancy
 - a. Radiation exposure from either V/Q scanning or CTPA is below safe levels for the fetus
 - b. Clinical signs can reliably diagnose pulmonary embolism in pregnancy
 - c. CTPA may expose the breast tissue to significant amounts of radiation
 - d. Pregnancy related changes in cardiac output increases the rate of non-diagnostic CTPA studies in pregnancy

3. Which of the following statements are true or false?
 - a. Prophylactic doses of low molecular weight heparin do not need to be stopped prior to neuraxial blockade
 - b. The longer term use of unfractionated heparin is associated with significant reductions in bone density
 - c. Venous thromboembolism is one of the leading causes of maternal mortality in the developed world
 - d. Obesity is a significant risk factor for venous thromboembolism in pregnancy

INTRODUCTION

Venous thromboembolism (VTE) and subsequent pulmonary embolism (PE), despite being relatively uncommon in pregnancy, is a leading cause of maternal mortality in the developed world. Pregnancy itself is associated with an increased risk of VTE. In addition to this, a number of other risk factors for VTE may be present, or may develop, during pregnancy. Unfortunately in a number of cases these risk factors are either unrecognised or untreated leading to preventable maternal morbidity and mortality.

This tutorial aims to highlight the importance of VTE/PE in obstetric patients and to examine the major risk factors associated with VTE/PE in pregnancy. It provides recommendations on the safe

management of labour and delivery for women on prophylactic or therapeutic anticoagulation. It will only briefly touch on issues related to the diagnosis and management of women with confirmed VTE/PE in pregnancy.

INCIDENCE AND MORTALITY

Despite pregnancy increasing the risk of VTE by 4-5 times, the overall incidence of VTE in pregnancy is low at approximately 2 per 1000 pregnancies (0.2%). The overall mortality associated with VTE or PE in pregnancy in developed countries is reported to be between 0.4-1.6 per 100,000 pregnancies. Approximately one third to one half of VTE/PE events occur in the post-partum period with the majority occurring within the first six weeks after delivery. In terms of antenatal events, approximately half occur in the first two trimesters, emphasizing the importance of early identification, risk assessment and appropriate pre-conception counseling for at risk women.

RISK FACTORS

A summary of major risk factors is shown in Table 1. All components of "Virchow's triad" are present in pregnancy. The gravid uterus obstructs venous return and in conjunction with venous dilatation and relative immobility promotes venous stasis. Pregnancy is a hypercoagulable state with an increase in several procoagulant factors and a reduction in natural anticoagulants such as protein C and S. Vessel wall injury also occurs during delivery. In addition to this there are a number of maternal specific risk factors which further increase the risk of VTE/PE. Of particular relevance to obstetric VTE, the underlying clinical condition may change during pregnancy and this may increase the risk of VTE/PE.

Maternal specific risk factors that have been identified include (but are not limited to) an age > 35, obesity, smoking, family history of VTE, varicose veins and immobility. Other than pregnancy itself, additional pregnancy specific risk factors include multiple pregnancy, preeclampsia, hyperemesis, multiparity and assisted reproduction technology. Risk factors surrounding the delivery and post-partum period include both planned and emergency caesarean delivery, placental abruption, post-partum infection and post-partum haemorrhage.

Specific risk factors

Obesity

Obesity is a common and consistent risk factor for VTE and PE in the pregnant and post-partum periods. Previous data from the UK Confidential Enquiry into Maternal and Child Health (CEMACH) have highlighted the importance of obesity as a risk factor - in one recent report two thirds of women who died from PE had a BMI > 25 and almost 20% were morbidly obese (BMI > 40). There is little evidence to guide appropriate dosing for low molecular weight heparin (LMWH) with obesity but it has been suggested that obese women should receive higher doses. A suggested weight based dosing regimen for LMWH is given in Table 2.

Previous history of VTE

A previous history of VTE is one of the most important risk factors for future VTE/PE. When assessing the risk in pregnant women it is important to ascertain whether the previous event was provoked (ie associated with an identified risk factor) as after long distance air travel or unprovoked (no identified risk factors). The risk of a recurrence in pregnancy is higher in women with a prior unprovoked or hormonally provoked (eg pregnancy or contraceptive pill) event.

Thrombophilias

A number of thrombophilias have been identified but their contribution to pregnancy associated VTE/PE is often unclear. In general and in decreasing order of risk, antithrombin deficiency, Factor V Leiden, Protein C deficiency and Protein S deficiency are the most important thrombophilias to consider. When associated with a family history of VTE/PE the risk increases dramatically.

Caesarean delivery

Both elective and emergency caesarean delivery are significant risk factors for VTE/PE. Emergency caesarean confers a higher risk than elective caesarean delivery. When compared to vaginal delivery there is approximately a four-fold increase in risk with emergency caesarean and a two-fold increase for elective caesarean deliveries. Previous UK maternal mortality reports have highlighted the seriousness of the issue and led to recommendations that all emergency caesarean deliveries receive prophylactic post-partum LMWH. In addition, elective caesarean deliveries with at least one additional risk factor (for example obesity, age >35) should also be considered for post-partum thromboprophylaxis.

Table 1: Major risk factors for VTE/PE in pregnancy (data obtained from various pregnancy related studies)

| Risk Factor | Adjusted OR |
|--|-------------|
| Age >35 | 1.4-1.7 |
| Obesity (BMI >30) | 1.7-5.3 |
| Active medical illness | 2.1-8.7 |
| Smoking | 1.7-3.4 |
| Family history VTE | 2.9-4.1 |
| Immobility | 7.7-10.1 |
| Varicose Veins | 2.4 |
| Multiparity (>2) | 1.6-2.9 |
| Multiple pregnancy | 1.6-4.2 |
| Preeclampsia | 3.0-5.8 |
| Assisted reproduction technology | 2.6-4.3 |
| Hyperemesis | 2.5 |
| <u>Additional Ante/Post Partum risk factors</u> | |
| Planned caesarean delivery | 1.3-2.7 |
| Emergency caesarean delivery | 2.7-4.0 |
| Placental abruption | 2.5-16.6 |
| Postpartum infection | 4.1-20.2 |
| Postpartum haemorrhage | 1.3-12.0 |

Table 2: Suggested weight based thromboprophylactic dosing for LMWH in pregnancy (Adapted from RCOG 2009 Green-top Guideline).

| WEIGHT | ENOXAPARIN | DALTEPARIN | TINZAPARIN |
|----------------|---------------------------------------|---------------------------------------|-------------------|
| <50 | 20 mg | 2500 units daily | 3500 units daily |
| 50-90 | 40 mg | 5000 units daily | 4500 units daily |
| 91-130 | 60 mg* | 7500 units daily* | 7000 units daily* |
| 131-170 | 80 mg* | 10 000 units daily* | 9000 units daily* |
| >170 | 0.6 mg/kg/day* | 75 units/kg/day* | 75 units/kg/day* |
| Treatment dose | 1 mg/kg 12 hourly or 1.5 mg/kg/day | 100 u/kg 12 hourly or 200 u/kg/day | 175 u/kg daily |

* may be given in two divided doses

PREVENTION OF VTE IN THE ANTENATAL PERIOD

As a significant number of VTE/PA events occur in the antenatal period it is recommended that an assessment of the risk of thromboembolism be carried in pregnant women at the earliest opportunity. Preconception counseling is important in women at particularly high risk of VTE/PA. Some women will develop complications during the pregnancy which may increase their underlying VTE/PE risk and hence their risk assessment should be repeated whenever a change in their clinical condition occurs (eg admission to hospital, post operatively) and preventative measures instituted accordingly.

Options for thromboprophylaxis

A number of options are available for thromboprophylaxis during the antenatal period, these should be considered in addition to traditional measures such as ensuring adequate hydration and mobility. Mechanical options include the use of graduated compression stockings or calf stimulation/pneumatic compression devices.

Pharmacological options are generally considered to be either LMWH or unfractionated heparin (UFH). Low dose aspirin is generally not recommended for VTE/PE prophylaxis. Warfarin crosses the placenta and is associated with an increased risk of congenital abnormalities (warfarin embryopathy) as well as spontaneous miscarriage, stillbirth and fetal and maternal haemorrhage. For this reason warfarin is generally only considered in women who are unsuitable for heparin or in some women with mechanical heart valves. Warfarin is however safe in breastfeeding and can be commenced between 5-7 days post delivery for women who need to resume long term anticoagulation.

In terms of the heparins, LMWH has a number of advantages over UFH for VTE/PE prophylaxis, especially when longer term management is required. Both are safe in pregnancy but LMWH generally requires only once daily dosing and doesn't require therapeutic monitoring. If the pregnant woman has renal impairment, creatinine clearance can be used as a guide to LMWH dosing. In addition, UFH is associated with heparin-induced thrombocytopenia and decreased bone density and osteoporosis with long term use. Symptomatic vertebral fractures have been noted in 2-3% of pregnant women receiving long term UFH in association with reductions in bone density of up to 30%. For this reason LMWH is the agent of choice in the antenatal period.

DIAGNOSIS OF VTE IN PREGNANCY

The potential consequences of VTE/PE are significant and associated with both morbidity and mortality for the expectant mother. Clinical symptoms and signs suggestive of DVT or PE can be useful for risk stratification, but because of the potential implications of the diagnosis, where resources are available objective radiological investigation is recommended. Interestingly, approximately 90% of DVTs in pregnant women are found on the left side, likely secondary to the effects of the gravid uterus compressing the inferior vena cava and compression of the left iliac vein by the right iliac artery.

D-dimer

The measurement of D-dimer levels in association with clinical assessment has been shown to be a potentially useful approach to excluding DVT in the non-pregnant population. With pregnancy the D-dimer levels increase as the gestation advances and hence pregnancy specific normal ranges are required. This may improve the utility of the combination of D-dimer testing and clinical assessment in pregnancy although robust data is currently lacking.

Suspected DVT-radiological assessment

The clinical assessment of women with a potential DVT, looking for signs such as unilateral leg swelling, redness and pain is not sensitive enough to exclude the presence of a DVT. Compression ultrasound scanning is the standard diagnostic test in many countries to assess for both proximal and distal DVT although it has a lower sensitivity for pelvic and iliac vein thrombosis. If a negative compression scan is obtained but the clinical suspicion remains high then a number of alternative options are available, including venography and magnetic resonance direct thrombus imaging.

Suspected PE-radiological assessment

As with DVT, the clinical features of a potential PE in pregnancy (shortness of breath, syncope, pleuritic chest pain) are insufficient to make an accurate diagnosis of PE and hence objective radiological assessment has also been recommended where possible. The two main options are ventilation/perfusion scanning (V/Q scan) and CT pulmonary angiography (CTPA). In the non-pregnant patient CTPA is often preferred over V/Q scanning because of its ability to diagnose other chest pathology as well as high rates of non-diagnostic V/Q scans. In contrast, in pregnant patients the rate of non-diagnostic V/Q scans is much lower and the pregnancy related increase in cardiac output increases the rate of sub-optimal and non diagnostic CTPA assessments.

Maternal and fetal radiation exposure

The potential exposure of the mother and her unborn child to radiation is of concern to both patients and their clinicians. In terms of the fetus, the radiation exposure associated with either a V/Q scan or CTPA is well below the threshold of 50mGy above which the risk of adverse effects begins to rise. CTPA exposes the mother to much higher levels of radiation and of particular concern is the exposure of the proliferating breast tissue to high levels of radiation and the potential for this to increase the lifetime risk of breast cancer. For this reason V/Q scanning is often the preferred test when available.

MANAGEMENT OF VTE IN PREGNANCY

The choice of agent for anticoagulation for the management of confirmed VTE and PE in pregnancy shares many of the principles discussed previously. There is a lack of adequately powered studies of management in pregnancy and hence many of the recommendations are extrapolated from non-pregnant studies. LMWH has been shown to be both effective and safe in the treatment of VTE and PE with advantages over UFH, particularly in relation to the development of heparin induced thrombocytopenia and reductions in bone density.

It is currently unclear whether treatment doses of LMWH should be given once daily (eg enoxaparin 1.5 mg/kg/day) or twice daily (eg enoxaparin 1 mg/kg/dose). There is increased clearance of LMWH in pregnancy which has led to the recommendation for twice daily dosing from some authors. Vena caval filters can be used in pregnancy but should be reserved for those women who are unable to be anticoagulated or who have recurrent events despite adequate anticoagulation. Thrombolysis should be reserved for women with life threatening complications of VTE such as massive PE with circulatory collapse.

MANAGEMENT OF ANAESTHESIA AND ANTI-COAGULATION IN PREGNANCY

It is important that the anaesthetist is consulted with regard to the appropriate planning of the labour and delivery process for women who are on prophylactic or therapeutic anticoagulation. Delivery will often need to be scheduled to minimise the risk of maternal and fetal haemorrhage, although it must always be remembered that despite appropriate planning some women will require delivery at short notice. Women who are on antenatal anticoagulation will almost certainly need post-partum anticoagulation and hence this should also be anticipated. The safety of neuraxial blockade in women receiving anticoagulation depends on a number of factors including the drug being used, the timing of the insertion, whether a catheter is left in situ and the timing of the catheter removal.

While the risk of a neuraxial haematoma in the obstetric population is relatively low (0.2-3.7 per 100 000 obstetric epidurals), most case reports describe periods of abnormal coagulation occurring at the insertion (and with epidural catheters, the removal) of the neuraxial block. For this reason it must be remembered that the coagulation status should be normalised for both the insertion and removal of a neuraxial blockade.

A number of consensus statements are available to guide appropriate management of neuraxial blockade and anticoagulation. In general, neuraxial blockade should be avoided in women with grossly impaired coagulation status although in some circumstances this will depend on the degree of impairment and the underlying co-morbid conditions. The insertion of an epidural catheter is generally

not recommended in women who will require full anticoagulation while the catheter is in place. All women who have had a neuraxial block should be monitored for evidence of a neuraxial haematoma for at least 24 hours after the insertion and removal and any concerns in this regard should be treated as a clinical emergency.

Anaesthesia and analgesia for labour and delivery

Women who are on prophylactic anti-coagulation

In women on prophylactic LMWH a minimum 12 hour period needs to occur between the previous dose and either the insertion or removal of a neuraxial block. There needs to be a minimum period of at least 2 hours after the insertion or the removal before the next prophylactic dose is administered, with at least 24 hours between doses. Previous experience with neuraxial blockade and twice-daily prophylactic LMWH was associated with a higher incidence of neuraxial haematoma, hence the need to ensure a 24 hour window between doses.

In women on prophylactic UFH (eg 5000 IU s/c tds) it has been suggested previously that in the non-pregnant population there does not appear to be an increased risk of neuraxial haematoma when a neuraxial block is performed in the presence of subcutaneous UFH. The risk of a neuraxial haematoma in women on prophylactic UFH may be less than with LMWH, but caution is still advisable and it may be preferable to avoid the insertion or removal of a neuraxial block within 6 hours of prophylactic UFH administration, and then to wait at least 1-2 hours after the insertion or removal before giving the next dose.

Women who are fully anti-coagulated

Women who are fully anti-coagulated prior to delivery present a number of challenges. With LMWH, this should be stopped between 24-36 hours prior to a planned induction and depending on the underlying risk, these women may require conversion to an intravenous UFH regimen. Women on intravenous UFH need at least 4-6 hours off an infusion prior to neuraxial blockade and ideally a normal aPTT should be documented prior to its insertion.

Therapeutic doses of LMWH should be withheld for at least 24 hours after delivery. In the post-delivery period it is preferable to remove any indwelling neuraxial catheters prior to recommencing full anticoagulation otherwise it complicates the removal of such catheters.

When it is considered that neuraxial blockade cannot be safely performed due to impaired maternal coagulation or recent doses of anticoagulants, a number of alternative analgesic options are available for labour pain relief. In addition to traditional techniques such as inhaled nitrous oxide, intravenous patient controlled analgesia with an opiate is gaining popularity. Of the currently available opiates, remifentanyl has a number of attractive properties although it does require close maternal observation and the use of electronic patient controlled devices, which may not be available in all settings.

Anaesthesia and analgesia for caesarean delivery

Much of the management principles are the same for women undergoing caesarean delivery.

Women who are on prophylactic anti-coagulation

The guidelines in this situation are the same for women requiring analgesia for labour and delivery. In general there should be at least a 12 hour time period between the last dose of LMWH and the performance of a neuraxial block, and at least 6 hours with UFH. It has been recommended that the first post-operative dose be withheld until 4 hours after the completion of surgery, with a 24 hour interval between ante and postpartum doses.

Women who are fully anti-coagulated

In women who are fully anticoagulated prior to delivery this should be stopped between 24 hours (LMWH) to 4-6 hours (UFH) pre-operatively. Given that these women are likely to require therapeutic anticoagulation in the post operative period it would appear sensible to avoid leaving a neuraxial catheter in place once full anticoagulation is required. The first dose of therapeutic LMWH should be given at least 24 hours postpartum. Some women will require emergent/unplanned delivery during periods of full or partial anticoagulation-in this situation the options include the reversal of UFH with protamine or the performance of general anaesthesia.

POST-PARTUM MANAGEMENT

The hypercoagulable state that exists during pregnancy takes several weeks to return to normal post delivery. Even though the majority of VTE events occur in the antenatal period, the early post-partum period represents one of the most at risk intervals and the overall risk per day is highest in the initial post-partum period. In addition to mechanical and pharmacological methods of VTE prevention attention should also be paid to ensuring early mobilisation, hydration and optimal pain relief.

Optimal duration of therapy

In women who are considered to be at intermediate risk of VTE (ie those that would warrant pharmacological prophylaxis) there is much debate as to the appropriate duration of therapy. The Royal College of Obstetricians and Gynaecologists (RCOG) recommend that a minimum of 7 days of pharmaco-prophylaxis be given. This is likely to cover the highest risk period for VTE events, although in some women a longer period of therapy may be warranted if additional risk factors are present.

In women who are considered to be at high risk of VTE the RCOG and other guidelines generally recommend a 6 week duration of therapy. A large study from Norway demonstrated that 96% of VTE events occurred in the first 6 weeks after delivery, with approximately 9% occurring in weeks 5 and 6 while data from the CEMACH reports would suggest that the risk of fatal VTE events is uncommon after 6 weeks post-partum.

When to commence prophylactic therapy in the post-partum period

Prophylactic LMWH should generally be commenced at least 4 hours after delivery or surgical completion. With high dose regimens it is recommended to wait until 24 hours after delivery because of the risks of post-partum haemorrhage, wound haematoma and intra-abdominal bleeding. With both UFH and LMWH there appears to be an increased risk of wound haematoma post-caesarean, with an incidence of approximately 2%.

In some situations it may be preferable to use UFH because of the ease of reversibility should bleeding issues arise.

NEURAXIAL HAEMATOMA

A neuraxial haematoma is a rare (between 0.2 to 3.7 per 100 000 obstetric epidurals) but potentially serious complication of spinal or epidural anaesthesia that can also occur spontaneously in the obstetric patient. It has the potential to cause permanent neurological injury as well as death. Of the cases reported, many occur in association with abnormal coagulation at either the time of the insertion, or in the situation of an epidural catheter, the removal of the catheter. For this reason it is important that the coagulation status of the mother be as normal as possible during insertion or removal. All women who have undergone neuraxial blockade should be informed of the potential warning signs of a neuraxial haematoma (among other potential complications) and provided with contact details and instructions of whom to contact should there be any cause for concern. These warning signs include persistent back pain or the onset of severe back pain, as well as unexpected sensory or motor findings (such as loss of sensory or motor function), especially when such findings are progressive in nature. It is important that these warning signs are communicated to the anaesthetist or acute pain service as a matter of urgency.

SUMMARY BOX

- Pregnancy related VTE and PE is a common cause of preventable maternal morbidity and mortality
- Most women who develop pregnancy related VTE/PE have identifiable risk factors
- Early risk assessment in pregnancy is recommended, with re-assessment performed should any change in condition occur, particularly any condition requiring hospitalization
- In addition to non-pharmacological methods, LMWH is safe and recommended for pharmacological prophylaxis
- With prophylactic LMWH there should be a minimum 12 hour period prior to neuraxial blockade, with the next dose being at least 2 hours after insertion or removal of a neuraxial block
- Prophylactic LMWH should commence between 4-8 hours post delivery, provided there is a 24 hour window between doses
- All women who receive a neuraxial block in conjunction with pharmacological VTE prophylaxis should be educated and monitored for evidence of a neuraxial haematoma
- Women at intermediate risk of VTE/PE should have 7 days of LMWH therapy whilst those at high risk should be treated for 6 weeks

ANSWERS TO QUESTIONS

- a. True
 - b. False: The incidence is approximately 2 per 1000 women, or 0.2%.
 - c. False: Clinical signs are unreliable and objective radiological assessment should be performed.
 - d. False: Warfarin is associated with an embryopathy, higher rates of congenital abnormalities, stillbirth and fetal and maternal haemorrhage.
 - e. False: Risk assessment should be performed in the early antenatal period and repeated with any change in the clinical condition.
- a. True
 - b. False: Clinical signs are unreliable and objective radiological assessment should be performed.
 - c. True
 - d. True
- a. False: Performing neuraxial blockade during periods of peak LMWH effect is associated with higher incidences of neuraxial haematoma.
 - b. True
 - c. True
 - d. True

REFERENCES and FURTHER READING

Nelson-Piercy C, MacCallum P, Mackillop L. Reducing the Risk of Thrombosis and Embolism During Pregnancy and the Puerperium Royal College of Obstetrics and Gynaecologists: Green Top Guidelines: RCOG, 2009

Kopp SL, Horlocker TT. Anticoagulation in pregnancy and neuraxial blocks. *Anesthesiol Clin* 2008; 26: 1-22