MANAGEMENT OF PREGNANT WOMEN WITH MECHANICAL HEART VALVES – A CASE BASED DISCUSSION

ANAESTHESIA TUTORIAL OF THE WEEK 214

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PREFACE

Pregnancy in women with mechanical heart valves is associated with an increased risk of maternal and fetal complications and managing the anticoagulation of these patients can be challenging. This case-based tutorial explores the peri-partum management of a woman with a prosthetic mitral heart valve who experiences complications following delivery.

INTRODUCTION

> *A 25-year-old lady presents to her medical practitioner at 6 weeks gestation. She is gravida 3 para 2 with two children delivered by spontaneous vaginal delivery at term.*
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> *During her first pregnancy she developed significant dyspnoea at 30 weeks gestation. Echocardiography demonstrated severe mitral regurgitation secondary to mitral valve prolapse. It is likely that she had asymptomatic mitral valve disease outside of pregnancy that became unmasked by the haemodynamic stress of pregnancy. Management prior to delivery consisted of diuretic therapy, rest and close observation. Following delivery she underwent mitral valve replacement with a Carbomedics metal mechanical valve and was commenced on life-long warfarin for anticoagulation. Her second pregnancy, two years later was uneventful and her baby was born by spontaneous vaginal delivery.*

What is this lady's risk of prosthetic valve thrombosis and how is this affected by her pregnancy?

What factors increase the risk of prosthetic valve thrombosis?

Prosthetic heart valves may be mechanical or tissue. Modern mechanical valves have the advantage of longevity but require life-long anticoagulation. Biological or tissue valves do not require anticoagulation, however unlike mechanical heart valves, they wear out over time often necessitating replacement.

Prosthetic heart valve thrombosis is a potentially devastating complication. The risk of valve thrombosis is quoted as being between 0.7 and 6% per patient per year (up to 1.3% for thrombosis causing obstruction to blood flow). This risk may rise to 25% in the absence of adequate anticoagulation .[1]

Thromboembolism rates in pregnant women with prosthetic heart valves have been reported to be between 7 to 23% per patient per year and half of these thromboembolic episodes arise from valve thrombosis.[1]

The risk of prosthetic valve thrombosis is higher with mechanical valves than with biological valves and is increased by the hypercoagulable state of pregnancy and any interruption to anticoagulation

therapy. Because of the differences in blood flow, the risk of valve thrombosis is higher in mechanical valves placed on the right side of the heart compared to the left and in mechanical mitral valves compared with aortic. Older mechanical valve designs are also associated with a higher risk of prosthetic valve thrombosis.

How could this lady's anticoagulation be managed during her pregnancy? What are the risks and benefits of the various options available?

Anticoagulation can be achieved using warfarin, unfractionated heparin (UFH), low molecular weight heparin (LMWH) or a combination of the above.

The risk of valve thrombosis due to inadequate anticoagulation has to be balanced against the risk of direct harm to the fetus by the anticoagulant used, along with the risk of haemorrhage to both the mother and fetus.

Warfarin

There is overwhelming evidence that warfarin offers the best protection against prosthetic valve thrombosis and avoiding this serious complication in the mother is also in the best interests of the unborn child. However, warfarin crosses the placenta and is associated with a high incidence of fetal loss and carries a risk of embryopathy. Warfarin embryopathy is characterised mainly by skeletal abnormalities and primarily occurs if warfarin is administered during the first trimester of pregnancy, particularly between the 6^{th} and 12^{th} week of gestation. The true incidence of warfarin embryopathy is difficult to establish since appropriate pathological assessment of many fetuses that are lost early in pregnancy may not occur. The incidence has been quoted as low as 1.6% of live births however skeletal deformity and nasal hypoplasia have been reported in up to 10% of babies exposed to warfarin.

The risk of birth defects secondary to warfarin is greatly reduced if warfarin is used outside the first trimester. Warfarin can also result in fetal and neonatal haemorrhage and maternal administration at the time of delivery significantly increases this risk.[2]

Heparin

Neither UFH nor LMWH cross the placenta and evidence suggests they do not directly harm the fetus. Compared with warfarin however, heparins of either type appear to provide less protection against prosthetic valve thrombosis.[2]

LMWH has advantages over UFH in that the risk of heparin-induced thrombocytopenia and osteoporosis are reduced. LMWH also has superior subcutaneous absorption, a longer half-life and a more predictable dose response.[2] A review of 81 pregnancies in 75 women with mechanical prosthetic heart valves treated with LMWH during pregnancy reported a high (8.6%) rate of valve thrombosis prompting one LMWH manufacturer to issue a warning regarding the use of its product for this purpose.[3] This followed the early termination of a study that found a higher than expected thrombosis rate in the LMWH group, compared with the UFH group, although this was subsequently thought to be due to inadequate dosing and monitoring, rather than the drug itself. [4]

Recommendations from an American consensus conference on antithrombotic therapy for patients with mechanical heart valves recommended three anticoagulation management choices: [5]

1. High dose (e.g. 17500 to 20000 units) subcutaneous UFH throughout pregnancy given twice daily, with monitoring to guide dosing (aiming for a 6-hour post-dose activated partial thromboplastin time (APTT) of twice the control level, or anti-Xa level maintained at 0.35 – 0.70 IU/ml).

2. LMWH (e.g. dalteparin 100 units/kg) subcutaneously given throughout pregnancy with anti-Xa monitoring to guide dosing (aiming for a 4-hour post dosing anti-Xa level of about 1.0 IU/ml).

3. UFH or LMWH therapy as above until the 13^{th} week of gestation, followed by warfarin until the middle of the third trimester, then restart UFH or LMWH therapy until delivery.

A large meta-analysis found no difference in the rates of miscarriage or stillbirth with any of these methods of anticoagulation. Warfarin used alone, however, led to an embryopathy rate of 6.4 %, which was completely eliminated by the use of heparin prior to 13 weeks of gestation[6].

The same analysis compared thrombosis rates (all types) and found the following:

- Warfarin throughout pregnancy - 3.9%
- Heparin throughout pregnancy - 33%
- Heparin in 1st trimester then warfarin thereafter - 9.2%

In the latter group, all of the thrombotic episodes occurred whilst on heparin. It would seem that the use of warfarin for anticoagulation in pregnant patients with prosthetic valves offers the best protection against thrombosis whilst first trimester substitution for heparin offers a great deal of protection to the unborn baby from the teratogenic effects of warfarin. There is also evidence that the use of aspirin (150mg once daily) can further reduce the risk of thrombosis in high-risk patients.[6]

Preconception counselling to enable early discussion of the additional risks that pregnancy may place on the heart should be seriously considered in women with known cardiac disease. Once pregnant, decisions on which approach to take must be discussed early and communicated to all involved in the care of her pregnancy. She should be informed of the potential risks and benefits of each option especially in the light of her own individual circumstances which may influence the risk of prosthetic valve thrombosis. Such factors include: position of valve (e.g. mitral vs. aortic), age and function of the mechanical valve, history of thromboembolic event while anticoagulated, atrial fibrillation and likely compliance with the different anticoagulation therapies.

> *As soon as her pregnancy is confirmed she is commenced on LMWH (tinzaparin, 7500 units twice daily) and her warfarin is stopped. Warfarin is recommenced at 16 weeks gestation and stopped at 36 weeks at which time she is re-started on LMWH (enoxaparin 90 mg twice daily). The different LMWH agents used reflected the different pharmaceutical formulations available to her primary and secondary care institutions. Aspirin 150 mg once daily is also administered during the periods she receives LMWH.*

Is it necessary to monitor LMWH therapy in this case and if so how can that be performed?

An advantage of treatment with LMWH is that monitoring of anticoagulation therapy is often not required due to the more predictable dose response compared to UFH. Dosing is usually calculated based on the weight of the patient but it has been shown that requirements increase as pregnancy progresses.[7] Proposed mechanisms for this effect include the increased glomerular filtration rate in pregnancy (LMWH is renally excreted), the increased volume of distribution (there is a 35-40% increase in plasma volume as pregnancy progresses) and the action of placental heparinases.

Whilst UFH interacts with anti-thrombin III to inhibit all components of the intrinsic pathway of coagulation, LMWH effectively blocks only factor Xa. A blood test can be performed at standardised intervals after LMWH administration to assess the anti-Xa levels as a marker of anticoagulation. Anti-Xa monitoring is useful in patients with renal impairment, extremes of weight and those on long-term therapy as well as high-risk cases like the patient described here.

An anti-Xa level around 1 IU/ml assayed from a blood test taken 4 hours after LMWH administration is considered to represent adequate therapeutic anticoagulation by many laboratories.

> *At 38 weeks gestation she is admitted to the delivery suite for a planned induction of labour. Her enoxaparin dose is omitted on this day with a view to recommencing anticoagulation following delivery.*
>
> *The haematology department is informed of her admission to hospital so that they can assist with laboratory monitoring of her coagulation status and provide advice in case complications arise. Blood for full blood count and coagulation is taken and a therapeutic anti-Xa level of 1.2 IU/ml is reported.*

Earlier in pregnancy she was counselled about options for pain relief in labour. She had been told that opioid analgesia or inhaled nitrous oxide and oxygen (Entonox) could be provided. In addition, she was informed that epidural analgesia was potentially acceptable if at least 24 hours had elapsed since her last dose of therapeutic LMWH. (If an epidural was inserted then subsequent LMWH dosing should not occur until 2 hours after epidural catheter removal).

With these precautions, she was advised that the risk of an epidural haematoma would be significantly reduced although she was counselled that a risk would still exist which may be higher in her case given her regular therapeutic LMWH dosing and treatment with aspirin.

Her labour proceeds uneventfully and she requires only Entonox for pain relief. A healthy boy is born by spontaneous vaginal delivery with minimal blood loss and she is discharged home later that day. Following delivery, warfarin is restarted with the aim of achieving her pre-natal therapeutic INR of between 2.0 and 3.0 and enoxaparin is administered in the dose used during her pregnancy to bridge the period until this INR is achieved.

Ten days after delivery she re-presents to hospital with a history of slow but ongoing bleeding from the vagina. Whilst her vital signs and blood tests are all within normal limits, she feels dizzy and unwell and is admitted for assessment and observation.

Her heart rate is 64; blood pressure 110/72 and she has a respiratory rate of 14.

She has continued to take warfarin since delivery and her INR is 2.0. Other investigations reveal:

Hb 11.2 g/dl
White cell count 5.8 x 10^9 / L
Platelets 195 x 10^9 / L

APTT ratio 1.20
Fibrinogen 2.8 g/dl
Anti-Xa level 1.32 IU/ml

What is the likely cause of this lady's bleeding and how should she be managed?

Although the exact quantity of blood loss is not known, this lady is most likely suffering from a post-partum haemorrhage (PPH). The traditional definition of PPH is blood loss of greater than 500ml after vaginal delivery and 1000ml after Caesarean section, but PPH is perhaps best defined as post-partum blood loss that makes the patient symptomatic (e.g. light headed, tachycardic, oliguric etc). PPH may be primary – blood loss within 24 hours of delivery, or as in this case, secondary – abnormal blood loss between 24 hours after delivery and 6 weeks post-partum.

The causes of PPH can be broadly grouped by the following four 'T's. It should be remembered that any one patient may have more than one cause of bleeding:

1. **Tone** – Uterine atony is the most common cause of PPH. Uterine contraction is essential following delivery to limit blood loss. Risk factors for atony include: an over-distended uterus (multiple pregnancy, fetal macrosomia, polyhydramnios), fatigued uterus (prolonged labour and/or augmented labour, administration of tocolytics) and an obstructed uterus (retained placenta, retained products of conception).
2. **Trauma** – Injuries sustained during delivery may cause significant amounts of bleeding.
3. **Tissue** – Retained products of conception may present as post-partum bleeding as it may prevent the uterus from adequately contracting and also act as a source of infection.
4. **Thrombin** – Any coagulation disorder acquired or inherited, may lead to PPH and also exacerbate any other cause.

The two common causes of secondary PPH are:

- Infection (endometritis).
- Retained products of conception.

Any cause of serious or potentially serious haemorrhage requires an assessment of the patient's airway, breathing and circulation, with adequate intravenous access, fluid resuscitation, cross matching of blood and measurement of haemoglobin, platelet count and coagulation. PPH in an anticoagulated patient with a prosthetic mitral valve is a serious complication and management is likely to be challenging and necessitate a multi-disciplinary approach.

This lady has no history of birth trauma nor any signs or symptoms consistent with sepsis. The only abnormal blood test is an INR of 2.0 due to warfarin therapy. Clinical examination however, reveals a poorly contracted uterus and a pelvic ultrasound examination shows retained products of conception within her uterus.

On the advice of the haematologist, her warfarin is stopped and anticoagulation is maintained with LMWH (enoxaparin 70mg twice daily).

Examination under general anaesthesia is performed with removal of products of conception. Despite this, she continues to slowly bleed and over the next 24 hours her haemoglobin falls to 6.5 g/dl and a 4 unit blood transfusion is administered. Her INR at this time is 1.1.

What other surgical options are available to control this lady's bleeding?

One option is the placement of an intrauterine balloon (e.g. Rusch, Bakri, or similar) to tamponade further bleeding.

Possible indications for this procedure are: [8]

1. Severe or refractory PPH secondary to uterine atony
2. Severe PPH due to retained products, continuing to bleed after evacuation of retained products of conception (ERPC)
3. Severe PPH secondary to coagulopathy
4. PPH following caesarean section
5. Prophylaxis if at very high risk of PPH

The balloon may be left in the uterus for 24 hours after which it is deflated and the patient observed for further blood loss.

In this case, a Rusch balloon is inserted into the uterus and inflated with saline. At 24 hours the balloon is deflated and removed, however a few hours hours later she starts to bleed again and the balloon is re-inserted.

What other options are available to treat this lady?

In view of her ongoing bleeding, other options include; complete reversal of anti-coagulation, utero-tonic therapy (if uterine atony persists) and a repeat ERPC if products of conception remain retained within the uterus.

Other, more definitive options include; interventional radiological techniques such as selective embolisation of bleeding vessels and surgical techniques including uterine artery ligation, placement of a B-lynch suture to physically compress the bleeding uterus and hysterectomy.

72 hours following ERPC her uterus is well contracted and a repeat ultrasound scan shows no further retained products of conception.

Blood tests reveal:

Hb 9.2g/dl
Platelets 162 x 10^9 / l
INR 1.1
Anti-Xa 1.1 IU/ml (therapeutic for her prosthetic mitral valve).

She continues to slowly bleed. Reversal of anticoagulation is considered but judged to place her at high risk of prosthetic valve thrombosis and surgical intervention while anticoagulated is deemed unsuitable.

She is therefore referred to the interventional radiology service for uterine artery embolisation.

What is uterine artery embolisation and how is it performed?

Uterine artery embolisation is a treatment first described in the Lancet in 1995. It has been recommended by the National Institute for Health and Clinical Effectiveness (NICE), the Royal College of Obstetricians and Gynaecologists and the Royal College of Radiologists for the treatment of heavy menstrual bleeding secondary to fibroids.[9] It has also been recommended and used successfully in the treatment of PPH.

Uterine artery embolisation is considered a safe, uterine-sparing procedure with a high success rate and a low complication rate. Its success rate for reducing haemorrhage in this clinical situation is thought to be greater than 92% - comparable to surgical uterine artery ligation but with the advantage of avoiding surgical access.[10]

The procedure is performed under local anaesthetic, with unilateral or bilateral femoral artery puncture as required. Micro-catheters are manipulated under fluoroscopic guidance into the relevant branches of the uterine artery via the anterior division of the internal iliac artery. Synthetic compounds are then injected to embolise the artery.

What are the reported complications of this procedure?

The complications of the procedure include the following:

- Immediate:
  - Groin puncture site problems including haematoma (minor 20-30%)
  - Contrast reactions
  - Uterine artery spasm
- Early:
  - Post-embolisation syndrome (pain, nausea, fever, flu-like illness with raised inflammatory markers managed symptomatically)
  - False aneurysm
  - Arterial thrombosis
- Late:
  - Vaginal discharge (16% at 12 months)
  - Amenorrhoea (7.3% at 12 months – thought to be due to temporary interference with ovarian blood supply)
  - Infection – endometritis, can be mild or very severe and may occur months after the procedure

The patient undergoes an uneventful uterine artery embolisation procedure and her intrauterine balloon is removed the following day with no subsequent bleeding. She recommences her warfarin therapy, LMWH is stopped once her INR is in the therapeutic range and she is discharged home two days later. Her recovery thereafter is uneventful.

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FURTHER READING

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