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Hematologic Complications of Pregnancy

Danielle M. Townsley, M.D., M.Sc.
Staff Clinician Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland

Abstract

Pregnancy induces a number of physiologic changes that affect the hematologic indices, either directly or indirectly. Recognizing and treating hematologic disorders that occur during pregnancy is difficult owing to the paucity of evidence available to guide consultants. This paper specifically reviews the diagnosis and management of benign hematologic disorders occurring during pregnancy. Anemia secondary to iron deficiency is the most frequent hematologic complication and is easily treated with oral iron formulations,; however care must be taken not to miss other causes of anemia, such as sickle cell disease. Thrombocytopenia is also a common reason for consulting the hematologist and distinguishing gestational thrombocytopenia from immune thrombocytopenia (ITP), preeclampsia, HELLP syndrome, or thrombotic thrombocytopenic purpura (TTP) is essential since the treatment differs widely. Occasionally the management of mother and infant involves the expeditious recognition of neonatal alloimmune thrombocytopenia (NAIT), a condition that is responsible for severe life-threatening bleeding of the newborn. Additionally, inherited and acquired bleeding disorders affect pregnant women disproportionately and often require careful monitoring of coagulation parameters in order to prevent bleeding in the puerperium. Finally, venous thromboembolism (VTE) during pregnancy is still largely responsible for mortality during pregnancy and the diagnosis, treatment options and guidelines for prevention of VTE during pregnancy are explored.

ANEMIA

Iron deficiency

The most frequent hematologic complication during pregnancy is anemia. A number of normal physiologic processes occur during pregnancy leading to the term “physiologic anemia of pregnancy”. The plasma volume increases (40–50%) relative to red cell mass (20–30%) and accounts for the fall in hemoglobin concentration. [1] However, if the hemoglobin falls below 11 gm/dL an evaluation for iron deficiency anemia (IDA) should be initiated since iron deficiency is responsible for the majority of anemias diagnosed during pregnancy. The increased demand on the bone marrow requires women to increase their daily iron intake from 18 mg per day to 27 mg per day.[2] An association between severe anemia (hemoglobin <9 gm/dL) and poor pregnancy outcome has been reported by multiple observational studies triggering the recommendation for universal iron supplementation at a

Author contact info: National Institutes of Health, 10 Center Dr., CRC 3-5216, Bethesda, MD 20892, Danielle.townsley@nih.gov, Telephone: 301-402-3477.

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dose equal to the Recommended Dietary Allowance.[3] Although prophylactic supplementation is controversial, the practice has been shown to increase gestation duration and increase infant birth weights compared to non-supplemented women.[4,5] The risk of adverse pregnancy outcomes is highest when maternal anemia is detected early during pregnancy (first trimester) possibly owing to the difficulty in distinguishing physiologic anemia from IDA in late pregnancy (third trimester).

Most women do not have adequate iron stores for pregnancy secondary to chronic blood loss from menstruation, and some may not tolerate oral iron therapies due to impaired ingestion or side effects further increasing their risk for IDA. Once the diagnosis of IDA is rendered intravenous iron will restore the deficiency rapidly,[6,7] however oral supplementation using 60–120 mg of elemental iron daily is typically adequate. In those women with severe anemia (hemoglobin <8.5 gm/dL) and low iron stores (ferritin <30 ug/L) intravenous iron is preferred. Similarly, if oral iron therapy is ineffective owing to side effects (usually gastrointestinal), intravenous iron is a safe option given the availability of type II iron complexes that are well tolerated. One should take care to avoid achieving high iron stores since some reports suggest prophylactic supplementation may be harmful to pregnant women that are not iron deficient.[8,9] Other causes of anemia

The megaloblastic anemias due to folic acid deficiency, and to a lesser extent vitamin B12 deficiency, can also be a cause of anemia during pregnancy. However folate deficiencies are rare in western populations where the diet is fortified with folate. Because of the increased risk of neural tube defects in women who are folate deficient, prenatal vitamins routinely contain supplemental folic acid (0.4 mg). The majority of folate deficiencies appear in the third trimester and treatment with oral folic acid at doses of 0.5mg to 1mg administered two or three times daily is usually adequate.[1] Other causes of hypochromic microcytic anemia should be sought. Specifically, even in asymptomatic women with sickle cell disease (SCD) or β-thalassemia, there are significant maternal and fetal complications that can arise during pregnancy. Mothers with SCD suffer more infections, thrombotic events, and pregnancy specific complications such as eclampsia, stillbirths or spontaneous abortions.[10–13] Furthermore, 77% of infants delivered from mothers with SCD are reported to have low birth weights, below the 50th percentile.[10] Unfortunately routine interventions with either transfusions or medication have not demonstrated efficacy in improving these outcomes and although the teratogenic effects of hydroxyurea remain controversial, most advise against its use during pregnancy.[14,15] The standard treatment should be directed towards early and aggressive treatment with either simple or chronic transfusions for severe SCD-related events (acute chest syndrome, vasoocclusive crisis or organ failure) or obstetric complications. However, the empiric use of transfusions or erythrocytapheresis has demonstrated conflicting results,[16,17] prompting the standard use of simple transfusions for severe anemia (hemoglobin < 6 gm/dL). Vasoocclusive crisis requiring hospitalization during pregnancy is common and while the management remains unchanged (IV fluids, supplemental oxygen, short-acting opiates), it is important to vigilantly monitor for both infectious complications and acute chest syndrome to ensure early treatment with antibiotics and transfusion support is provided.

Less common causes of acquired anemia in pregnancy are aplastic anemia[18] and autoimmune hemolytic anemia. [19] The diagnosis of aplastic anemia during pregnancy is made when pancytopenia and a hypocellular bone marrow is present. Typically the recommendation to abort the pregnancy is made to women in early stages of pregnancy and, for those in later stages, transfusion support is given in lieu of immunosuppression or bone marrow transplantation. In many cases the cytopenias improve after delivery of the infant and further treatment is avoided. A similar resolution of anemia is observed post-delivery amongst cases of autoimmune hemolytic anemia during pregnancy.[19,20]

THROMBOCYTOPENIA

Differential diagnosis of thrombocytopenia in pregnancy

Similar to the finding of anemia in pregnancy, thrombocytopenia is also common, occurring in approximately 8–10% of pregnancies,[21] and usually secondary to physiologic changes during gestation, namely an increase in blood volume, platelet activation, and increased platelet clearance. Gestational thrombocytopenia accounts for the majority of thrombocytopenias during pregnancy (Table 1) and most cases are mild (100 – 150,000/uL) and not associated with any adverse events for either the mother or baby. Although thrombocytopenia may worsen as the pregnancy progresses, the platelet count rarely drops below 70,000 – 80,000/uL [22] and typically resolves within days to weeks postpartum.

The evaluation of thrombocytopenia should be restricted to analysis of the peripheral blood as follows: smear review, complete blood count, reticulocyte count, direct antiglobulin test, liver function tests, thyroid function tests, antiphospholipid antibodies, lupus serology, viral screening, and coagulation tests including von Willebrand disease (VWD) type IIb assays in women with a bleeding history. Routine bone marrow biopsies are unnecessary.

Immune thrombocytopenia

Thrombocytopenia that occurs during the first trimester or platelet counts dropping below 80,000/uL at anytime during pregnancy should trigger an evaluation for immune thrombocytopenia (ITP). ITP is the second most common cause of thrombocytopenia after gestational thrombocytopenia and although it can occur at any time during pregnancy, it typically appears in the first trimester. A prior history of ITP is highly suggestive, but not required.[23] Similar to ITP occurring in the nonpregnant state, antiplatelet antibodies have not proven to be diagnostically sensitive or specific. Furthermore, they have not proven useful in predicting risk of neonatal thrombocytopenia.[24] The blood smear will typically show either large or normal platelets and although women may have concomitant anemia with hypochromic and microcytic erythrocytes, the remainder of the smear should be normal; the presence of schistocytes, blasts or atypical lymphocytes indicate a different etiology (Table 1). Fortunately, two-thirds of women with ITP during pregnancy will only require observation and, for unclear reasons, women with a history of ITP prior to pregnancy are less likely to require intervention.[23] Treatment of ITP during pregnancy is similar to treatment of ITP in the nonpregnant patient. In the first and second trimesters corticosteroids or intravenous immunoglobulin (IVIG) are typically rendered if the platelet count falls below 20–30,000/uL, bleeding occurs, or a procedure is required.[25] However, there is no data supporting a specific platelet threshold at which to begin treatment. It is important to note that there is little data concerning the use of corticosteroids versus IVIG in pregnancy and most studies have been observational in nature. In general, corticosteroids and IVIG are considered safe in pregnancy, but corticosteroids have side effects that need to be considered prior to initiation. For example, corticosteroids may exacerbate gestational diabetes mellitus or hypertension.

In the third trimester thrombocytopenia can worsen and therapy with either IVIG or corticosteroids may be instituted sooner based on risk of maternal hemorrhage during delivery. There is no role for routine cesarian section; rather, the choice of delivery method should be based solely on obstetric considerations. If a caesarean section or spinal anesthesia is planned, a short course of corticosteroids or IVIG is reasonable to increase the platelet count above 75,000/uL in preparation for the procedure.[26] Neonatal ITP is infrequent and when it occurs rarely causes severe thrombocytopenia (platelet count < 50,000/uL). The incidence of intracranial hemorrhage or death is reported to be around 1%.[21] A history of thrombocytopenia in a previous affected sibling can predict thrombocytopenia occurring in

the neonate; however accurately predicting neonatal platelet counts is difficult since there is no direct correlation with the maternal platelet count, and scalp vein sampling has proven unhelpful.[22]

For those cases refractory to IVIG and/or corticosteroids, splenectomy is recommended and can be performed safely in the 2nd and 3rd trimesters.[27] Splenectomy during the first trimester is generally avoided for fear of provoking preterm labor; there may exist a role for laparoscopic splenectomy but more data is needed.[28] Other therapeutic options used safely during pregnancy include azathioprine[29] and anti-D immunoglobulin[30] however there are no studies evaluating azathioprine as treatment for ITP during pregnancy. Although rituximab is not typically recommended, its use during pregnancy has been described and is associated with temporary suppression of neonatal B-cell development when administered during the 3rd trimester. [31] There is no data on the use of thrombopoietin receptor agonists during pregnancy.

Preeclampsia and HELLP syndrome

A variety of disorders characterized by thrombotic microangiopathy can also cause thrombocytopenia during pregnancy and can pose a diagnostic challenge to the clinician due to their overlapping features. Preeclampsia is commonly responsible for thrombocytopenia occurring in the 2nd and 3rd trimester and characterized by new-onset hypertension and proteinuria after 20 weeks' gestation. Roughly 20–50% of women with preeclampsia will develop thrombocytopenia and although thrombocytopenia is occasionally the sole manifestation of preeclampsia, the severity of thrombocytopenia typically parallels the underlying preeclampsia. Less than 5% of preeclamptic women will develop severe thrombocytopenia (platelets < 50,000/uL) making the use of platelet transfusions rarely necessary. Several trials have investigated the use of aspirin in preventing preeclampsia, especially in high-risk individuals, showing modest effects. More recently a randomized trial was unable to demonstrate a benefit from 100mg daily aspirin starting at 12 weeks gestation.[32]

Inadequate placentation early in pregnancy and systemic endothelial dysfunction is responsible for the pathogenesis of preeclampsia,[33] but the exact mechanism causing thrombocytopenia is unknown. Recent data using angiogenic markers to distinguish preeclampsia from other causes of thrombocytopenia occurring during pregnancy are promising but will require further validation.[34] The mainstay of therapy is prompt delivery of the fetus if the gestational age is ≥34 weeks.

The HELLP syndrome occurs in 10% of women with preeclampsia and is characterized by Hemolysis, Elevated Liver enzymes and Low Platelets. The microangiopathic hemolytic anemia, elevated lactate dehydrogenase (LDH>600 U/mL), increased aspartate aminotransferase (≥70 U/mL) and thrombocytopenia (platelets < 100,000/uL) help to identify this entity in women with preeclampsia.[35] Women may be symptomatic with nausea, malaise and right upper quadrant abdominal pain secondary to obstruction of blood flow in the hepatic sinusoids. Like with preeclampsia, treatment is directed at expeditious delivery of the fetus. Corticosteroids are sometimes utilized to improve thrombocytopenia prior to delivery, although this remains controversial. 20% of cases of HELLP syndrome are identified in the postpartum period and women are at risk for clinical deterioration in the 24–48 hours postpartum with thrombocytopenia persisting up to 4 days following delivery.

Distinguishing between severe HELLP syndrome and other disorders such as thrombotic thrombocytopenic purpura (TTP) and acute fatty liver of pregnancy (AFLP) can be difficult. Pregnancy can trigger an acute episode of TTP, typically during the end of the 3rd trimester or during the postpartum period.[36] A variety of physiologic changes occur during pregnancy

that may potentiate the risk of developing TTP, e.g. hypercoagulability and an observed decrease in ADAMTS13 activity levels during late pregnancy. Prompt and aggressive treatment with plasmapheresis and urgent delivery of the fetus (when possible) is indicated when TTP is suspected given the risk of death from disseminated microvascular thrombosis causing severe neurologic abnormalities and renal failure. Differentiating TTP from HELLP syndrome is occasionally only possible when abnormalities persist in the weeks following delivery. A high LDH to AST ratio may be helpful in distinguishing TTP from HELLP,[37] and the liberal use of plasma exchange is reasonable given that several case series report improvement in outcomes for both severe HELLP and AFLP.[38,39]

Neonatal alloimmune thrombocytopenia

The hematologist may be consulted for the newborn infant with severe thrombocytopenia secondary to neonatal alloimmune thrombocytopenia (NAIT). While most cases are mild, NAIT is the most common cause of intracranial hemorrhage in newborn infants[40] and is caused by transfer of maternal antibodies raised against alloantigens (most commonly HPA-1a and HPA-5b) carried on fetal platelets.[41] This is in contrast to the passive transfer of platelet autoantibodies that occurs in pregnant women with ITP whereby the infant rarely develops severe thrombocytopenia. Infants with NAIT can present with severe bleeding manifestations in the hours to days following birth and can have severely low platelet counts (< 10k/uL). Although NAIT can be present with the firstborn infant, exposure to fetal blood at the time of delivery contributes to the severe disease more likely to be seen in subsequent infants.[42] The feared complication of intracranial hemorrhage occurs in 10–20% of infants with NAIT and at least 80% of bleeds occur prenatally. The treatment for a first affected neonate with bleeding or severe thrombocytopenia (<30,000/uL) is typically transfusion of ABO compatible random donor platelets in addition to IVIG.[43] Transfusion of maternal platelets can also be used, but must be washed to remove the offending antibody or there is risk of worsening the thrombocytopenia and delaying recovery of the platelet count by weeks to months.[40] In subsequent pregnancies a number of management strategies should be employed that include HPA genotyping of the father to determine the likelihood that the next fetus will be affected, and risk stratification based on the presence of HPA antibodies and the severity of previous affected siblings to determine antenatal therapy.[40,44] Antenatal therapy typically consists of IVIG and prednisone initiated between 12 and 20 weeks gestation followed by elective delivery at 37–38 weeks gestation.

BLEEDING DISORDERS

Bleeding complications in pregnant women can occur as the result of an inherited or acquired coagulopathy. Acquired bleeding disorders during pregnancy usually arise acutely during massive postpartum hemorrhage when uterotonics or sutures have failed. Over the subsequent 1–4 months following delivery, acquired hemophilia can develop secondary to an antibody against a coagulation factor.

Manifestations of a previously unrecognized bleeding disorder are more likely to manifest in women during pregnancy and childbirth. The consulting hematologist should keep this in mind when evaluating women with bleeding complications that occur during pregnancy or the postpartum period. A prior history of menorrhagia or gynecological complications (hemorrhagic ovarian cysts, endometriosis, endometrial hyperplasia)[45] may indicate an underlying bleeding disorder since the prevalence of undiagnosed bleeding disorders in this population is reported to be as high as 20%.[46] Although VWD and hemophilia carriage is responsible for the majority of cryptic bleeding disorders amongst women, a small minority may have platelet dysfunction or rare factor deficiencies.[46] There are a number of case reports detailing the type of bleeding events experienced by women with bleeding disorders

and they include subchorionic hemorrhage, miscarriage, placental abruption, placenta previa, and secondary or delayed postpartum bleeding.[45,47–50]

Although pregnancy is associated with alterations in coagulation factors to promote a hypercoagulable state, this is not always sufficient to overcome the bleeding tendency in women with underlying bleeding disorders. Fibrinogen, factor VII, factor VIII, factor X, von Willebrand factor (VWF) and plasminogen activator inhibitor type 1 (PAI-1) levels rise during pregnancy, while free protein S decreases. Most women will have improvement in their bleeding disorder secondary to these changes, however they are at risk for significant worsening immediately following delivery.

Women with known inherited bleeding disorders should be cared for by a multidisciplinary team of specialists that include a coagulation disorders specialist, obstetrician and anesthesiologist familiar with their management. There is a lack of adequate data to guide prevention of bleeding in affected women. Most practice is therefore guided by expert opinion. According to the Medical and Scientific Advisory Council (MASAC) recommendations in 2009, treatment should be given prior to invasive procedures or delivery based upon levels of coagulation factors when checked once or twice during the third trimester for most inherited bleeding disorders (Table 2).[51] Pregnant women with VWD can have significant bleeding complications, mainly observed in the postpartum period if the VWF activity levels are < 50 IU/dL.[52] Therefore, plasma concentrates and desmopressin (DDAVP) are utilized before procedures or delivery.

Type I VWD rarely requires treatment since the levels of VWF and FVIII rise sufficiently by the time of delivery. However with all types of VWD, immediate and delayed postpartum hemorrhage can occur despite prophylaxis and therefore these patients require close monitoring for up to two weeks postpartum. If additional agents are needed to control bleeding, combined oral contraceptives and anti-fibrinolytics can also be utilized.

Type IIb VWD is characterized by enhanced affinity of the abnormal VWF binding to platelets and leading to thrombocytopenia during pregnancy. The thrombocytopenia typically worsens in the third trimester and DDAVP is usually avoided since its administration can worsen the thrombocytopenia. Type III VWD requires support with VWF concentrates throughout pregnancy and will not benefit from DDAVP.

Severe postpartum hemorrhage is a complication of delivery that in the majority of cases will not be due to an inherited coagulopathy. The hematologist may be called to assist in controlling hemorrhage that is obstetrical in nature and a consequence of abnormal separation and expulsion of the placenta as that which occurs with uterine atony.[53] Expected blood loss in this setting is estimated around 500 mL with a vaginal delivery. The patient may have developed a coagulopathy acutely secondary to hemodilution, disseminated intravascular coagulation (DIC), or ALFP (Acute Fatty Liver of Pregnancy) Additional reasons for postpartum hemorrhage include placenta accreta, HELLP syndrome and amniotic fluid embolism. Treatment is aimed at normalizing the coagulation disturbance with plasma, cryoprecipitate, platelet and packed red cell transfusions.[53] It is recommended to use transfusions of blood products to maintain fibrinogen levels above 100 mg/dL, hemoglobin above 8gm/dL, platelets above 75 K/uL and a prothrombin time and activated partial thromboplastin time ratio greater than 1.5. Baseline fibrinogen levels less than 200 mg/dL are predictive of the severity of post partum hemorrhage and suggest the need for multiple blood transfusions and surgical intervention.[54] Recently tranexamic acid and recombinant activated factor VII (rFVIIa) have been used in this setting, however more data is needed to determine safety and efficacy during pregnancy.[55,56]

Acquired hemophilia

The occurrence of peripartum bleeding associated with a prolonged activated partial thromboplastin time (aPTT) in a woman without a personal or family history of bleeding deserves evaluation for acquired hemophilia. This is an immune-mediated process that leads to the creation of autoantibodies against coagulation factors (typically factor VIII) and is associated with life-threatening bleeding amongst most patients that requires urgent diagnosis and treatment. The condition is associated with pregnancy[57] as well as with malignancies and autoimmune diseases. Unlike congenital hemophilia where hemarthroses and trauma related deep muscle bleeds largely occur, acquired hemophilia tends to be associated with spontaneous bleeding in mucosal sites (gastrointestinal, lung and urogenital) and in subcutaneous tissue, and with retroperitoneal or intracranial bleeding.[58] The disorder typically occurs in the weeks to months following delivery with ranges reported between 21 and 120 days,[59] however delays in diagnosis suggest it presents in the antepartum also. The diagnosis is made by evaluating the prolonged aPTT with a 1:1 mixing study at 0 and 2 hours to exclude factor deficiency. Tests should also be performed to rule out heparin or lupus anticoagulant effect. Subsequent assays should be performed to evaluate factor VIII inhibitor titers using the Bethesda assay.[60] Treatment is usually directed at achieving hemostasis to treat the acute bleeding episode and inhibitor eradication to prevent subsequent bleeding. First line-treatment for major bleeding episodes typically includes activated prothrombin complex concentrates (aPCC) or rFVIIa to bypass the inhibitor. Corticosteroids in combination with cyclophosphamide, IVIG or rituximab have been used with varying success to eradicate the pathologic autoantibody,[59] but there is no data directly comparing these agents. Additionally, in many women the antibody will spontaneously remit without immunosuppression.[57] Management of patients with mild to no bleeding is less clear and includes numerous strategies aimed at avoiding invasive procedures and monitoring the inhibitor titer.[61]

THROMBOSIS AND THROMBOPHILIA

Venous thromboembolism

The rapid recognition and treatment of venous thromboembolism (VTE) during pregnancy is essential since VTE is a major cause of maternal mortality. The risk of thrombosis increases as pregnancy progresses and subsequently peaks during the puerperium. The elements of Virchow's triad (hypercoagulability, stasis, endothelial damage) underlie the pathogenesis of VTE in pregnancy. Firstly, the *hypercoagulable* state is created by an increase in coagulation factors, acquired resistance to activated protein C, fall in free protein S, and impaired fibrinolysis. Secondly, diminished venous flow to the lower extremities creates *stasis*. And thirdly, *endothelial damage* occurs during vaginal delivery or cesarean section.

Most VTEs in pregnant women are left sided and ileofemoral owing to the compression of the left ileac vein by the gravid uterus. Similar risk factors exist for pregnant and nonpregnant women, e.g., prior VTE, immobility, obesity and smoking. Pregnancy-specific conditions also contribute to the risk for VTE during pregnancy and include preeclampsia, assisted reproductive techniques, hemorrhagic complications and twin pregnancies.[62,63] Although compression duplex ultrasound of the entire proximal venous system is considered the first-line test for diagnosis of DVT in pregnancy, it is important to note that if iliac vein thrombosis is suspected further imaging with magnetic resonance venography, contrast venography or pulsed Doppler may be required. D-dimer levels should be interpreted cautiously since they can be inconsistently elevated throughout pregnancy and their predictive value has not been validated.[64] The diagnosis of pulmonary thromboembolism (PE) tends to pose a greater challenge to the clinician because of the fear of exposing the fetus to radiation imposed by radiographic tests. When available, ventilation/perfusion (V/

Q) lung scans are preferred over computed tomography pulmonary angiography (CTPA) because V/Q lung scans carry a higher (less??) radiation exposure to the fetus. However, CTPA should not be withheld if suspicion of PE is high given the mortality associated with the condition.[65]

Low-molecular-weight heparin (LMWH) is the recommended treatment for pregnant women with VTE.[66] Twice daily dosing should be considered given the altered pharmacokinetics of the drug during pregnancy, and treatment should be extended 6 weeks beyond delivery to provide a minimum duration of therapy of 3 months. In general, there is no need to monitor anti-Xa levels for women on LMWH unless extremes of weight exist (< 50k kg or >90 kg) or renal insufficiency is present. Since vitamin K antagonists cross the placenta and are teratogenic, their use is contraindicated during pregnancy, but can be used postpartum given the insubstantial secretion in breastmilk.

Women who are on anticoagulation with warfarin for a prior VTE should be changed to LMWH prior to 6 weeks of gestation to avoid adverse effects on the embryo.[66] There is little data to support how to manage anticoagulation at the time of delivery. Most recommend a planned delivery for women on therapeutic anticoagulation in order to reduce the dose of anticoagulation prior to delivery, and thereby minimize the bleeding risk during induction of labor or elective cesearean section.[65] Neuraxial anesthesia can also be safely administered only if the LMWH has been held for at least 24 hours. LMWH is generally preferred over unfractionated-heparin (UFH) because of its efficacy and side effect profile.[67] However, in the case of massive life-threatening PE, UFH is sometimes preferred because of its rapid effect. Thrombolytic therapy may also be warranted for life-threatening PE followed by infusion of UFH since there is some data showing thrombolytics can be safely administered to pregnant women.[68] Fondaparinux is typically reserved for those with heparin-induced thrombocytopenia (HIT) given the limited safety data in pregnancy. The newer agents, such as anti-Xa inhibitors and oral thrombin inhibitors should not be used during pregnancy until efficacy and safety data during pregnancy is demonstrated.

Prevention of VTE in women with thrombophilia

It is important to identify those women who may have an increased risk of VTE during pregnancy and therefore merit intervention with thromboprophylaxis. Many women will have a history of prior VTE or even a preexisting thrombophilia but determining when the risk is sufficiently high to warrant daily LMWH or UFH is highly controversial and likely stems from our limited knowledge of the natural histories of the various thrombophilias. Results from the MEGA-study, a large population-based case study evaluating cases of first VTE as compared to controls, noted that the risk of VTE was 5-fold increased during pregnancy and further increased to 60-fold during the first 3 months after delivery.[69] For carriers of factor V Leiden and prothrombin 20210A mutation, the risk was 52-fold and 31-fold compared to nonpregnant controls respectively. Since the greatest threat for VTE occurs in the postpartum period, most recommend prophylactic anticoagulation during this time period for women who have had a prior VTE or who have a known thrombophilia.[66] However, it is not clearly established whether women with a previous VTE have an increased risk of recurrence during pregnancy and therefore require prophylaxis. Half of all pregnancy associated VTE events occur in women with heritable thrombophilia; however the background incidence of VTE during pregnancy is rather modest, 1 in 1000 deliveries. Furthermore, the rates of pregnancy associated VTE among women with inherited thrombophilias are conflicting.[70–72] Consequently, the recommendation to provide prophylaxis to women without a prior VTE and who have an underlying thrombophilia, remains controversial. With the exception of homozygosity for the thermolabile methylene tetrahydrofolate reductase variant (MTHFR C677T), most inherited thrombophilias increase the risk of thrombosis during pregnancy and the presence of a positive family history further

increases the risk. The current guidelines from CHEST (2012) recommend that among those women without a prior VTE, only those who have a positive family history and are known to be homozygous for factor V Leiden or the prothrombin G20210A gene mutation receive antepartum prophylaxis.[66] Contrary to prior dogma, deficiencies of the endogenous anticoagulants (antithrombin, protein S, and protein C deficiency) are associated with a low to moderate risk of VTE during pregnancy. Recently, higher-quality studies have demonstrated that the VTE risk from antithrombin deficiency, typically regarded as a high-risk thrombophilia, was possibly overestimated.[73,74] Consequently, guidelines support the use of postpartum (not antepartum) prophylaxis for antithrombin, protein S, and protein C deficiency only when women also have a positive family history of VTE.

Conclusions

Many hematologic problems develop in pregnancy or can be triggered by the pregnant state. Normal physiologic changes during pregnancy can alter hematologic indices during pregnancy and make recognition of pathologic states difficult. Pregnancy can exacerbate underlying hematologic disorders as well as predispose to life-threatening hematologic emergencies. These conditions are a significant source of morbidity and mortality during pregnancy that has implications for both the mother and the fetus. Unfortunately, the lack of well-controlled prospective studies to guide treatment decisions creates significant challenges for the hematology consultant.

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Table I

Causes and treatment of maternal thrombocytopenia in pregnancy

Cause		Treatment
Gestational thrombocytopenia	75% ($2^{nd}/3^{rd}$ trimester)	No treatment required, resolves spontaneously after delivery
Preeclampsia	15–20% ($2^{nd}/3^{rd}$ trimester)	Delivery if ≥34 weeks. Platelet transfusions to support procedures
Immune thrombocytopenia	1–4% ($1^{st}/2^{nd}$ trimester)	IVIG or corticosteroids if platelets <30 k/uL. Splenectomy, azathioprine as second-line
HELLP syndrome	Rare	Delivery if ≥34 weeks. Transfusions if platelets <20 k/uL. Plasmapheresis for refractory or atypical cases
Acute fatty liver of pregnancy (AFLP)	rare	Termination of pregnancy. Plasmapheresis for refractory or atypical cases
TTP	rare	Plasmapheresis and delivery if ≤34 weeks
SLE	rare	Platelets < 95 k/uL indicate treating lupus flare
Antiphospholipid antibody syndrome	Rare (associated with thrombocytopenia in 30% of cases)	Anticoagulation therapy to prevent fetal loss. Treat as ITP if platelets < 30–50 k/uL.
Type IIb VWD	rare	Platelet transfusions, factor replacement
Viral infections	rare	Screen for CMV, EBV, HCV, HIV, HBV
Bone marrow failure (congenital or acquired)	rare	Transfusion support until delivery

Table 2

Management of bleeding disorders during pregnancy

Disorder	Treatment
Fibrinogen deficiency (bleeding phenotype)	Fibrinogen concentrate or cryoprecipitate to maintain fibrinogen >100 mg/dL
Factor XIII deficiency (severe)	FXIII replacement therapy monthly
Factor XI deficiency	Check levels prior to invasive procedures and delivery. Give prophylactic FXI if levels <15 IU/dL, not to exceed >70 IU/dL. Other treatment includes tranexamic acid, recombinant FVIIa.
Acquired hemophilia (factor VIII inhibitor)	aPCC or rFVIIa, +/− immunosuppression
Hemophilia carriers	Give recombinant FVIII or FIX at delivery and 3–5 days postpartum to maintain levels >50 IU/dL. C-section indicated to prevent intracranial bleeding.
VWD, type I and IIa	Check vWF panel prior to invasive procedures and delivery. Prophylaxis generally not required. Treat with factor replacement (vWF-FVIII plasma concentrates), DDAVP, tranexamic acid and combined oral contraceptives for hemorrhage.
VWD, type IIb	May have worsening thrombocytopenia during pregnancy, support with platelet transfusions, factor replacement (vWF-FVIII plasma concentrates). DDAVP contraindicated.
VWD, type III	Factor replacement throughout pregnancy (vWF-FVIII plasma concentrates). DDAVP contraindicated.