REVIEW
O&G Forum 2016;26:15-22

Haematological conditions in the obstetric patient

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Abstract
Haematological abnormalities are frequently encountered in the obstetric patient. Cytopenias are common, with anaemia and thrombocytopenia predominating. Many other haematological conditions are seen during pregnancy, however, in this review, I intend to describe the common abnormalities and the management thereof.

Introduction

Cytopenias are frequently encountered in the obstetric patient. Anaemia is the most common abnormality with thrombocytopenia also prevalent. To investigate and manage cytopenias in pregnancy it is imperative to understand the normal physiological changes. To this end, I will initially describe the normal physiological changes and then proceed to discuss the investigation and management of the more common abnormal conditions.

Physiological changes in pregnancy

Red cells- reduction in haemoglobin due to dilutional anaemia (increase in plasma volume with increase in red cell mass not as prominent).
haemoglobin drops by 1-2 g/dl.
modest increase in MCV (4fl on average).
haematological changes can take 4-5 months to return to pre-pregnancy levels.

White cells- leucocytosis with an increase in the lower limit of the reference range up to 6000 x 10^9/l.
mainly neutrophil leucocytosis.
can have a left shift and toxic changes.
lymphocytes decrease in the 1st and 2nd trimester but increase in the 3rd.
absolute monocytosis.
no change in eosinophils and basophils.
WCC can further increase during delivery.
can take 4-6 weeks to recover.

Platelets- decrease during pregnancy, particularly in the 3rd trimester – Gestational thrombocytopenia.

Coagulation- prothrombotic state due to increase in fibrinogen, coagulation factors and VWF.
can remain elevated 8-12 weeks post-partum.
reduction in natural anticoagulants (protein S).

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Approach to cytopenias in pregnancy

Anaemia

Anaemia is the most frequent haematological abnormality in pregnancy (estimated 30-40%) and is defined as a haemoglobin of <11g/dl in the 1st trimester, <10.5g/dl in the 2nd and 3rd trimesters and <10g/dl in the postpartum period. For this reason, a full blood count should be performed at booking and at 28 weeks gestation. Apart from dilutional anaemia, the most common cause of anaemia in pregnancy remains iron deficiency (IDA) (most common cause worldwide affecting 1.6 billion). It is manifested by a microcytic hypochromic anaemia with reduced serum iron, transferrin saturation and ferritin. Since it is the most frequent cause of anaemia, pregnant women with a reduced haemoglobin should all have an evaluation for IDA. IDA occurs due to the increased bone marrow demand and reduced iron stores prior to pregnancy resulting from menstruation and inadequate dietary intake. For this reason, daily iron intake should be increased in pregnancy from 18mg to 27mg per day. Studies showing an association between poor pregnancy outcome (preterm delivery, low birth weight, possibly placental abruption and increased peripartum blood loss) and severe anaemia led to the initiation of supplemental iron during pregnancy. In addition, anaemia also affects the pregnant mother increasing risk of or severity of infection, poor performance and disturbances of postpartum cognition and emotions. The practice of prophylactic supplementation is however controversial, but given the incidence of iron deficiency in our population group, supplementation is likely justified.

Management entails the replacement of iron either via the oral or parenteral routes. This can be done in patients who present with a microcytic anaemia prior to iron studies (except if a known haemoglobinopathy is present). This practice is both cost and time effective and diagnostic. If no response is seen in two weeks, then further testing is indicated. Oral iron at a dose of 60-120mg should be adequate. If the anaemia is severe (<8.5g/dl) or if oral iron is not tolerated, or malabsorption

is present, then intravenous iron is favoured. Intravenous iron is safe during pregnancy but should not be given prior to confirmation of the IDA (low ferritin levels). It is contraindicated in the 1st trimester, if there is a history of anaphylaxis or reactions to intravenous iron, active acute or chronic infection or chronic liver disease. Potential benefits include the more rapid increase in haemoglobin and better replacement of iron stores. In South Africa, three intravenous iron preparations are available, viz. *Venofer, Cosmofer* and *Ferinject. Cosmofer* has the advantage of administration of the total body dose while Ferinject can be infused over a much shorter period and upto a maximum dose of 1000mg. (15mins vs *Cosmofer* 6 hours). *Cosmofer* is however cheaper. The dose required should be calculated according to the body weight and haemoglobin deficit but generally a dose of 1000mg for the average patient is sufficient.

Calculation of iron deficit

Weight {kg} x (Target Hb – Actual Hb) {g/l} x 2.4 + Iron stores {mg}
Iron stores 500mg if weight > 35kg or 15 mg/kg if weight < 35kg

Despite monitoring and treatment, some patients may still require additional treatment at the time of delivery or immediately postpartum. In this instance, blood transfusion with packed red cells may be required. Transfusion thresholds are variable and although a guideline of <10g/dl is advised, comorbidity, age, cardiac compromise, symptomatic anaemia and risk of bleeding should be taken into account. Where possible, iron replacement therapy should first be considered.

Megaloblastic anaemia

Megaloblastic anaemias present with a macrocytic anaemia and may also result in a pancytopenia. As a result, any patient presenting with a macrocytic anaemia should be tested for vitamin B12 and folate levels.

Folate deficiency is caused mainly by inadequate intake. Replacement with oral folic acid is advised for patients with confirmed deficiencies. An adequate dose for replacement is 0.5 -1mg twice or thrice daily or a single 5mg daily dose for convenience.

Vitamin B12 deficiency, although less frequent also requires consideration and is treated with intramuscular vitamin B12 injections. A practical replacement schedule is as follows: 1000ug daily for 1 week, then 1000ug weekly for 4 weeks followed by 1000ug monthly for 6 months.

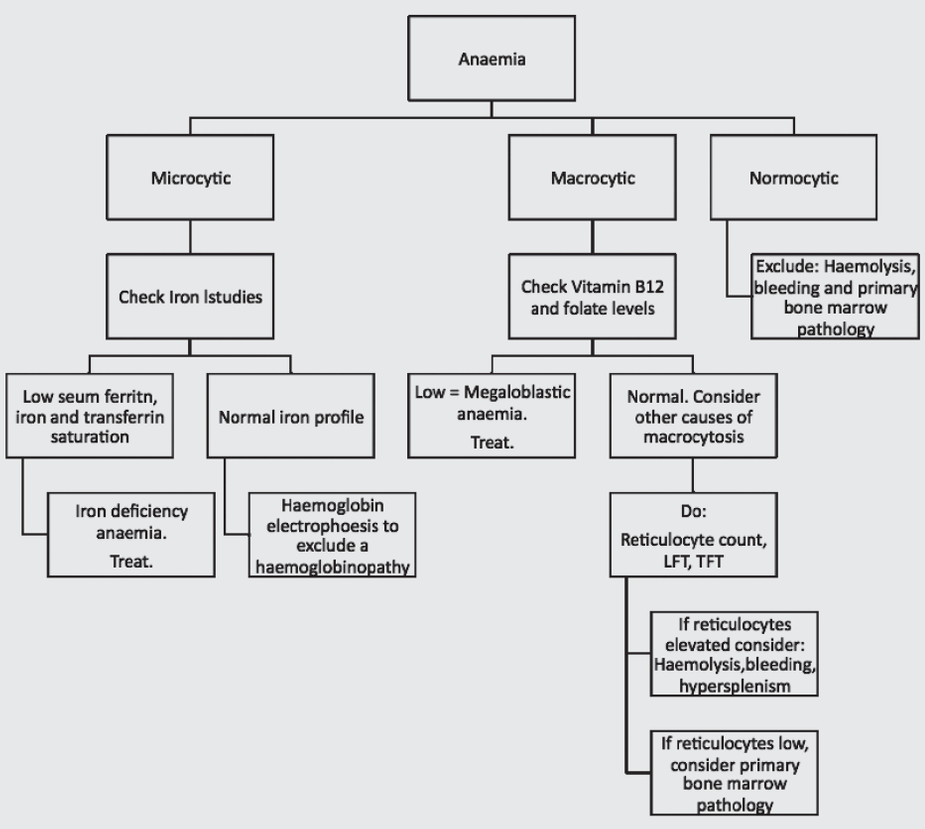
Other causes

Other causes of microcytic anaemias are haemoglobinopathies such as Thalassaemia and Sickle cell anaemia. In South Africa, patients with Thalassaemia are seen mainly in the Asian population and to a lesser extent people of Mediterranean descent. As a result of migration, patients from central Africa with Sickle cell Anaemia may also be encountered.

An Autoimmune haemolytic anaemia is diagnosed when patients present with a macrocytic anaemia, reticulocytosis, unconjugated hyperbilirubinaemia, reduced haptoglobin levels and a positive direct Coomb's test. Treatment includes immunosuppressive therapy (initially corticosteroids) and red cell transfusions when necessary. It is difficult to crossmatch compatible blood for these patients but transfusion of the "least incompatible" units are advised.

Another less common causes of anaemia in pregnancy is Aplastic anaemia. It is diagnosed in patients presenting with a pancytopenia and a hypocellular marrow. Aplastic anaemia early in pregnancy should be treated with termination. Later on in the pregnancy, symptomatic transfusions are required with re-evaluation of treatment postpartum. It may improve post-delivery.

Practical approach to Anaemia



Thrombocytopenia
Thrombocytopenia is defined as a platelet count of <150 x 10^9/l. It is the second most prevalent haematological abnormality only to anaemia. It affects 6-10% of all pregnancies. Causes vary from gestational thrombocytopenia to primary immune mediated thrombocytopenia (ITP), microangiopathic haemolytic anaemias (MAHA) – pre-eclampsia, HELLP etc., secondary immune thrombocytopenia (secondary to viral infections and autoimmune diseases and others). The following investigations are advised for the workup of pregnant patients presenting with a thrombocytopenia.

Initial tests
- FBC and peripheral blood smear
- Coagulation screen (INR , aPTT, fibrinogen and d-Dimer)
- Liver function tests
- Viral screen (HIV, HCV, HBV)

Further testing if clinically appropriate
- Autoimmune screen
- Antiphospholipid antibodies
- DAT (direct Coombs test)
- Thyroid function tests
- VWF type IIb testing

Gestational thrombocytopenia
Gestational thrombocytopenia is by far the most common cause accounting for 70-80% of all cases. It generally presents with platelet counts of >80 x 10^9/l with the majority of patients (two thirds) presenting with a platelet count of 130-150 x 10^9/l. It is a diagnosis of exclusion and is most common during the mid-second trimester to the third trimester. It is suggested that haemodilution, activation and accelerated clearance of platelets is responsible. The distinction between gestational thrombocytopenia and ITP is sometimes problematic. ITP often presents earlier with lower platelet counts (anything <100 x 10^9/l but can be <50 x 10^9) while gestational thrombocytopenia rarely presents with platelet counts <80 x 10^9/l. The diagnosis is unlikely with platelet counts <80 x 10^9/l with only rare cases presenting with platelet counts between 40-50 x 10^9/l. Patients with gestational thrombocytopenia have no history of thrombocytopenia (except in previous pregnancies) while the platelet counts return to normal within 1-2 months post-delivery and the foetus/newborn baby does not present with thrombocytopenia. It requires no active management except monitoring. If platelet counts drop below 50 x 10^9/l a trial of steroids may be indicated to differentiate it from ITP.

ITP (immune thrombocytopenic purpura)
ITP is the most common cause of thrombocytopenia in early pregnancy. It is caused by immune mediated destruction of the platelets by platelet antibodies. It is not exclusive to pregnancy but has an increased incidence in pregnancy. As stated above, patients present with platelet counts <100 x 10^9/l. It more often presents early in pregnancy with platelet counts declining as the pregnancy progresses. The development of thrombocytopenia later in pregnancy does not exclude the diagnosis of ITP.

Treatment earlier on in the pregnancy is not required, unless the platelet count falls below 30 x 10^9/l or if the patient presents with bleeding. Later on in the pregnancy when epidural anaesthesia is required or a procedure expected, then treatment can be initiated.

Management of ITP
ITP in pregnancy is treated similar to non-pregnancy ITP. First line therapy remains oral corticosteroids with a response rate of 70-80% quoted in the literature. Oral prednisone/prednisolone is preferred. A dose of 10mg daily can be commenced and increased as required to achieve the desired platelet increment. Doses of >30mg are seldom required. Alternatively, a higher dose (e.g. 20-30mg / day) can be commenced and titrated appropriately. An initial response can be expected after 2-4 days with a peak response at 4 weeks. High doses should be used with caution given the potential side effects (hyperglycaemia, weight gain, exacerbation of hypertension and adverse pregnancy outcomes). If the platelet count is >30 x 10^9/l and no bleeding is present then treatment can be held off until later in the pregnancy when a higher platelet count is required for epidural anaesthesia or a surgical procedure. In the case of epidural anaesthesia, steroids can be commenced 10 days to 2 weeks prior to expected delivery. Again, a dose of 10mg daily, increased if required can be commenced. A safe platelet count for epidural anaesthesia has not been clearly defined but some centres use a cut-off of 80 x 10^9/l. A platelet count of >100 x 10^9/l should certainly be adequate. Treatment with platelet transfusions is not appropriate for epidural anaesthesia since the effect may be short lived or inadequate. Mode of delivery should be according to obstetric indications since ITP is not an indication for caesarean delivery. However, since the neonate may also present with thrombocytopenia, procedures with increased risk of haemorrhage to the foetus (forceps, vacuum extraction and foetal scalp sampling) should be avoided.

Uncomplicated vaginal can safely be performed at platelet counts >50 x 10^9/l, with reports of safe deliveries in women with platelet counts ranging from 30-50 x 10^9/l. However, since a caesarean section may be unexpectedly required, it is safer to aim for a platelet count >50 x 10^9/l when approaching term. If patients fail to respond to oral steroids, other alternative therapies are available. Intravenous immunoglobulin (IVIG – *Polygam in SA*) is a safe alternative and has the advantage of a more rapid response than steroids. A dose of 1g/kg once off or in two divided doses over two days can be used. It is however expensive and should only be used when indicated. Combinations of steroids

and IVIG are also appropriate and when IVIG is used, it is often used it in combination with steroids to achieve a more rapid response. Platelet transfusion should only be used in cases of active bleeding or emergency procedures when the platelet count is deemed to be inadequately low. Combinations of IVIG and high dose methylprednisolone can also be used.

ITP treatment options	
First line	Steroids, IVIG
Second line	Combination steroids and IVIG Splenectomy
Third line	Azathioprine Anti D

Splenectomy can be done in refractory cases with significant bleeding and or toxicity to other treatments. It is reported to be safest in the second trimester when anaesthetic risk to the foetus is minimal and uterine size will not complicate the procedure.

Other therapies have been used but are relatively contra-indicated. Azathioprine and Anti D are such examples but should be used with caution. Anti D can induce a haemolytic anaemia while Azathioprine is associated with immune impairment to the foetus. Both of these agents have though been used in pregnancy with success.

Other agents used in standard ITP such as Cyclosporine A, Monoclonal antibody therapy (*Rituximab*) and Thrombopoietin receptor agonists (*Romiplostim, Eltrombopag*) should not be used, although use in pregnancy has been described.

Other agents such as Vincristine, Cyclophosphamide, Danazol and Mycophenolate mofetil are completely contra-indicated.

Thrombotic microangiopathies

Pre-eclampsia/HELLP

Preeclampsia complicates 6% of all pregnancies with thrombocytopenia encountered in up to 50% of patients, worsening with the degree of preeclampsia. The thrombocytopenia may precede the other manifestations of pre-eclampsia and thus requires a high index of suspicion in the late second and third trimesters.

HELLP syndrome (*H*aemolysis, *E*levated liver function tests, and *L*ow *P*latelets) affects 0.5-0.9% of all pregnancies and develops in 10% of patients with preeclampsia.

It is defined by:

- microangiopathic haemolytic anaemia,
- lactate dehydrogenase (LDH) > 600 U/mL,
- increased aspartate aminotransferase (> 40–70 U/mL, depending on the series),
- thrombocytopenia (platelet count < 100,000, or in some series, 150,000).

Thrombocytopenia is often worse in HELLP than in pre-eclampsia but distinction between these disorders and the other microangiopathies (TTP/HUS) is sometimes difficult.

The management of both of these disorders is to stabilise the patient medically and then deliver the foetus promptly. If the gestation is <34weeks then treatment with steroids to enhance foetal lung maturity should be followed by delivery. In both of these conditions, recovery is followed by delivery within a few days but thrombocytopenia can be persistent for several weeks postpartum. Occasionally, Pre-eclampsia and HELLP can also present postpartum and should be considered as a cause of postpartum thrombocytopenia.

TTP/HUS

TTP and HUS belong to the group of thrombotic microangiopathies. They are not exclusive to pregnancy but are seen in higher frequencies in pregnancy. They are often difficult to differentiate from each other and from the other thrombotic microangiopathies. TTP classically presents with the pentad:

- Thrombocytopenia (often severe)
- Microangiopathic haemolytic anaemia (MAHA) – as manifested by anaemia, red cell fragments (schistocytes) in the peripheral blood smear,

Differentiating between ITP and gestational thrombocytopenia		
	ITP	**Gestational thrombocytopenia**
Platelet count	<100, can be <50	seldom <80 (unlikely <50)
Onset of thrombocytopenia	Early	mid 2nd trimester to 3rd
Response to steroids	Yes	No
Recovery post pregnancy	Possible	Yes
Neonatal thrombocytopenia	Yes	No

evidence of haemolysis (elevated reticulocyte count, hyperbilirubinaemia etc.)
- Neurological dysfunction
- Renal dysfunction
- Fever

All of the pentad features are not required to make the diagnosis, however a minimum of a thrombocytopenia with features of MAHA is required. Neurologic dysfunction is the next most common manifestation of classic TTP with varying incidences of the other manifestations. Because of the high morbidity and mortality associated with TTP, a high index of suspicion is required. In our setting, patients with HIV who are already at higher risk of TTP should be considered more frequently. Patients who present with a MAHA and thrombocytopenia without any other suspected aetiology should be considered and treated for TTP.

Pathogenesis of TTP

TTP results due to a deficiency or an inhibitor to the Von Willebrand factor cleaving protein *ADAMTS13*. This deficiency results in an excess of ultra large Von Willebrand factor multimers. These multimers bind platelets in excess thus leading to the thrombocytopenia. The neurological, renal and other organ manifestations are caused by these ultra large VWF multimer bound platelets causing obstruction in the vascular circulation. As the red blood cells pass through these obstructed vessels they haemolyse which leads to the microangiopathic haemolytic anaemia.

The gold standard for the treatment of TTP is plasma exchange with response rates of up to 80%. Plasma exchange should not be delayed and initiated promptly at an initial rate of 1 – 1.5 times the plasma volume per day. Corticosteroids may be added to the treatment but their benefit has not been clearly determined in clinical trials. In our setting, we commence with plasma exchange and add corticosteroids if there is an inadequate response or in severe cases. Plasma infusion (Fresh Frozen Plasma - FFP) has been used as an alternate therapy and has been demonstrated in a local study to be as equally efficacious as plasma exchange in HIV positive non-pregnant patients. Despite this, it should not be considered as first line treatment and possibly can be used while arranging plasma exchange. High doses of FFP are required with doses of 30ml/kg/day advised in the non-pregnant patient group.

Haemolytic uraemic syndrome (HUS) is a more heterogeneous disease and can present with the same pentad of symptoms as TTP. It has been suggested that in TTP, neurologic dysfunction is more common while in HUS renal dysfunction predominate. The most common form of HUS (90% of cases) is caused by an infection with Shiga-toxin producing Escherichia coli (particularly types O157:H7 and O104:H4) while atypical HUS is the most common form of HUS in pregnancy.

HUS is treated similarly to TTP with plasma exchange but with poorer responses and patients often develop chronic renal insufficiency. Anticoagulation and antiplatelet therapy has not shown any benefit.

HIV (secondary immune mediated)

HIV associated immune thrombocytopenia is always a consideration in our local setting. One would expect it to be more prevalent in South Africa but a recent local study showed no increased prevalence or severity. It presents very much like ITP and treatment strategies are similar. Steroids can be used but, due to infection risks, intravenous immunoglobulin is preferred. HIV may however be associated with others causes of thrombocytopenia including increased risk of TTP and malignancies. Nutritional deficiencies may also be more common and should be considered in patients presenting with cytopenias.

DIC (disseminated intravascular coagulation)

DIC may arise in pregnancy from several obstetric causes. It is a consumptive coagulopathy caused by tissue factor rich material released into the maternal circulation. This then leads to activation of coagulation with a subsequent consumption of coagulation factors and a severe hypofibrinogenaemia. Placental abruption, amniotic fluid embolism, uterine rupture and retained placental products may all lead to DIC. It is manifested by a thrombocytopenia, anaemia, coagulopathy (increased PT, aPTT, reduced fibrinogen) and an elevated d-dimer. The treatment principles centre around the identification and treatment of the underlying cause. In addition, the coagulopathy should be corrected with plasma while platelet transfusions may be required to maintain a platelet count of at least $> 30 \times 10^9$/l.

Miscellaneous causes

Acute fatty liver of pregnancy

Presents in the third trimester with nausea, vomiting, malaise, right upper quadrant pain and cholestatic jaundice. Treatment is symptomatic with blood products and correction of the coagulopathy.

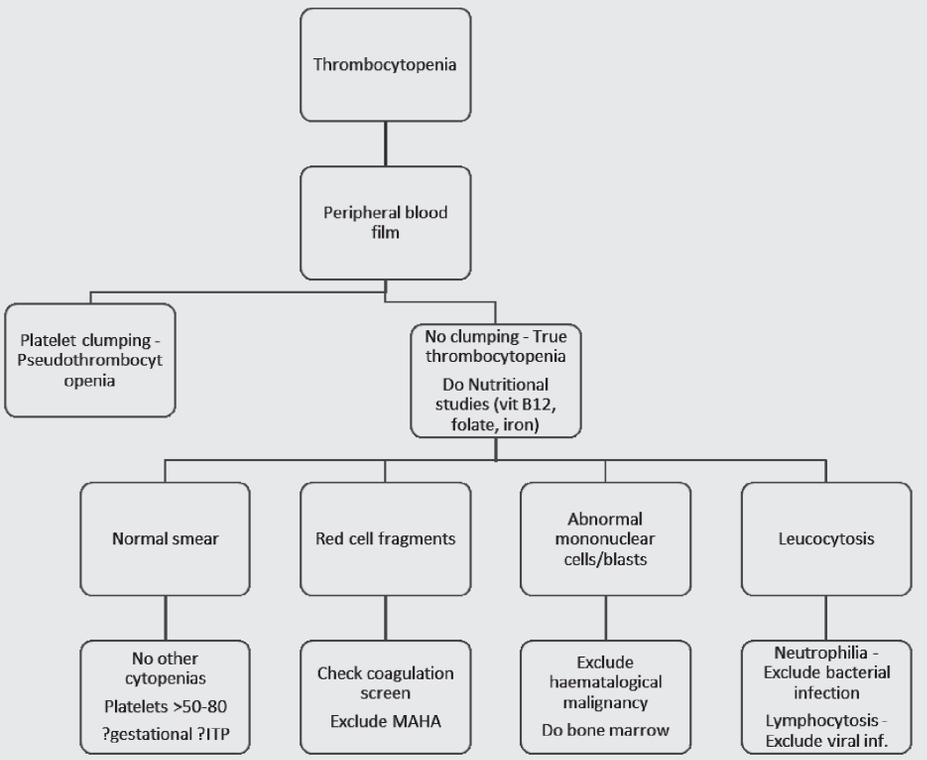
Drugs

Many drugs are associated with thrombocytopenia. A careful drug history is thus advised in all instances of thrombocytopenia in pregnancy.

Inherited thrombocytopenias

This is a rare cause of thrombocytopenia, both in the pregnant patient and the general population. Patients may have a positive family history and examination of the peripheral smear may show large pleomorphic platelets and neutrophil inclusions (Dohle bodies). The most common example is the May-Hegglin anomaly. Treatment is supportive with platelet counts rarely falling low enough for concern.

Practical approach to thrombocytopenia



Thrombosis

The risk of venous thromboembolism (VTE) in pregnancy is increased. This is as a result of hypercoagulability, venous stasis and endothelial damage during delivery and caesarean section. It should promptly be diagnosed and treated since it is a major cause of maternal mortality. Thrombosis more often occurs in the left ileo-femoral vein due to compression of the left iliac vein by the gravid uterus.

Duplex Doppler ultrasound of the venous system should be requested if suspicion of a DVT presents. Occasionally, venography may be required if strong suspicion is present. D-dimers may be elevated in pregnancy and should be interpreted with caution. A VQ scan should be requested for suspicion of Pulmonary Embolism and is preferred over CT pulmonary angiography due to less radiation risk to the foetus.

Treatment of VTE in pregnancy should be with LMWH at 1mg/kg (*Clexane* (enoxaparin)) s.c twice daily and should continue for six weeks post-partum to achieve a minimum duration of therapy of 3 months.

Vitamin K antagonists (warfarin) are contra-indicated in pregnancy but may be used postpartum (minimal secretion in breast milk).

To reduce the risk of bleeding, it is recommended that delivery should be planned. If epidural anaesthesia is planned, LMWH should be withheld for at least 24 hours.

Patients already on warfarin prior to pregnancy should be converted to LMWH prior to six weeks of gestation.

Unfractionated heparin is seldom used today but may be required in patients with massive PE and haemodynamic instability.

The new/novel anticoagulants (eg *Xarelto* and *Pradaxa*) are currently contra-indicated in pregnancy.

Thrombophilia

Thrombophilia refers to the increased susceptibility to thrombosis. Apart from pregnancy, which is an increased risk state for thrombosis, other acquired and inherited causes of thrombophilia exists. Prime examples of inherited thrombophilic states include deficiencies of Protein S, C and Antithrombin. The Factor V Leiden mutation and the Prothrombin gene mutation (G20210A) are also inherited causes for thrombosis and are amongst the most common causes of inherited thrombophilia. They are however less common in our setting and confined mainly to Caucasian patients. The Antiphospholipid antibody syndrome (which will be discussed separately) is not only associated with thrombosis and thrombocytopenia but also a reason for pregnancy loss. Rarely, increased levels of coagulation factors (such as increased Factor VIII levels) have also been associated with thrombosis. The diagnosis of inherited thrombophilia in pregnancy may be challenging. Inherited thrombophilias should preferably be diagnosed prior to pregnancy and appropriate management instituted when the patient falls pregnant. This requires prospective testing in high risk patients who either present with a history of recurrent thrombosis, thrombosis of unusual sites, adverse reproductive history or have a significant family history.

Apart from increased thrombotic risk, it is also postulated that the heritable thrombophilias may be associated with pregnancy loss and or infertility. More research is required to further elaborate on this association and to better direct future management.

Management of thrombophilia in pregnancy

The management of pregnant patients with thrombophilia is controversial. It is important to determine who is at highest risk for VTE and to treat this group prophylactically with anticoagulation. It is clear that the highest risk of VTE is in the postpartum period and hence many advocate prophylactic anticoagulation during this period for those with a

confirmed thrombophilia or patients who have had a prior VTE. There is good evidence that VTE risk is significantly increased in patients with the Factor V Leiden and the Prothrombin gene mutations, 52 fold and 31 fold increased risk respectively.

Current guidelines recommend that among women without a prior VTE, only those who have a positive family history and are known to be homozygous for the Factor V Leiden or the Prothrombin gene mutation should receive antepartum anticoagulation. Women with Antithrombin, Protein C, or Protein S deficiencies are at low to moderate risk of VTE in pregnancy and should thus receive postpartum anticoagulation only when they also have a positive family history of VTE. Pregnancy associated venous thromboembolism is a strong risk factor for recurrence and hence it is recommended that patients with a previous thrombosis in pregnancy should be anticoagulated for the duration of pregnancy and 6 weeks post-partum.

Antiphospholipid antibody syndrome

The antiphospholipid antibody syndrome (APS) is a condition characterised by recurrent pregnancy loss, thrombosis (arterial or venous) on the background of persistently positive antiphospholipid antibodies. Obstetric manifestations include: single or recurrent foetal loss up to or beyond 10 weeks; recurrent foetal loss (three or more) before 10 weeks gestation and ; single or recurrent foetal loss before the 34th week because of eclampsia or pre-eclampsia (see diagnostic criteria). Arterial thrombosis is more common in the cerebral circulation while venous thrombosis is more common in the deep venous circulation of the lower extremities. Other manifestations of APS include thrombocytopenia, livedo reticularis (dermatologic manifestation), skin ulcers, valvular heart disease and transient ischaemic attacks. These manifestations are not part of the diagnostic criteria but their presence, together with pregnancy complications or arterial or venous thrombosis should raise suspicion of the disease. APS may be primary or secondary to an autoimmune disorder. Catastrophic APS is a severe form of the disease which presents with multi organ failure (3 or more organ thrombosis) and carries a high mortality of up to 50%. The diagnosis of APS is based on demonstrating one clinical and one laboratory criterion.

Revised classification criteria for the APS.

Clinical criteria

1. *Vascular thrombosis*
   One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by imaging or Doppler studies or histopathology, with the exception of superficial venous thrombosis.
   For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. *Pregnancy morbidity*

(a) One or more unexplained deaths of a morphologically normal foetus at or beyond the 10th week of gestation, with normal foetal morphology documented by ultrasound or by direct examination of the foetus, or

(b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (a) eclampsia or severe pre-eclampsia defined according to standard definitions, or (b) recognized features of placental insufficiency,

(c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.

Laboratory criteria

1. Anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. >40 GPL or MPL, or >the 99th percentile, or >mean + 3SD of 40 healthy controls), on 2 or more occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay.
2. Lupus anticoagulant present in plasma, on 2 or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on Lupus Anticoagulants/Phospholipid-Dependent Antibodies).
3. Anti-b2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma, present on 2 or more occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay, according to recommended procedures.

Definite APS is present if at least one of the clinical criteria and one of the laboratory criteria are met, with the first measurement of the laboratory test performed at least 12 weeks from the clinical manifestation.

Management

The treatment of obstetric APS is somewhat controversial with numerous studies reporting different outcomes. Aspirin alone has not been demonstrated to improve pregnancy outcome while two prospective studies comparing aspirin alone vs. aspirin with unfractionated heparin have demonstrated improved pregnancy outcomes in the aspirin and heparin group. However, these findings were not replicated in two further studies comparing aspirin and aspirin with LMWH. The current ACCP guidelines recommend that in patients with APS and three or more pregnancy losses, low dose aspirin together with prophylactic or low dose unfractionated heparin or LMWH should be used.

Bleeding

Bleeding occurring in pregnancy can be either as a result of thrombocytopenia, coagulation disorders, platelet function abnormalities or trauma. Patients presenting with bleeding should as a baseline have a full blood count (emphasis on platelet count), PT/INR and aPTT done. Aside from the aforementioned thrombocytopenic conditions, coagulation disorders may be responsible for bleeding. Examples of such disorders are Von Willebrand disease and haemophilia carrier status. Von Willebrand disease is by far the most common inherited bleeding disorder and arises due to a quantitative or qualitative decrease in Von Willebrand factor. It should be considered in patients with a history of bleeding and possibly a positive family history. Women with inherited bleeding disorders will more likely present with bleeding post-partum and hence correction of the coagulopathy is advised prior to procedures and delivery. Type IIb Von Willebrand disease not only presents with a coagulopathy but also can present with thrombocytopenia.

Acquired haemophilia is a condition which may present with severe bleeding. This disorder can lead to life threatening bleeding and requires prompt diagnosis and treatment. It is associated with pregnancy, autoimmune diseases and malignancies. It presents unlike congenital haemophilia where haemarthroses is the common manifestation. Here mucocutaneous bleeding predominates. It should be considered in patients presenting with bleeding and a prolonged aPTT without a personal or family history of an inherited coagulation disorder. This is an immune mediated process arising from the development of inhibitors to coagulation factors, most commonly Factor VIII. Treatment principles include supportive measures with transfusion of blood products and administration of inhibitor bypassing agents. Once bleeding is controlled, inhibitor eradication therapies are initiated.

Conclusion

Haematological conditions in pregnancy are common ranging from anaemia to thrombocytopenia and thrombosis. Anaemia is the most common haematological abnormality encountered in pregnancy, though thrombocytopenia is likely the most challenging to investigate and treat. More research is required in some areas to better understand the pathophysiology and hence improve management and outcome. A logical approach is necessary in the workup of these disorders, while treatment requires a multidisciplinary approach. Close co-operation between the obstetrician, haematologist and laboratory is integral to efficient diagnosis and effective management.

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