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Managing haematological disorders during pregnancy

Mickey B.C. Koh, MD, PhD ^{a,b,*}, Zhen Tang Lao, MD ^c,
Elizabeth Rhodes, MD ^a

^a Dept of Haematology, St George's Hospital and Medical School, London, UK

^b Blood Services Group, Health Sciences Authority, Singapore

^c Dept of Haematology, Singapore General Hospital, Singapore

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The management of patients with pre-existing haematological disorders during pregnancy can be particularly challenging. The potential maternal and foetal toxicities from treatment regimens including chemotherapy for malignant haematological disorders mean that joint management between obstetricians and haematologists is essential for achieving good outcomes for both mother and baby. Patients with inherited or acquired disorders of haemostasis including platelets (essential thrombocythaemia) and coagulation (antiphospholipid syndrome) resulting in a pro-thrombotic state also require special consideration as pregnancy is generally considered to be a pro-thrombotic condition which could exacerbate the pre-existing disorder. The choice, timing and duration of anti-coagulation or anti-platelet therapy require careful coordination during the antenatal, perinatal as well as postnatal periods to ensure that both maternal and foetal risks are taken into consideration. Pregnancy in women with sickle cell disease has long been identified as high risk with medical and pregnancy related risks being more common compared to women without it. A range of foetal risks have also been reported but improvement in outcomes has been seen with better obstetric and haematological care and the emphasis on multidisciplinary teamwork. The meticulous management of iron overload and risks associated with repeated blood transfusions extends into the care of pregnant women with other haemoglobinopathies like thalassaemias.

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* Corresponding author. Department of Haematology, St George's Hospital and Medical School, Blackshaw Road, London SW17 0QT, UK. Tel.: +44 208 725 3545; Fax: +44 208 725 2859.

E-mail address: Mickey.koh@stgeorges.nhs.uk (M.B.C. Koh).

Sickle cell disease and pregnancy

Introduction

The term sickle cell disease (SCD) or disorder refers to a group of conditions caused by the autosomal recessive inheritance of the 'sickle' gene which is a result of a point mutation on the gene encoding the B-globin chain in haemoglobin to produce sickle haemoglobin (HbS). SCD includes homozygous HbS disease (HbSS or sickle cell anaemia) as well as the compound heterozygotes combining HbS with other abnormal haemoglobins such as HbC causing HbSC disease, HbS with B-thalassaemia causing HbSB⁺thalassaemia disease or HbSB⁰thalassaemia disease and with other rarer haemoglobins such as HbD, and HbO^{-Arab}.

SCD is the most common inherited condition worldwide with the World Health Organisation (WHO) estimating at the end of the last century that over 300 000 children born each year are affected by a haemoglobinopathy (70% of which are SCD) and 250 million people (4.5% of the world population) carrying a potentially clinically relevant haemoglobinopathy gene [1]. In the UK it is thought that there are over 12 000 individuals with the disease and that there are 300 babies with SCD born each year. It is estimated that there are 100–200 pregnancies in women with SCD each year in the UK [2,3]. SCD is prevalent in those with backgrounds from tropical regions, particularly sub-Saharan Africa, India, the Caribbean and the Middle-East with two-thirds of the 300 000 affected individuals born each year being born in Africa [1].

Pregnancy in women with SCD has long been identified as high risk with medical and pregnancy related risks being more common compared to women without SCD. A range of foetal risks have also been reported. Studies over time have not always been consistent with qualifying that risk in pregnancy but developed countries have seen an improvement in outcome with the improvement of obstetric and haematological care and the emphasis on multidisciplinary teamwork. The challenge is that as patients with SCD live longer more will go on to become pregnant with the potential of having organ impairment by time of conception. The goal in management of a woman with SCD who is of child bearing potential and wishes to conceive is to educate the patient and the health care providers, optimise her medical condition prior to conception, manage pregnancy with a multidisciplinary approach so as to reduce the risks to mother and baby and provide safe peri- and post-natal care.

Pathology and clinical presentation

Over the first year of life in an unaffected individual foetal haemoglobin (HbF) is replaced by adult haemoglobins (HbA and HbA₂). HbA is made up of 2 alpha chains and 2 beta chains whilst HbA₂ is 2 alpha chains and 2 delta chains and HbF is made of 2 alpha chains and 2 gamma chains.

Sickle cell anaemia (HbSS disease) is due to the production of abnormal haemoglobin due to a single amino-acid substitution in the beta globin chain resulting in glutamic acid being replaced by valine at the 6th position and HbS is produced instead of HbA. Someone with sickle cell trait (a carrier of SCD) will produce both HbA and HbS and is often described as HbAS [4].

HbS will form complex polymers in its deoxygenated state resulting in the abnormal shape of the red blood cells seen in sickle cells. This repeated polymerisation and depolymerisation also causes the sickle cells to be more rigid. These cells often fail to move through smaller blood vessels not just due to their rigidity but also due to an increased adhesion to other red blood cells and to the vascular endothelium by increased expression of adhesion receptors [5]. This disrupted flow then causes regional tissue hypoxia which can lead to severe pain and tissue damage.

The abnormal red blood cells are also fragile and the polymers are held together by weak forces. In SCD, the red blood cells have a greatly reduced life span (often less than 25 days compared to the 120 days of normal red blood cells) and this is the cause of the haemolytic anaemia seen in the disease. The bone marrow, despite a markedly increased erythropoiesis, cannot match production to the rate of red cell destruction [6,7].

The main sickling disorders (HbSS, HbSC and HbSBthalassaemia) have similar clinical pictures with varying severity. Patients are anaemic with notable parameters of haemolysis (reduced haemoglobin

concentration, raised reticulocyte count, raised lactate dehydrogenase and bilirubin.) They are usually hyposplenic having auto-infarcted their spleen in early childhood.

HbSS is usually the more severe phenotype with patients suffering from more complications and lower baseline Hb values compared to the compound heterozygotes such as HbSC and HbSBthal. Studies that have included patients from different genotypes show that individuals with the less severe genotypes can still suffer from severe complications during pregnancy and so all patients with a sickling disorder should be managed as those with HbSS disease [8].

Patients suffer from both acute events ('crises') and chronic organ involvement and impairment. The most common crisis is a vaso-occlusive painful bony crisis which presents, with or without a trigger such as dehydration or infection, with relentless, severe pain often requiring admission to hospital and treatment with opiates. At times acute events can be life threatening and this includes not only complications from acute painful crises but also haemorrhagic or ischaemic strokes, acute chest syndromes and overwhelming infection. Chronic haemolysis can lead to chronic kidney disease (proteinuria, papillary necrosis), pulmonary hypertension, retinopathy, avascular necrosis and leg ulcers [4].

SCD is a life limiting disease previously associated with very early mortality but patients are now surviving longer with the average life expectancy in the a study from the mid 1990s reporting a life expectancy of over 40 in those with HbSS disease (and over 60 in HbSC disease) [9]. This is continuing to improve and most affected children born in the UK are now expected to reach reproductive age, be in better health and consequently more affected women are attempting pregnancy.

Maternal and foetal risks

There are variable reports on the risks that can affect pregnant women with SCD and the foetus but it is clearly accepted that pregnancy is riskier in those with SCD than in those without. It is also clear that outcomes are improving with time.

The evidence regarding risks to both mother and foetus in SCD comes from variety of studies which are usually observational, often retrospective and sometimes the experience of a single centre.

Women with SCD appear to be susceptible to medical complications including increased infection, venous thrombo-embolism and an increase in sickle cell related painful episodes ('crises') and associated increased antenatal hospitalisation. There are also reports of increased pregnancy related complications affecting themselves and the foetus including pre-eclampsia, pregnancy induced hypertension, increased foetal morbidity, foetal growth restriction, lower gestational age at delivery (pre-term labour) and increased caesarean section rates [10–14].

One American study showed a marked fall in maternal death rate from before 1972 (4.1%) and after 1972 (1.7%) that was attributed to better medical and obstetric care. The same study showed improvement in foetal and perinatal deaths from 52.7% (pre 1972) to 22.7% (post 1972) [8].

For these reasons pregnant women should be managed as high risk, in a unit experienced in managing women with SCD with a multidisciplinary approach. Whenever possible, pregnancies should be planned, with pre-conception counselling and medical optimisation by the patient's haematologist. These women should be considered at risk, not just for medical complications (including increased sickle cell crises) but also for pre-eclampsia, preterm labour and small for dates babies [13,14].

Management of pregnancy

In the UK there are clinical guidelines from the Royal College of Obstetricians and Gynaecologists for the management of sickle cell in pregnancy and standards of care from both haematology and the sickle cell community [14,4].

Pre-conception

Ideally all women with SCD will be under the care of a haematologist since diagnosis (in the UK this should be from birth.) Family planning discussions should form part of the regular medical reviews from adolescence.

Those patients planning a pregnancy should have the opportunity to discuss the risks involved to both themselves and the foetus. At this stage they should have an up – to – date organ assessment to identify any complications of SCD which may need special consideration during pregnancy, particularly nephropathy, pulmonary hypertensions, iron overload and retinopathy. Investigations should include blood pressure measurement, echocardiogram, urinalysis for protein content, fundoscopy, iron overload assessment if on a regular transfusion programme by serum ferritin measurement and appropriate imaging. In those with organ impairment and abnormal investigational results, the relevant specialties should be involved in a discussion with patient and the haematologists about increased risks and specific management.

Preconception is also the best time to provide genetic counselling. Testing of the baby's father for their haemoglobinopathy status should be discussed and offered. This allows the identification of high-risk partnerships (where the chances of having an affected offspring is 25% or greater) and the couple can discuss the inheritance patterns, options for pre-natal diagnosis and termination [15].

Women planning a pregnancy should have a full medication review. Prophylactic penicillin (routinely taken as prophylaxis due to their hyposplenic state) should be continued as should their routine folic acid. All patients should be up to date with their vaccinations as well (patients in the UK are recommended to have had at least 1 vaccine against Meningococcal C and Haemophilus influenza B, 5 yearly vaccinations against pneumococcus, yearly influenza vaccinations and Hepatitis B vaccination.) [4].

There may also be medications that should be stopped before conception and during pregnancy due to its effect on foetal growth and development. This includes hydroxycarbamide often used for disease modification, iron chelators for iron overload, ACE-inhibitors used in sickle nephropathy and these patients should have a management plan for alternative strategies when the normal medication cannot be continued. There should also be a plan for analgesia requirements during pregnancy (it is recommended to avoid non-steroidal anti-inflammatory drugs (NSAIDs) before 12 weeks and after 28 weeks of pregnancy and to avoid tramadol).

Antenatal

Once pregnancy is confirmed women with SCD should have their antenatal care provided by a multidisciplinary team. The improvement in maternal and foetal morbidity has been attributed to the improvement in obstetric and haematology care and specifically to the multidisciplinary work in the form of comprehensive centres in at least one large US study [10].

Patients should be managed by the team who care for the high-risk pregnancies.

All reviews and investigations that have been mentioned in the pre-natal section should be done as soon as possible if preconception planning has not occurred.

During pregnancy a woman's management can be considered as partly additional obstetric care and partly management of sickle cell during the pregnancy.

Additional obstetric care

Additional medication that is given in the UK includes low dose aspirin as prophylaxis against pre-eclampsia [16] and consideration of low-molecular-weight-heparin if additional risk factors are present and when hospitalised including previous personal VTE, family history of VTE, known thrombophilia, other medical co-morbidities, parity, older age, obesity, severe varicose veins, pre-eclampsia, immobility, multiple pregnancy and current sepsis or dehydration [17] Iron supplementation should only be given in the presence of documented iron deficiency (anaemia will occur due their SCD, some patients will also be microcytic due to their haemoglobinopathy and some patients will actually have increased iron stores due to previous transfusions.). Folic acid supplementation, however, should be continued throughout pregnancy.

All patients should have a blood sample sent for red cell antibodies and full extended phenotype so if blood transfusions are required blood can be matched against full rhesus type.

Due to the increased risk of urine infections [10], pregnancy induced hypertension and pre-eclampsia, blood pressure measurements and urinalysis should performed at every visit and in the UK, monthly urine samples are sent for microbiological evaluation. In addition to the routine

scanning offered for all pregnant women, it is recommended that extra growth scans be performed every 4 weeks after 24 weeks. A viability scan should also be offered in early pregnancy (7–9 weeks gestation) [14].

Management of sickle cell disease during pregnancy

It is well documented that there is often an increased risk of sickle cell crises during pregnancy and increased hospitalisation rates. The patients should be educated about new triggers during pregnancy that may precipitate a crises (dehydration, vomiting, infection and over-exertion).

Acute sickle crises are not uncommon in pregnancy and as in the non-pregnant cohort; an acute painful crisis is the most common presentation. Patients should be encouraged to present for medical review early and there should be a low threshold for admission.

Crises should be managed urgently and management is generally similar to that of patients who aren't pregnant except for extra meticulous care about what medication including analgesia is allowed during pregnancy. In the case of an acute painful crisis patients should be seen in timely fashion and have analgesia offered within 30 minutes (often crises require parenteral opiates and patients may have their own protocols or pain plans). Patients should be reviewed for underlying triggers and any suggestion of infection or dehydration should be treated. It is important to be vigilant for other severe manifestations of sickle cell crises such as an acute chest syndrome (chest pain, hypoxaemia, fever, lung infiltrates on radiographs) and stroke. Patients often require supplementary hydration and oxygen as well. Life threatening crises may require urgent exchange blood transfusion and management on a critical care unit [4,13,14].

Patients requiring analgesia should be reviewed regularly to monitor efficacy of their medication and for any signs of toxicity. Patients who are admitted should be managed on a haematology ward if they are presenting in early pregnancy and those presenting later should be managed in a level 2 obstetric bed [14].

There is no conclusive evidence that routine or prophylactic blood transfusions are of benefit during pregnancy though patients may benefit on individual basis. Some studies show improvement in painful crises but no effect on maternal or foetal outcomes [19]. Transfusion is not without risk or burden; in particular the risk of alloimmunisation (the formation of additional red cell allo-antibodies) can be significant. Patients with SCD are immunogenic and it is not uncommon for them to form antibodies that can lead to delayed haemolytic transfusion reactions, haemolytic disease of the foetus and the newborn and also make future cross matching of blood difficult. Blood is routinely fully matched for rhesus antibodies and Kell in the UK to reduce this risk.

Transfusions are usually reserved for the acute management of severe crises and this is often an exchange transfusion (to reduce the HbS fraction as well as raising the Hb and haematocrit). An exchange transfusion is the gold standard treatment for a life threatening crisis such as stroke or acute chest syndrome. Top up transfusions may be needed for the treatment of an episode of acute anaemia. Acute anaemia may be due to severe haemolysis, sequestration or infection with parvovirus – B19. This virus is a self-limiting infection that temporarily halts red blood cell production for approximately 10 days with an associated reticulocytopenia. If an infection with parvovirus is confirmed in pregnancy, there is a risk to the foetus as well and patients should be managed by a foetal medicines unit as well [20,21].

Other roles for transfusion in SCD and pregnancy include the continuation of a transfusion programme for those managed that way prior to pregnancy, consideration of prophylactic transfusions in those with severe disease prior to pregnancy, those with a twin pregnancy (with an expected higher complication rate) and those who needed hydroxycarbamide prior to pregnancy. Those who need an emergency transfusion for the management of an acute severe crisis usually go on to have regular transfusions for the rest of the pregnancy [14].

Patients can suffer from any of the complications of SCD during pregnancy and so involvement of haematologists as part of their multidisciplinary care is essential.

Intrapartum

Delivery should, where possible, take place in a hospital that can manage both high risk pregnancies and SCD. A delivery and analgesia plan should be in place after anaesthetic review in the third

trimester. Patients are often offered an elective birth after 38 weeks gestation but this is not universal and many centres will support allowing spontaneous labour until 40 weeks [13].

The mode of delivery should be decided due to obstetric factors and sickle cell disease per se should not preclude normal vaginal delivery. Special consideration should be given to patients who have avascular necrosis of the hips who may struggle to maintain certain positions and externally rotate their hips.

If presenting early in labour patients should be admitted and the full multidisciplinary team informed. Patients should be offered good and early analgesia (usually regional) to reduce labour pains as there is an increased risk of sickle crises with protracted labour. They should be well hydrated (often requiring intravenous fluids) well oxygenated and kept warm. Patients should be well monitored for signs of sickle cell crises during this period and in the immediate post-partum period. There should be a low threshold for initiating antibiotic treatment if there is any sign of infection including fever.

If a caesarean section is planned or needed urgently general anaesthetic should be avoided where possible to reduce risks of sickle crises.

Post-partum

Patients should be monitored and kept hydrated and well oxygenated until ready for discharge. They should have veno-thromboembolism prophylaxis whilst in hospital and on discharge as per indications for their mode of delivery (currently 6 weeks following caesarean section) [14,17]. Patients and healthcare workers should be educated to remain vigilant for the development of crises once at home and the need to seek medical attention and urgent treatment. If the child is at risk of having inherited a form of SCD then there should be plans in place for the testing of the child before discharge from hospital. Patients should have contraceptive advice before discharge (progesterone containing methods are usually first line due to the theoretical thrombotic risk in oestrogen containing preparations and increased infection risk with the copper intra-uterine device.)

Haematological malignancies

Management of a haematological malignancy during pregnancy can be a challenging process. Due to the relative rarity of this situation, there is often no consensus on the optimal management of the patient. There should be close coordination with the obstetrician and the managing haematologist to ensure optimal maternal and foetal outcomes. We reviewed the evidence and guidelines available for the management of selected haematological malignancies and present the summary below.

Acute leukaemia

The diagnosis of acute leukaemia during pregnancy is a devastating event for the patient and family, necessitating prompt, difficult decisions in the setting of a rapidly evolving condition that is potentially life threatening. Thankfully, such occurrences are rare with a prevalence of approximately 1 in 100000 pregnancies. [47]

Acute leukaemia is a medical emergency which can result in complications of thrombosis, haemorrhage and leukostasis. Treatment should be administered without delay upon diagnosis to avoid adverse outcomes for both mother and foetus [48]. In patients who are diagnosed with acute leukaemia during the first trimester, termination of pregnancy should be advised due to the extremely high likelihood of foetal complications during the administration of intensive chemotherapy, especially stem cell transplantation [49,50]. During the second and third trimester, chemotherapy had been administered with relatively satisfactory outcomes. Chemotherapeutic agents such as anthracyclines, cyclophosphamide, cytarabine and vincristine have been successfully used in pregnant patients with leukaemia although many are either case reports or involving small series and caution should still be exercised in all cases [51–53]. For example, although anthracycline use has been associated with a small risk of foetal toxicity including death, malformations and prematurity, a normal foetal outcome occurred in 73% out of the 160 patients analysed [54]. The use of methotrexate in the second trimester has been associated with a small risk of adverse

neuropsychological and developmental outcomes in the foetus [55], and hence should be omitted until the third trimester.

Pregnancy termination during the 2nd and 3rd trimester is therefore not compulsory but regular monitoring of the mother and foetus is advised. Delivery should be planned and ideally postponed to a non cytopaenic period [50].

Usage of supportive therapy such as granulocyte colony stimulating factor and common prophylactic antibiotics are considered safe during pregnancy [56]. One exception, however, is the use of cotrimoxazole for pneumocystis pneumonia prophylaxis, because of its potential anti-folate activity and an alternative, such as dapsone should be used instead.

Delivery should be planned in close coordination with the haematologist to reduce the risk of complications of cytopaenia and treatment delay. If stem cell transplantation is required, early delivery should be considered.

Thrombotic and thrombophilic disorders

Pregnancy is associated with a hypercoagulable state. During normal pregnancy, concentrations of factors VII, VIII, X, von Willebrand factor and fibrinogen are increased while free protein S level is decreased. In addition plasminogen activator inhibitor levels are increased, resulting in reduced fibrinolysis [57,58].

Thromboembolic disorders are a major preventable cause of maternal death, accounting for 1 – 1.5 deaths per 100,000 deliveries in the developed countries [14,59]. The risk of venous thromboembolism (VTE) steadily increases throughout the course of the pregnancy. In first 6 weeks postpartum, VTE increases even further, with one retrospective study reporting an odds ratio of VTE of 84 during this period [41]. Most of these events would occur in the form of a lower limb proximal deep vein thrombosis (DVT), possibly due to the compression of the common iliac vein by the common iliac artery. About a fifth or a quarter of VTE is due to pulmonary embolism. (PE) A previous history of thrombosis is the most significant risk factor for the development of a VTE [60,61]. The risk of a recurrent VTE during pregnancy is also exacerbated due to the procoagulant state in pregnancy. The presence of a thrombophilic condition, such as antiphospholipid syndrome, factor V Leiden, and deficiencies of antithrombin III, protein C and protein S also increases the risk of thrombosis during pregnancy. Depending on the type of thrombophilia, the excess risk can range from 2 to 34 times that of a pregnant female without thrombophilia [61].

In the case of a new onset VTE, the diagnostic pathway needs to be modified in pregnant patients. The routine measurement of D-dimer, which is commonly elevated in pregnancy, is not recommended [62]. In patients presenting with signs and symptoms suggestive of a DVT, such as lower limb swelling and tenderness, compressive ultrasonography (CUS) is the investigation of choice [63]. In the event of a negative test and in cases of high clinical suspicion, a repeat ultrasound should be performed in 3 days to 1 week. Magnetic resonance venography can also be considered in the event of a negative scan and a suspicion of an iliac vein DVT [63,64].

Patients with pulmonary embolism (PE) typically presents with dyspnoea, chest pain, tachycardia and in severe cases, hemodynamic instability. If symptoms of DVT are present, CUS can be performed, and anticoagulation started if DVT is found. In patients without symptoms of DVT, a ventilation/perfusion (V/Q) scanning should be performed to identify a potential PE [65]. CT angiography may not necessarily be contraindicated as the small risk of maternal and foetal radiation exposure does not override the potentially severe consequences of an undiagnosed or misdiagnosed PE [66].

Anticoagulation with low molecular weight heparin (LMWH), which is shown to be safe in pregnancy, is currently the standard of care. A weight adjusted dosing is generally recommended [67]. In patients with renal impairment, tinzaparin may be the preferred agent as no dose adjustment is required as long as creatinine clearance is above 20 ml/minute [67]. Unfractionated heparin (UFH) should be considered in patients at high risk of bleeding or near the period of delivery due to its shorter half-life and the availability of a reversal agent. If epidural anaesthesia is required, UFH can be stopped 4 to 6 hours before the procedure, while LMWH should be stopped at least 24 hours before [68].

After delivery, LMWH may be restarted 12 to 24 hours after delivery once haemostasis is reasonably secured. In patients who require more than 6 weeks of anticoagulation postpartum, they can be safely

bridged to warfarin. Duration of anticoagulation in a pregnancy related VTE is generally 3 to 6 months or until 6 weeks postpartum, whichever is the longer period.

As mentioned previously, the most significant risk factor the VTE development during pregnancy is a prior history of VTE, and the presence of a thrombophilic condition such as antiphospholipid syndrome or antithrombin III deficiency [61]. In these groups of patients, pregnancy should be a planned process to reduce the risk of both foetal and maternal adverse events.

Patients who are already on full dose anticoagulation should continue to be anticoagulated throughout pregnancy. Warfarin, being the long term anticoagulation of choice in non-pregnant patients, should be switched to low molecular weight heparin (LMWH) the moment a pregnancy test becomes positive due to its association with developmental defects [69,70]. Some patients may even opt to switch to LMWH while attempting pregnancy to reduce the risk of early foetal loss associated with warfarin.

For patients with a prior history of unprovoked or pregnancy related VTE, prophylactic dose anticoagulation with LMWH should be given antepartum. In patients with thrombophilic conditions without a prior history of VTE, they can be monitored closely without pharmacologic prophylaxis [68]. However, should the patient acquire another risk factor such as pre-eclampsia or caesarean delivery, prophylactic anticoagulation should be initiated and continued until 6 weeks postpartum.

Special mention needs to be made for women with APS, an autoimmune condition associated with autoantibodies targeting various phospholipids, resulting in pregnancy complications and a hypercoagulable state [71]. According to the revised Sapporo criteria, APS can be diagnosed when one clinical and one laboratory criteria have been met as listed in Table 1 [71]. Those not normally on anticoagulation are usually commenced on prophylactic LMWH during pregnancy while those already on therapeutic anticoagulation should continue LMWH during pregnancy as described above.

In women with recurrent miscarriages associated with APS, the efficacy of heparin combined with aspirin has been well established [73–75]. It is recommended that LMWH or unfractionated heparin combined with low dose aspirin should be administered once pregnancy is confirmed and throughout the duration of the pregnancy. Low dose aspirin is the treatment of choice in patients with APS and pre-eclampsia or intrauterine growth restriction in the previous pregnancies [76]. Similar to other patients at high risk of pregnancy related thromboembolism, women with a history of thrombosis and APS should be offered anticoagulation with LMWH antenatally until 6 weeks postpartum.

Summary

Improvement in treatment strategies including the development of novel target therapies for haematological malignancies and better iron chelation in haemoglobinopathies has seen more women attaining child bearing age. Close monitoring and meticulous multi-disciplinary care has also meant more successful pregnancy outcomes and this has clearly been demonstrated for patients with sickle

Table 1

Definition of Antiphospholipid Syndrome (requires at least one clinical and one laboratory criteria to be fulfilled).

Clinical criteria
One or more episodes of arterial, venous or small vessel thrombosis
More than three unexplained spontaneous miscarriages before 10th week gestation with maternal anatomic or hormonal and chromosomal abnormalities excluded
One or more unexplained death of a morphologically normal fetus at or after 10th week gestation
One or more pre-term births of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe pre-eclampsia, or recognized features of placental insufficiency
Laboratory criteria (positive on 2 or more occasions, at least 12 weeks apart)
Presence of lupus anticoagulant in plasma
Anti-cardiolipin IgG and/or IgM present in medium or high titre in plasma or serum (>40 GPL or MPL units, or > the 99th percentile)
Glycoprotein I IgG and/or IgM antibody in serum or plasma (titre > the 99th centile)

cell disease. The use of LMWH has also enabled women with significant thrombophilic tendencies successfully managed through pregnancy, balancing the antenatal and postnatal prothrombotic risks with the potential bleeding that can be seen during delivery. Looking ahead, the recent introduction of various novel anticoagulants may change the landscape of anticoagulation and the management of high risk patients during pregnancy.

Practice points

- 1) Sickle cell disease (SCD) is the most common inherited condition worldwide. It is a result of abnormal haemoglobin production and patients suffer from acute crises (usually severely painful) as well as chronic organ dysfunction and reduced life expectancy.
- 2) With improved care patients with SCD are living longer and now most women will survive to child bearing age.
- 3) Pregnancy in women affected by SCD is high risk with increased problems seen for both the woman and the foetus. These complications include increased sickle cell crises and admissions, infections, pre-eclampsia, intra-uterine growth restriction and lower gestational ages. Outcomes have improved with better obstetric and haematology care and close multi-disciplinary working.
- 4) Obstetric care for the patients should start at adolescence to include pre-pregnancy advice (including contraception and genetic counselling) as well as increased and regular monitoring through the antenatal, perinatal and postnatal periods. The patient should be managed with close consultation between the managing obstetrician and haematologist to optimize patient and foetal outcomes.
- 5) Acute leukaemia presenting during pregnancy is considered a medical emergency; treatment should be administered without delay. During the first trimester, termination of pregnancy is advised due to high risk of adverse foetal outcomes.
- 6) Venous thromboembolism during pregnancy can be diagnosed using readily available investigation modalities. However, a D-dimer is not reliable during pregnancy.
- 7) Patients at high risk of venous thromboembolism should receive low molecular weight prophylaxis during pregnancy.

Research agenda

1. The safe use of both traditional chemotherapies and various novel targeted therapies in the management of haematological malignancies during pregnancy.
2. The comparison of newer anticoagulants compared to the traditional agents (warfarin and LMWH) in pregnancy.
3. Optimal management of very high risk patients with a significant thrombotic history or recurrent miscarriages.

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