INTRODUCTION
Recent advances in management of haematological disorders have resulted in improved patient outcomes. An increasing number of pregnant women with haematological disorders are presenting during the perinatal period. It is essential for the anaesthetists to understand the pathophysiology of the disease and principles of management. This tutorial aims to focus on haemoglobinopathies and thrombophilia disorders in pregnancy and their implications on anaesthetic management.

HAEMOGLOBINOPATHIES
Haemoglobinopathies are autosomal recessive inherited disorders that are characterised by abnormalities of one of the globin chains in the haemoglobin molecule (Figure 1). This can be due to reduced synthesis of normal globin proteins (e.g. thalassaemia) or defective
synthesis (e.g. sickle cell disease). Haemoglobinopathies commonly present with anaemia of varying severity. Preconception counselling and antenatal screening for diagnosis is offered to patients with known haemoglobinopathies. Perinatal multi-disciplinary management involves haematology, obstetrics, cardiology and anaesthesiology.

THALASSAEMIA

Thalassaemia syndromes are heterogeneous groups of inherited disorders characterised by reduced or absent globin chain subunits of haemoglobin. For example, there is reduced synthesis of beta- and alpha-globin chains in beta and alpha thalassaemia respectively. This causes precipitation of globin within the red cell leading to fragility and cell death (Figure 2). Thalassaemia presents with a spectrum of clinical features.

- **Homozygous beta thalassaemia (thalassaemia major)** is a severe form of disease resulting in transfusion-dependent anaemia.
- **Homozygous alpha-thalassaemia major**, also called Hb Barts (Hydrops Fetalis) is characterised by the absence of alpha chains so gamma globulin tetrarmeres are formed. This condition is fatal in utero and results in spontaneous abortion.
- **Heterozygous form (thalassaemia trait)** is a less severe disease due to reduced synthesis of either alpha or beta chains presenting as mild to moderate microcytic anaemia.

Survival of patients with beta thalassaemia major has greatly improved with regular blood transfusions and chelation therapy. Repeated red cell transfusions eventually lead to complications due to iron deposition in major organs. Experience in the management of pregnant women with thalassemia major remains limited as it affects fertility.

Cardiac failure is the primary cause of death in 50% of patients with beta thalassaemia. Regular electrocardiography and echocardiography is recommended for monitoring cardiac function. Cardiovascular magnetic resonance imaging (MRI) can be performed to assess myocardial iron load and is safe to perform in pregnancy. MRI can assess the risk of developing heart failure and arrhythmias secondary to myocardial siderosis. Iron deposition in other organs may cause diabetes, hypothyroidism, liver dysfunction and extramedullary erythropoiesis.

Commonly used chelating agents include: desferroxamine methesylate (subcutaneous or intravenous infusion), deferiprone, and deferasirox.

**Figure 1.** Autosomal recessive inheritance of thalassaemia

### Obstetric Anaesthetic Management

<table>
<thead>
<tr>
<th>Airway</th>
<th>Extramedullary erythropoiesis can cause maxillofacial deformities (e.g. maxillary hypertrophy and high arched palate). Bag mask ventilation and intubation may be difficult.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Restrictive lung disease can be present due to lung fibrosis and chest wall deformities secondary to extramedullary erythropoiesis.</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Myocardial dysfunction is common directly due to iron deposition and secondary to chronic anaemia. A recent assessment of function by echocardiography is essential prior to anaesthesia. Measurement of plasma iron and ferritin levels guide chelation therapy in the peri-operative period.</td>
</tr>
<tr>
<td>Haematological</td>
<td>Preoperative haemoglobin should be maintained above 10 g/dL. As soon as the parturient is admitted to labour ward, a group and screen sample should be sent as these patients often have red cell antibodies (from repeated transfusions). Intraoperative cell salvage is recommended where available.</td>
</tr>
</tbody>
</table>

Neuraxial anaesthesia

Increased incidence of spinal deformities and osteoporosis can cause difficulty in establishing neuraxial blockade, but it is not contraindicated. Severity of thrombocytopenia should be evaluated before neuraxial anaesthesia in parturients with hypersplenism.

Venous thromboembolism is common in post-splenectomy patients. Use of anti-thrombotic compression stockings, LMWH and early mobilisation is recommended.

Universal precautions should always be observed. Post-operative antibiotic prophylaxis and vaccinations are indicated in patients post-splenectomy to prevent infection with encapsulated organisms.

Related comorbidities such as diabetes, liver disease and hypothyroidism should be managed in the perioperative period.
SICKLE CELL DISEASE

Sickle cell disease (SCD) is a congenital haemoglobinopathy due to mutation in chromosome 11 causing glutamate in the sixth position of beta chain to be replaced by valine, resulting in HbS instead of HbA. HbS is unstable and precipitates in hypoxic conditions (PaO₂ < 5.2 – 6.5 kPa, SpO₂ 85%). Homozygous SCD (almost 100% HbS) results in chronic haemolytic anaemia, sickle cell crises, multi-organ damage and early death. Heterozygous sickle cell trait or carrier (HbS 30–40%) results in mild anaemia. Sickling (Figure 3) in these patients will only occur if PaO₂ is below 3.2 – 4.0 kPa (SpO₂ 40%). SCD is associated with increased incidence of maternal and foetal complications such as spontaneous miscarriage, premature labour, acute painful crisis, foetal growth restriction and maternal mortality.

Obstetric Anaesthetic Management

Prevention of sickle cell crisis: Up to 50% of patients with SCD will have an acute crisis during pregnancy. Principles for prevention of sickle cell crisis:

- Effective pain management: Early labour epidural insertion is recommended for analgesia. Intra-thecal opioids, epidural analgesia and/or intravenous/oral opioids should be considered for post-operative analgesia following caesarean section. Recurrent pethidine administration should be avoided due to risk of seizures.
- Avoid dehydration: Starvation periods should be minimised, allow free oral fluids and administer intravenous fluids if needed.
- Avoid hypoxia and acidosis: Supplemental oxygen should be used to target oxygen saturations ≥95%. Shivering should be avoided as this increases oxygen consumption. Acidosis from hypercapnia should be avoided under general anaesthesia. Arterial blood gas analysis should be used if saturations are low.
- Avoid hypothermia: Maintain ambient temperature in theatre/delivery room to prevent hypothermia. Use active warming methods and monitor the patient’s temperature.
- Routine antibiotic prophylaxis is indicated as per operative procedure being undertaken.

Haematological Considerations

- There is an increased incidence of red cell antibodies due to multiple blood transfusions. This risk of alloimmunisation is significantly decreased if blood is matched for the C, E and Kell antigens. Cross-matched blood should be CMV-negative.
- If acute exchange transfusion is required for the treatment of a sickle complication, it may be appropriate to continue the transfusion regimen for the remainder of the pregnancy.
- High-risk pregnant women (e.g. multiple gestation, multiparity) should be considered for regular top-up transfusions.
- Cell salvage is contraindicated in patients with SCD due to sickling of red cells during processing of blood.
- Iron-overload is common in patients receiving repeated blood transfusions. Serum ferritin levels and the effects of iron deposition in the body should be considered and investigated (see thalassaemia).

Cardiac dysfunction can occur due to iron overload following repeated red cell transfusions. Electrocardiography and echocardiography should be performed to assess cardiac function (see thalassaemia).

Pulmonary hypertension may occur secondary to repeated veno-occlusive crises leading to lung infarction and fibrosis.

Important anaesthetic considerations in thalassemia major

- Beta thalassaemia major causes transfusion-dependent anaemia. Iron overload is treated with chelation therapy.
- Parturients potentially have a difficult airway due to maxillofacial abnormalities; secondary to extramedullary erythropoiesis.
- Oxygen delivery may be decreased from anaemia and altered oxygen carrying capacity of red cells.
- Cardiac failure is common due to myocardial iron deposits. Cardiac function should be assessed.
- Neuraxial anaesthesia can be challenging due to spinal deformities.
Important anaesthetic considerations in sickle cell disease

- Sickle cell disease is a homozygous condition where sufferers have almost 100% haemoglobin S levels. Repeated veno-occlusive crises cause widespread organ damage.
- Multidisciplinary management should involving obstetricians, anaesthetists, haematologists and the pain management team.
- Appropriate measures should be taken to prevent triggers for sickle cell crisis.
- Sickle cell disease is a contraindication for cell salvage.
- Multiple red cell antibodies are common due to repeated blood transfusions; cross-matched CMV-negative blood should be available.
- Opioid-based analgesia can be considered as an alternative to neuraxial analgesia during sickle cell crisis, however some patients exhibit opioid tolerance.

THROMBOPHILIAS

Thrombophilia is a condition characterised by a predisposition to thrombus formation due to disruption of the normal balance between pro-thrombotic and anti-thrombotic mechanisms. Inherited thrombophilias occur due to deficiency of one of the natural anti-coagulants. Thrombosis and thromboembolism were the leading cause of direct maternal deaths in the UK in 2010-12.¹

The normal physiological changes that occur in pregnancy make it a hypercoagulable state. There are also anatomical alterations during pregnancy which increase the risk of venous thromboembolism, e.g. lower limb venous stasis secondary to aorto-caval compression. Vessel wall damage occurs after vaginal delivery and caesarean section. Thus, all the three factors of Virchow’s triad are present during pregnancy and in the post-partum period, increasing the risk of thromboembolism. In those parturients with an underlying inherited thrombophilia, the risks of a thrombotic event are further increased and this may be their first presentation.

These patients are also at increased risk of developing intrauterine growth retardation, recurrent pregnancy loss, placental abruption, pre-eclampsia and also haemolysis, elevated liver enzymes and low platelets (HELLP syndrome).

Haemostatic changes during pregnancy.⁸,⁹

Pro-thrombotic changes are characterised by significantly increased levels of clotting factors VII, VIII, X, fibrinogen and von Willebrand factor. Anti-thrombotic mechanisms are less efficient due to reduced activity of protein S and increased resistance to activated protein C (APC). Activity of fibrinolytic inhibitors and plasminogen activator inhibitors are also increased.

### Inherited Thrombophilias

<table>
<thead>
<tr>
<th>Inadequate inhibition of coagulation (Higher risk of thrombosis)</th>
<th>Acquired Thrombophilias</th>
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</thead>
<tbody>
<tr>
<td>Antithrombin deficiency</td>
<td>Anti-phospholipid syndrome</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>Anti-phospholipid Antibodies: lupus anticoagulant, anti-cardiolipin antibodies, or β2 -glycoprotein 1 antibodies</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>Acquired antibodies to clotting factors</td>
</tr>
</tbody>
</table>

| Increased pro-coagulant activity (Lower risk of thrombosis) | |
|---------------------------------------------------------------| |
| Factor V Leiden mutation                                     | |
| Prothrombin G20210A mutations                                 | |

**Figure 3:** Classification of thrombophilias

**FACTOR V LEIDEN**

Factor V Leiden mutation is a common cause of inherited thrombophilia. This mutation in the factor V gene renders factor V resistant to the action of APC despite normal factor V levels. Affected parturients have a 5-10 fold increased risk of developing venous thromboembolism.

**ANTITHROMBIN DEFICIENCY**

Antithrombin is synthesised in the liver. It inhibits clotting by inhibiting thrombin and factors Ixa, Xa, Xla and Xlla. Heparin potentiates the effect of the thrombin-antithrombin complex. Congenital antithrombin deficiency is a heterozygous condition with decreased production. Antithrombin deficiency can be acquired usually due to increased consumption (e.g. sepsis, disseminated intravascular coagulation).
PROTEIN C/ PROTEIN S DEFICIENCY
Protein C is a vitamin K-dependent glycoprotein produced in the liver. It is activated by thrombin to APC on the cell membrane. APC, along with its cofactor protein S, inhibits coagulation by inactivating factors Va and VIIIa. Protein C/Protein S deficiencies lead to continued activity of factor Va and factor VIIIa, thus predisposing parturients to thrombosis.

Depending on the assessment of risk of thromboembolic events, parturients with one of the above inherited thrombophilias may receive anticoagulation during pregnancy. The anaesthetic considerations for the anticoagulated parturient are stated below.

ANTIPHOSPHOLIPID SYNDROME (APS)
This is an autoimmune condition characterised by the presence of antibodies to membrane phospholipids (lupus anticoagulant or anti-cardiolipin antibodies). The antibodies inhibit phospholipid-protein complexes which play a role in haemostasis. However, the exact mechanism for thrombosis in this condition is not known.
APS is associated with increased risk of:
- Venous and arterial thrombo-embolic episodes
- Recurrent miscarriages
- Pre-eclampsia
- Placental abortion
- Cardiac complications, such as coronary thrombosis
- Pulmonary hypertension

Patients are commonly treated with prophylactic LMWH and aspirin from early pregnancy. LMWH should be continued after delivery as the risk of thromboembolic events is highest in the post-partum period.

Prevention of venous thromboembolism during pregnancy and puerperium

- All women should have a risk assessment for venous thrombosis pre-pregnancy or during early pregnancy.
- Risk assessment should be repeated if women are hospitalised or develop other intercurrent problems. Risk assessment should be repeated again intra-partum or immediately post-partum.
- Women with previous venous thromboembolism associated with antithrombin deficiency or APS, should be offered thromboprophylaxis with higher dose LMWH (either prophylactic or therapeutic) antenatally and this should be continued for 6 weeks post-partum or until returned to oral anti-coagulant therapy after delivery.
- Women should be managed in conjunction with a haematologist with expertise in thrombosis in pregnancy.

Anaesthetic considerations for patients on low molecular weight heparin

- Central neuraxial block should be avoided for at least 12 hours after a prophylactic dose of LMWH and 24 hours after a therapeutic dose of LMWH. Use of unfractionated heparin may be considered.
- LMWH should be avoided for at least 4 hours after spinal anaesthesia/removal of epidural catheter.
- The epidural catheter should not be removed for at least 12 hours after the most recent dose of LMWH.
- The first prophylactic dose of LMWH should be given as soon as possible after delivery unless there is postpartum haemorrhage, or the parturient received neuraxial anaesthesia.
- In case of coagulopathy, severe antepartum or postpartum haemorrhage or suspected intra-abdominal bleeding, mechanical methods of thromboprophylaxis (e.g. intermittent compression stockings) help reduce risk until it is deemed safe to administer the first dose of LMWH.
- Parturients receiving antenatal LMWH before elective caesarean should have the timing and dose of LMWH adjusted to allow an adequate window for neuraxial anaesthesia.

SUMMARY
Management of pregnant women with pre-existing haematological disorders can be challenging. A clear understanding of the disease process and implications on anaesthetic management is essential. In patients with haemoglobinopathies, red cell antibodies are common due to repeated blood transfusions, therefore cross-matched blood should be readily available during the peripartum period. Particular attention should be given to the timing of central neuraxial blockade if the patient is receiving anticoagulation.
ANSWERS TO QUESTIONS

1. Thalassaemia:
   a. False: Thalassaemia is an autosomal recessive inherited disorder
   b. False: Alpha thalassaemia major (Barts Hydrops Fetalis) is incompatible with life and causes early pregnancy loss
   c. True: Cardiac disease due to myocardial iron deposition secondary to repeated blood transfusion occurs in 50% of the patients
   d. False: Intra-operative cell salvage is not contraindicated
   e. True: Characteristic facial features due to extra-medullary erythropoiesis can problems with airway management

2. Regarding anaesthetic management of sickle cell disease in pregnancy:
   a. True: Sickle cell crisis can be prevented by avoiding hypoxia, acidosis, hypothermia.
   b. True: Pain can precipitate sickle cell crisis; early labour epidural is recommended
   c. True: Red cell antibodies are common due to repeated blood transfusions
   d. False: Cell salvage causes sickling of red cells and should be avoided
   e. True: Normothermia should be maintained to prevent sickle cell crisis

3. Inherited thrombophilia disorders:
   a. True: Thrombophilia increases the risk of thrombosis
   b. False: Protein C and Protein S inhibit coagulation by inactivating factors Va and Vlla.
   c. False: Treatment should be continued for 6 weeks post-partum or until oral anticoagulation therapy is restarted
   d. False: Central neuraxial block should be avoided for 24 hours after a therapeutic dose
   e. False: Oral anticoagulants are teratogenic and should be avoided during the first trimester. Warfarin is occasionally used in high-risk parturients, e.g. mechanical heart valve.

REFERENCES AND FURTHER READING


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