Pregnancy

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Pregnancy

There are many reasons why a hematologist would be asked to see a woman who is (a) contemplating pregnancy but has a coagulation disorder or a family history of one, (b) pregnant and having either bleeding or thrombotic problems, (c) in labor and having a coagulopathy, or (d) in the postpartum period and having a coagulation concern. This chapter addresses the four issues separately, but begins by addressing the normal physiologic coagulation related issues that occur during a normal pregnancy and delivery.

Changes in Clotting Factors During Pregnancy (See Table 17.1)

During pregnancy, Factor VIII:C and FVIII von Willebrand factor (FVIII:VWF) levels rise steadily (Dossenbach-Glaninger et al. 2004), fibrinogen, factors VII and X also rise, but the levels of Factors II, IX, XII, and XIII stay about the same. Indeed, fibrinogen levels rise threefold (de Boer et al. 1989). Some studies of pregnant women show FXI level rising and some show a fall (Glueck et al. 2010). There are also changes in some of the naturally occurring anticoagulants. Protein C and antithrombin III levels stay constant, but Protein S levels fall (Faught et al. 1995). Fibrinolysis is reduced during pregnancy but can rise to normal within 1 h of delivery. Pregnancy induces an impairment of fibrinolysis through an increase in tissue plasminogen activator inhibitor-1 (PAI-1). Also, the placenta synthesizes plasminogen activator inhibitor-2 (PAI-2). Once the placenta is delivered, this substance's concentration falls rapidly and may be at a very low level within 1 h of delivery (Van Wersch and Ubachs 1991).

If one considers the logical needs of a pregnant woman as she approaches the birth process, it would make sense for the coagulation system to favor excessive clotting over excessive bleeding at the time of delivery. As the fetus is expelled, the placenta starts separating from the uterine wall, exposing a large surface of vessels which, for 9 months, were committed to O_2 exchange between maternal uterine arterioles and capillaries and the placental surface. As the uterus contracts after birth, there is physical tamponading of these vessels, but due to increases in clotting factor levels and decreases in fibrinolysis, the estimated blood loss from a normal delivery is usually about 500 cc (Sloan et al. 2010), and 1,000 cc for caesarean section.

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Table 17.1 Changes in coagulation factors during pregnancy

Factors that rise	Factors that stay the same	Factors that fall	Factors that rise and fall (or for which there are conflicting data)
Factor VIII:C	Factor II	Protein S	Factor V
Factor VIII: von Willebrand Factor	Factor IX	Plasminogen	Factor XI
Factor VII	Factor XII		
Factor X	Factor XIII		
Fibrinogen	Protein C		
Plasminogen activator inhibitors (PAI-1 and 2)	Antithrombin		

Women Contemplating Pregnancy Who Have Established Coagulation Abnormalities

A woman who knows that she has either an acquired or congenital coagulation disorder may present to the consulting hematologist seeking advice on how to handle that disorder during pregnancy and delivery. This section will deal separately with several of these disorders.

Bleeding Disorders During Pregnancy

von Willebrand's Disease

An extensive discussion of von Willebrand's Disease (VWD) is found in Chap. 4 of this book. Here, there will be a brief review of this disorder and then a longer discussion of the pregnancy and labor/delivery issues.

VWD is very common, affecting 2 % of the total population. Gradually, during the 9 months of gestation, levels of VWF protein at labor have risen three times as much as pre-pregnancy levels. VWD is divided into three types; type 1, type 2, and type 3. Type 1, which affects approximately 80 % of all those with VWD, usually has a minor effect on the pregnant woman. With the physiologic rise of FVIII:VWF levels through pregnancy, by the time the woman delivers, she may have normal VIII:VWF levels (Kujovich 2005). Women with type 2 or 3 VWD have no changes in the VIII levels, so they may require more attention to achieve hemostasis. Type 2A VWD is characterized by a more extensive fall of FVIII:Ristocetin Cofactor (FVIII:RCo) compared with FVIII:Antigen (FVIII:Ag) and lowered or absent levels of high and intermediate molecular weight VWF multimers. The lower the VIII:RCo, the more severe the bleeding. Type 2B VWD is caused by a genetically altered VIII:VWF molecule that has increased affinity for platelet membrane glycoprotein IB. As the VWF level rises during pregnancy, this can lead to a greater degree of thrombocytopenia. As platelets aggregate more, there may be a paradoxical increased risk of thrombosis. Type 3 VWD is characterized by very low levels of all VWF multimers and low levels of VIII:C, VIII:Ag, and VIII:RCo. These women experience no rise in their levels of these factors during pregnancy, and can have significant bleeding during pregnancy and during the postpartum period (Mannucci 2001).

If the consultant knows a woman has VWD and becomes pregnant, it is advisable to check FVIII levels every 2–3 months until the time of delivery, and continue checking up to 2 months postdelivery. The severity of bleeding complications correlates best with depth of VIII: RCo levels. Levels of 50 IU/dL (lower end of normal, normal being defined as roughly 50–150 IU/dL) are usually adequate for normal vaginal delivery or caesarean section. Levels below 50 IU/dL may require treatment with DDAVP (postpartum) or von Willebrand factor concentrates. Since VWF levels fall quickly after delivery, doses of DDAVP postpartum may help to prevent postpartum delayed hemorrhage (Lee et al. 2006). Other options include Humate P. If one looks at the package insert for Humate P, dosing is based on VIII:RCo units. A caesarean section should be considered a "major" surgical procedure,

and a normal vaginal delivery with episiotomy might be considered a little less risky, but it is not a "minor" procedure. Therefore, the dose of humate P prior to a planned or emergent C-section should be initiated with a loading dose of 50–75 IU/kg, and subsequently dosed at 40–60 IU/kg every 8–12 h for 3 days. It is imperative to maintain a nadir of 50 IU/dL of VIII:RCo. After 3 days, as long as the woman is not bleeding significantly, one may begin dosing every 24 h of 50 IU/kg (Lee et al. 2006).

DDAVP causes egress of VIII:C and VWF from Weidel Palade bodies in the endothelium. It is very useful in mild hemophilia and milder forms of Type I VWD to prevent bleeding after minor procedures. DDAVP does not cause uterine contractions, so may be used during pregnancy (Ray 1998), though most consultants wait until labor is well along before using it. If it is used daily, severe symptomatic hyponatremia can occur. Hypotonic saline should be avoided and women should be on fluid restriction. DDAVP should be avoided in Type 2B VWD because it exacerbates the thrombocytopenia.

Type 2N (Normandy) VWD

One of the subtypes of Type 2 VWD, the type 2N, is due to a genetic mutation affecting the site where VWF binds to the FVIII molecule. Multimer patterns are normal. FVIII:RCo and VIII:Ag levels are normal, but FVIII:C levels are very low—this condition can be easily confused with hemophilia A. Inheritance is autosomal recessive, however, and not X-linked recessive as in hemophilia A. These individuals do not have a good rise in FVIII level with infusions of FVIII:C, and should receive Humate P if their levels of FVIII:C are <50 IU/dL (Dennis et al. 2000).

Hemophilia (Factor VIII:C or Factor IX Deficiency)

Since hemophilia A (FVIII:C deficiency) and hemophilia B (FIX deficiency) are X-linked recessive disorders, women in these families are (often) carriers, and would be expected to have 50 % of normal levels. However, if there is severe Lyonization, the FVIII:C or IX level can be much lower. As these women approach labor, if their VIII:C or IX levels are <50 IU/dL, they may require DDAVP if VIII deficient or recombinant IX, if IX levels are <50 IU/dL. FIX levels do not rise during pregnancy like VIII:C does, so IX carriers may be more likely to bleed than VIII carriers.

FXI Deficiency

This deficiency status is common among Ashkenazi Jews. FXI is synthesized in the liver and deficiency is of autosomal recessive transmission. Levels below 20 % are associated with bleeding during surgery. Curiously, some individuals with severe deficiency (<1 % activity) do not bleed with surgery. Also, bleeding risk can vary over time, so a young person with homozygous deficiency (<1 %) may do fine with hernia repair at age 16, but can have severe bleeding during labor and the postpartum period.

There are conflicting data as to what happens to FXI levels during normal pregnancy. Some studies show an increase and some show a decrease (Martin-Salces et al. 2010). If a woman has less than 40 IU/dL at the time of labor/delivery, replacement with FFP is recommended (Myers et al. 2007; Lee et al. 2006). In Europe, there is a FXI concentrate available, but its use has been associated with thrombosis.

Uncommon Clotting Factor Deficiencies

Women who have FXIII deficiency have an elevated rate of miscarriage. To maintain pregnancy, these individuals need infusions of cryoprecipitate or FFP throughout their pregnancy and for up to 4 days postpartum (Burrows et al. 2000; Lee et al. 2006). Women who are hypofibrinogenemic or afibrinogenemic may also manifest difficulty maintaining pregnancy, and they too require infusions of cryoprecipitate. In women who are severely VII deficient, and who have a history of bleeding with surgery, the use of recombinant VII

A in the peripartum and for 3 days postpartum period at a dose of 15 μg/kg every 6 h is recommended (Burrows et al. 2000).

Platelet Disorders

There are several lifelong qualitative platelet disorders which can impact the outcome of pregnancy. Glanzmann's thrombasthenia is due to a deficiency of glycoprotein II B and III A (fibrinogen receptor) on the surface of platelets, which causes an inability for fibrinogen to serve as a bridge between platelets during aggregation. PT and PTT are normal, fibrinogen levels are normal, but platelet aggregation is flat line to all agonists. Platelet flow cytometry can document the severity of deficiency of II B/III A. This test is recommended to establish this diagnosis as well as to understand the severity of the bleeding risk.

Women with Glanzmann's thrombasthenia usually have menometrorrhagia, and bleeding can be severe and life threatening. Platelet transfusions are necessary to achieve hemostasis for surgery. Antifibrinolytics can help prevent hemorrhage with simple trauma (DiMinno et al. 2009).

If a woman with Glanzmann's thrombasthenia becomes pregnant, infusions of platelets during delivery, preferably single donor platelets, can help prevent severe bleeding. This should be done even if the patient has a normal platelet count. Postpartum hemorrhage can be abated with further platelet transfusion (Monte and Lyons 2002). There are case reports detailing the use of recombinant FVIIa in this setting. It is prudent to wait until after delivery to infuse this potent procoagulant because of concern for what it might do to compromise the placental circulation and the attendant effects on the fetus (Phillips et al. 2009; Poon et al. 2004).

Hermansky–Pudlak Syndrome

This syndrome is due to a combination of oculocutaneous albinism, a platelet storage pool defect, and a lysosomal storage accumulation of ceroid lipofusion. There are nine types and all are inherited as an autosomal recessive defect. These individuals usually have a mild bleeding diathesis, and this is best determined by taking a good history, but they typically exhibit pulmonary fibrosis around age 40, and that complication is the usual cause of death.

The genetic defect is a mutation of the HPS gene (many variants, e.g., HSP1, HSP3, HSP4). Each of these has been found on the long arm of chromosome 10. Some subtypes are seen in individuals of Puerto Rican ancestry and other subtypes are more common in Ashkenazi Jews.

Electron microscopy of platelets demonstrates an absence of dense bodies. Platelet aggregation studies demonstrate decreased platelet aggregation responses to ADP, arachidonic acid, collagen, and epinephrine with loss of secondary aggregation. The platelet aggregation to ADP at higher concentrations (20 μM) may normalize. The stimulated dense granule release responses to ADP (5 μM), arachidonic acid, collagen, and epinephrine are nearly absent. PFA-100 platelet function screen testing demonstrates prolongation of both col/epi and col/ADP cartridges.

Oftentimes platelet transfusions are necessary to achieve hemostases if the bleeding risk is higher, but for minor procedures, DDAVP may be all that is necessary, and this has been used for providing epidural analgesia during labor (Spencer and Rosengren 2009).

Bernard–Soulier Syndrome

This is a platelet disorder inherited as an autosomal recessive defect, which leads to a loss of, or less than normal amount of, glycoprotein IB on the platelet surface. This glycoprotein is the receptor for von Willebrand factor. The platelet count is low and the platelets are large. Bernard–Soulier platelets do not aggregate in the presence of ristocetin, and this defect is not corrected when normal plasma is added, a distinguishing feature between Bernard–Soulier syndrome and VMD.

Labor and delivery can proceed in women with this, but if the level of glycoprotein is very low, prophylactic platelet transfusion may be necessary. Again, platelets are the mainstay of treatment, but in milder cases, DDAVP and antifibrinolytics can help slow or prevent bleeding (Saade et al. 1991; Peaceman et al. 1989; Rahini et al. 2005).

Immune Thrombocytopenic Purpura

This is probably the most common and important consult for a hematologist who deals with pregnant patients. A woman who has a known diagnosis of immune thrombocytopenic purpura (ITP) may present a challenge to the obstetrician, hematologist, and pediatrician of the soon-to-be-born child. If she is only mildly affected and her platelet count is near normal, no special interventions may be needed. However, if her platelet count is very low, such as less than 20,000/μL, and since the antibodies mediating her platelet destruction can cross the placenta and affect the fetus' platelet count, the treating team may have two severely thrombocytopenic patients for whom they must care—the mother and the fetus (Gill and Kelton 2000).

A normal woman tends to drop her platelet count throughout pregnancy because of increased plasma volume (dilutional effect). This is called "gestational thrombocytopenia," and may be difficult to distinguish from mild ITP (Levy and Murphy 2002). If a woman does have a normal platelet count before pregnancy, then drops her platelets during pregnancy, and then platelets return to normal after pregnancy, and the baby is born with a normal platelet count, one may refer to her episode of thrombocytopenia as "gestational thrombocytopenia." Generally, gestational thrombocytopenia is defined as platelet counts between 100,000 and 150,000/μL. Often the platelets are a little larger than normal. Platelet counts between 70,000 and 100,000/μL may still be considered due to gestational thrombocytopenia, but the physician should assiduously rule out other causes of thrombocytopenia, such as HIV, hepatitis, lupus, and lupus anticoagulant positivity. This is a very important consideration. Admittedly, these tests are routinely done as soon as a woman is known to be pregnant, but it may be prudent to repeat some of these tests, as clinically indicated. It is also prudent to check the peripheral smear as the pregnancy proceeds, especially looking for schistocytes, and also making sure that white cell morphology is not changing, which can occur in a neoplastic process.

Women who drop their platelet count during pregnancy and raise their blood pressure, may be presenting with unique syndromes such as HELLP, preeclampsia, or DIC, and these will be discussed below.

The American Society of Hematology (ASH) published a clinical practice guideline on ITP in 1996 and it was updated in 2011 (Neunert et al. 2011). There is a section on ITP and pregnancy in the original guideline and, in the 2011 update, there was little change. Arbitrary platelet count levels of <10,000, 10,000–30,000, and >30,000 were used to guide decision making. If a woman has ITP and is pregnant, and her platelets are >30,000/μL and is not bleeding, nothing needs to be done except monitor her with periodic complete blood counts. If the platelet count is lower and there is bleeding, treatment is indicated. Both prednisone, at a dose of 1 mg/kg/day, and IVIgG, at a dose of 400 mg/kg daily for 5 days, or 1 g/kg daily for 2 days were considered appropriate and safe for both the woman and the fetus. There was commentary and caution in the guidelines about steroid induced diabetes and depression. It was recommended to avoid cyclophosphamide and vinca alkaloids because of teratogenicity. Splenectomy was not encouraged during pregnancy because of increased risk of preterm labor during first trimester, and it is technically difficult to do in the third trimester (Felbinger et al. 2007).

There is a separate section on "Treatment of ITP during labor & delivery" in the guidelines (Neunert et al. 2011). Measurement of fetal platelet count can be achieved with percutaneous umbilical blood sampling (PUBS), but that was not encouraged due to risks, especially fetal demise. Fetal scalp puncture/sampling can only occur once labor has commenced and the fetal head is already well down the birth canal. Ultimately, the guideline recommends that "ITP management during labor and delivery is based on an assessment of maternal bleeding risks associated with epidural anesthesia and with delivery and the minimum platelet counts required to

safely undergo these procedures" (Neunert et al. 2011). There was no evidence to support specific platelet count thresholds that are safe in the anteor peripartum period. In a single center retrospective review of labor management of 119 mothers with ITP, epidural anesthesia was given for a maternal platelet count <50 K in one case, and 50–75,000 in six cases. Vaginal delivery was carried out in 82 % of deliveries and in 18 %, C-sections were performed. One quarter (25 %) of the neonates were born with thrombocytopenia, but there were only rare events of severe bleeding (Webert et al. 2003). Caution should note that this was a Canadian study, and the litigious climate in the USA would likely sway a treating obstetrician to perform C-sections more frequently in mothers with ITP.

Management of the baby, once born, to a mother with ITP necessitates careful monitoring of the platelet count. Platelets may fall during the first week of life. IVIgG is generally given to the baby to maintain a safe platelet count, until the maternal antibodies mediating the fetus' thrombocytopenia have cleared.

Thrombotic Disorders During Pregnancy (See Table 17.2)

This part of the chapter will be divided into two parts. The first section will deal with those individuals with known underlying thrombotic disease who are contemplating pregnancy, and the second part will discuss those women who become pregnant and develop an unexpected thrombotic disorder during pregnancy or postpartum.

Table 17.2 Venous thromboembolism (VTE) in pregnancy

Pregnant women have a fourfold to fivefold increased risk of VTE compared with nonpregnant women
80 % of VTE events in pregnancy are venous with a prevalence of 0.5–2.0 per 1,000 pregnant women
VTE accounts for 1.1 deaths per 100,000 deliveries, or 9 % of all maternal deaths in the USA
75–80 % of VTE are deep vein thromboses (DVT), and 20–25 % are due to pulmonary embolism (PE). One half of these events occur during pregnancy and one half occur during the postpartum period

Thrombophilic Women Before Pregnancy (See Tables 17.3 and 17.4)

It is not uncommon for a woman with a known hypercoagulable state to come to her physician questioning her risks if she were to become pregnant. These women may be completely asymptomatic, and have been tested for thrombophilia because of a family member who was identified as having a thrombophilic disorder. They may be completely asymptomatic at the time of the consult, but they may have had a previous manifestation of venous thromboembolic disease. They may have never been pregnant before, or they might have been pregnant and had a miscarriage, or even may have had a completely normal pregnancy and delivery in the past.

Pregnancy is a prothrombic state for many reasons. There are clotting factor changes with elevations of procoagulant factor levels (de Boer et al. 1989; Glueck et al. 2010) and decreases of endogenous anticoagulant factors (Faught et al. 1995), such as Protein S, impaired fibrinolysis (Van Wersch and Ubachs 1991), and an acquired resistance to the action of activated Protein C. There is venous stasis and hormonally driven increases in the distensibility of the veins in the legs and pelvis. Also, the gravid uterus sits directly on the veins draining the legs and by physical force tends to slow down the flow of blood out of the legs.

Table 17.3 Indications for thrombophilia testing prior to or during pregnancy[a]

Testing recommended
Personal history of thrombosis
First-degree relative with known thrombophilia and history of thrombosis
Testing should be considered
Family history of thrombophilia
Prior unexplained fetal death associated with abnormal placental pathology
Prior severe onset preeclampsia (<34 weeks gestation)
Prior severe intrauterine growth retardation (IUGR)

[a]Testing is more likely to be helpful for thrombophilias with high risk for thrombosis (e.g., antithrombin deficiency) rather than Factor V Leiden

Table 17.4 Thrombophilia screening tests in pregnancy[a]

Factor V Leiden
Prothrombin gene mutation
Antithrombin deficiency
Deficiency of Protein S and C[b]
Anticardiolipin antibodies and lupus anticoagulants
Cutoff value for free protein S antigen in the second trimester <30 % Cutoff value for free protein S antigen in the third trimester is <24 % [a]Screening for MTHFR is not indicated [b]Do not screen for Protein S during pregnancy or while on oral contraceptives

Table 17.5 Venous thromboembolism (VTE) prophylaxis in pregnancy and postpartum

Consultation with maternal–fetal medicine is recommended for:
Patient diagnosed with high-risk thrombophilia
Patient with prior VTE event
Patient taking long-term anticoagulation therapy prior to pregnancy
Patient with valvular heart disease or arrhythmia
Patient started on anticoagulation therapy during this pregnancy by outside physician without clear indication
Patients should be informed of the risks, benefits, side effects, and alternatives to anticoagulation medication
Complicated cases may require consultation with vascular medicine or hematology-oncology to determine an individualized management plan
Patients requiring long-term anticoagulation should be referred to a coumadin clinic after delivery

Table 17.6 Classification of thrombophilia (obstetric viewpoint)

High-risk thrombophilias
Factor V Leiden (FVL) homozygous
Prothrombin Gene (PTG) mutation homozygous
FVL heterozygous and PTG heterozygous
Antithrombin deficiency
Low-risk thrombophilias
FVL heterozygous
PTG mutation heterozygous
Protein C deficiency
Protein S deficiency

Maternal deep vein thromboses and pulmonary emboli occur in about 0.05–0.2 % of all births. Pulmonary embolism is a major cause of maternal death (Dresang et al. 2008). Thrombophilic states also interfere with normal placental function and can lead to miscarriage, especially due to antiphospholipid antibodies (Derksen et al. 2001). This acquired autoimmune disorder may be a reason why a woman might have given birth normally, at first, and then once acquiring the thrombophilic defect, begin to have miscarriages.

The most common thrombophilic defects that are examined in the laboratory now are (1) Factor V Leiden, (2) prothrombin gene 20210 mutation, (3) lupus anticoagulant, and (4) presence of a myeloproliferative state. By far, the more common reasons for a clinically driven risk for VTE are smoking, obesity, family history of VTE, and a sedentary lifestyle (see Tables 17.5 and 17.6).

If a woman has a history of being on oral contraceptives for years without developing a VTE, the chance that an underlying congenital thrombophilic state like homozygous (more risk) or heterozygous (less risk) FV Leiden will cause VTE during pregnancy, is lower (Dizon-Townson et al. 2005). If she had a fractured leg, and did not develop a VTE while in a cast for several weeks, that too is a soft finding favoring that she would not develop a VTE with pregnancy.

Homozygosity for genetic defects like FV Leiden (Heit et al. 2005) and prothrombin gene mutation (Gerhardt et al. 2000) is obviously worse than heterozygosity. However, if a mother is homozygous for the MTHFR mutation without a rise in homocysteine level, there is no increased risk for VTE (Varga et al. 2005).

Some women have more than one thrombophilic state, and there are synergistic effects when more than one thrombophilic state is present. As stated in the "Thrombotic Risk Factors" chapter of this text, heterozygosity for Factor V Leiden or prothrombin gene 20210 mutation confers only a small increased risk for VTE. However, if there is combined heterozygosity, the risk is greater. A pooled analysis of case–control studies found odds ratios for VTE of 4.9 and 3.8 for Factor V Leiden and prothrombin G20210A mutations, respectively, but an odds ratio of 20 in double heterozygotes (Emmerich 2001; see this reference in Price and Minichiello's chapter in this text).

On the other hand, if one screens the general population of pregnant women, without a causative question arising during a normal OB/patient relationship, very low rates of VTE are demonstrated. In one study (Lindqvist et al. 1999), there

was no case of VTE during pregnancy or during the postpartum period in a large group of women found to be heterozygous for FV Leiden by general screening. It is for this reason that screening for thrombophilic states is *NOT* recommended.

Antithrombin deficiency carries an even higher risk than the other commonly tested congenital thrombophilias (Yamada et al. 2001). Depending upon how one defines the level of an antithrombin deficiency, rates of 1 in 3, or up to 1 in 250 pregnancies may be associated with VTE.

If a woman is known to be antithrombin deficient and has been receiving LMWH to prevent clotting during pregnancy, one can administer exogenous recombinant antithrombin concentrates. These can be given at a dose of 50 U/kg prior to delivery. One should aim to keep the plasma antithrombin level near 100 % activity until the time is appropriate to reinitiate LMWH after the delivery. One may need to give this daily for up to 7 days (Hellgren et al. 1982; Schulman and Tengborn 1992).

How to Diagnose DVT/PE in a Pregnant Woman?

A woman who is pregnant and comes to the doctor with shortness of breath, chest pain, hemoptysis, unexplained hypoxia, or a painful or swollen leg should be tested for suspected PE and/or DVT. Sometimes, it is very hard to know when to pursue this workup, because many normal pregnant women have swollen legs and can be short of breath from carrying the extra weight. The testing used should have the lowest possible radiation exposure to the fetus. Which trimester the woman is in makes this question more imperative because the fetus is more sensitive for teratogenicity with radiation exposure in the earliest phases of pregnancy, i.e., first trimester, and can tolerate this potential insult much better closer to term (Winer-Muram et al. 2002).

Because of anatomic considerations, many more DVT's occur in the left leg than in the right (Scarsbrook et al. 2006). This is because the right internal iliac artery is in such close proximity to the left iliac vein. During pregnancy, the gravid uterus pushes back over this area and compresses the left iliac vein more than the right. In some series, the left leg is the site of DVT 85 % of the time (Ginsberg et al. 1992). This phenomenon is often referred to as the May–Thurner Syndrome.

Doppler venous ultrasound of the leg is the most helpful tool in establishing a DVT diagnosis. It is noninvasive and uses no radiation. It is highly sensitive and specific. It is a little less reliable in a woman who has a distant history of DVT, because the technician performing the study, and the ultrasonographer reading the scan, may have difficulty distinguishing an old clot from a new clot. In some centers, D-dimer is a test drawn to aid in deciding if a clot is present. This test is more unreliable during pregnancy because the D-dimer level rises, usually above the normal range, as a normal pregnancy progresses (Kline et al. 2005).

When a vein is affected by DVT in the more proximal locations (closer to the inferior vena cava, or IVC, or external iliac vein), the Doppler venous ultrasound may be less helpful to establish a diagnosis. Some centers use magnetic resonance venography without gadolinium to establish an IVC or iliac vein thrombosis diagnosis (Fraser et al. 2002). Gadolinium contrast is to be avoided during pregnancy because this agent freely crosses the placenta. When excreted by the fetal kidneys, it stays in the amniotic fluid until birth. It has the potential to cause toxic side effects to the fetus/infant.

Calf vein DVT's are not as common as one would think during pregnancy, occurring in around 8 % of women who develop a DVT during pregnancy. Many of these spontaneously involute, so serial Doppler studies are helpful in determining whether extension occurs into the more proximal veins, necessitating anticoagulant therapy.

For pregnant women with suspected pulmonary embolism, it is important for them to undergo proper radiographic testing, especially CT pulmonary angiography. Reducing the amount of radiation to the woman and the fetus can be achieved, and still get an acceptable image. There are national radiologic and nuclear medicine guidelines on how to reduce the radiation dose, as well

as IV contrast dose for pregnant women (Pahade et al. 2009). Ventilation perfusion scanning also can be accomplished with use of lower doses of radiation. It is also important for all radiology departments to identify whether a female patient is pregnant. Documentation of discussions with pregnant patients about radiation to be received, and putting this documentation in the radiology report, may mitigate the medicolegal risk (Pahade et al. 2009).

What Anticoagulant to Use? (See Tables 17.7, 17.8 and 17.9)

If a woman is having a DVT or PE, or if a woman with a defined increased risk for miscarriage or DVT/PE is identified and a decision has been made she needs anticoagulation, there are several choices of medication to use. If there are delays in testing for DVT/PE either because of being in a small facility without adequate radiographic equipment, or it is the middle of the night, or staff are not available, it is recommended to anticoagulate first, and then work on diagnosis later. Coumadin is contraindicated during pregnancy because it harms the fetus (Vitale et al. 1999). There is some debate about this, but the preponderance of literature recommends against using coumadin during pregnancy. Coumadin's teratogenicity is greatest during the first trimester when limb buds are forming. Maternal ingestion of coumadin affects the coagulation status of the fetus. Bleeding into the developing limb buds causes stippled epiphyses (thus shortened limbs), cerebral hemorrhage, and underdevelopment of the nose.

It is much preferred to use an agent that does not cross the placenta. There is the most experience using unfractionated heparin (UFH) and low molecular weight heparin (LMWH). There is a greater risk of osteoporosis and heparin-induced thrombocytopenia with UFH, so LMWH is the preferred choice (Greer and Hunt 2005; Greer and Nelson-Piercy 2005). Some women develop allergy to LMWH (for example, hypersensitivity skin reactions), and alternatives for it include direct thrombin inhibitors (leprudin and argatroban), or fondaparinux. The latter agent binds to antithrombin and potentiates antithrombin-mediated inactivation of factor Xa. It is a pentasaccharide, and because of its relatively small size, it does cross the placenta, but to a low level (Dempfle 2004). It does not cross react with HIT antibodies, so it can be used in the rare woman who develops HIT during pregnancy.

If LMWH is used during pregnancy, it is best to monitor factor Xa levels. FVIII levels rise during pregnancy and makes the PTT unreliable for assessing true anticoagulant activity for heparin. Anti-factor Xa levels of 0.3–0.7 IU/mL are considered therapeutic for heparin. For LMWH, peak levels are measured 4 h post-injection and trough levels are monitored just prior to a next injection (trough level). The target anti-Xa level

Table 17.7 Anticoagulation regimens for pregnancy and the postpartum

Prophylactic low-molecular-weight heparin (LMWH)[a]
Enoxaparin 40 mg subq once daily
Therapeutic LMWH
Enoxaparin 1 mg/kg every 12 h[b]
Minidose prophylactic unfractionated heparin (UFH)
UFH 5,000 U subq every 12 h
Prophylactic UFH
UFH 5,000–7,500 U subq every 12 h in first trimester
UFH 7,500–10,000 U subq every 12 h in the second trimester
UFH 10,000 U subq every 12 h in the third trimester, unless aPTT is elevated
Therapeutic UFH (also referred to as weight adjusted, full treatment dose)
UFH 10,000 U or more subq every 12 h in doses adjusted to target aPTT in the therapeutic range (1.5–2.5 times control) 6 h after injection
Postpartum anticoagulation
Prophylactic LMWH/UFH for 6 weeks or vitamin K antagonists for 6 weeks with a target INR of 2.0–3.0, with initial UFH or LMWH therapy overlap until the INR is 2.0 or more for 2 days
Surveillance
Clinical vigilance and appropriate objective investigation of women with symptoms suspicious for DVT or PE

[a]Although at extremes of body weight, modification of dose may be required

[b]May target an anti-Xa level in the therapeutic range of 0.5–1.0 U/mL for twice daily regimen; slightly higher doses may be needed for a once-daily regimen

Table 17.8 Recommended thromboprophylaxis for pregnancies complicated by low-risk inherited thrombophilia

Scenario	Antepartum	Postpartum
Low-risk thrombophilia without previous VTE	Surveillance without anticoagulation therapy or prophylactic LMWH or UFH	Surveillance without anticoagulant therapy or postpartum anticoagulation
Low-risk thrombophilia with a single previous episode of VTE—not receiving long-term anticoagulation	Prophylactic or intermediate dose LMWH/UFH or surveillance without anticoagulation	Postpartum anticoagulation therapy or intermediate dose LMWH/UFH

Table 17.9 Recommended thromboprophylaxis for pregnancies complicated by high-risk inherited thrombophilia

Scenario	Antepartum	Postpartum
High-risk thrombophilia without previous VTE	Prophylactic LMWH or UFH	Postpartum anticoagulant therapy
High-risk thrombophilia with a single previous episode of VTE—not receiving long-term anticoagulation	Prophylactic, intermediate dose, or adjusted dose LMWH/UFH	Postpartum anticoagulation therapy or intermediate or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be at least as high as antepartum treatment)

for LMWH is generally 0.5–1.0 IU/mL (Greer and Hunt 2005; Greer and Nelson-Piercy 2005).

An acute proximal DVT or PE during pregnancy necessitates full dose therapeutic doses of anticoagulation. LMWH is probably the preferred treatment. LMWH should be given twice per day at a dose of 1 mg/kg subcutaneously (subq) or dalteperin 100 u/kg subq every 12 h. When the decision is made to use UFH, a pre-heparin PTT is obtained, and an IV bolus is given, usually 80 U/kg bolus followed by 18 U/kg/h to maintain an anti-Xa level of 0.3–0.7 IU/mL for heparin. After 5 days of IV UFH, the pregnant woman is converted over to full dose subcutaneous UFH or LMWH at therapeutic doses for the remainder of the pregnancy and for 6 weeks after delivery.

As the time of delivery approaches, one must hold the UFH or LMWH. If a planned C-section occurs, one stops the LMWH 24 h prior to delivery. Epidural catheters should not be placed unless the last LMWH dose was given at least 12 h before. One should not restart LMWH until at least 2–4 h after the catheter is removed (Meslovitz et al. 2005). There have been many case reports of epidural hemorrhage and irreversible neurologic sequelae when LMWH is used too close in time to the insertion or removal of epidural catheters (Wysowski et al. 1998).

If delivery is not a planned C-section, mothers should be alerted to stop LMWH at the onset of labor pains. One can switch to unfractionated heparin at 36 weeks. If labor is precipitous, and there is still a likelihood of circulating LMWH still present, one should avoid placing an epidural. Protamine sulfate does not reverse the full anticoagulant effect of LMWH. It only reverses about 60 %. If a woman on LMWH has a prolonged labor, and is at very high risk for recurrent VTE, one can use IV UFH to bridge the woman, stopping 6 h prior to delivery (Gibson 2009).

After the baby is born, one should be certain hemostasis is appropriate before reinitiating any anticoagulants. Inspection of episiotomy or C-section incisions must demonstrate no ongoing bleeding before one can be satisfied that it is safe and prudent to start giving either UFH or LMWH again. One may also start coumadin soon after UFH or LMWH has been restarted. It is wise not to start coumadin first, to avoid the dreaded complication of warfarin-induced skin necrosis (Chan et al. 2000). One should not stop the UFH or LMWH until the INR has reached a therapeutic level after a minimum 5 day overlap. This is usually 2.0, unless the mother has lupus anticoagulant, in which case a therapeutic INR might be much higher (Bijsterveld et al. 2000). In that

setting, a therapeutic INR is that INR that occurs when the factors II and X levels are at 20 % or below. That INR level might be 3 or 4, or even potentially higher (Osinbowale et al. 2009). The duration of anticoagulation depends upon when in pregnancy the VTE occurred, the underlying congenital or acquired risk factors for thrombophilia, and other coexisting risk factors, like smoking or obesity (Prandoni et al. 2007). In an uncomplicated VTE with minimal or no risk factors, and it was just the pregnancy itself that tipped the balance to thrombosis, postpartum anticoagulation should continue for 6 weeks, or for a minimum of 3 months total duration, if the VTE occurred late in pregnancy (White et al. 2008; Prandoni et al. 2011; Bates et al. 2012). If the woman has antithrombin deficiency or lupus anticoagulant, long-term anticoagulation is mandated. It is safe to breast feed the infant if the woman is receiving postpartum anticoagulation. Coumadin, UFH, LMWH, and fondaparinux do not enter the breast milk (Schindler and Graham 2011).

If a pregnant woman cannot tolerate any anticoagulation for a DVT or PE, then an IVC filter should be placed. These might be pregnant women with GI bleeding (non-modifiable sources of GI bleeding like hereditary hemorrhagic telangiestasia, or Osler–Weber–Rendu syndrome), or cerebral aneurysms. If a woman has recurrent VTE despite therapeutic anticoagulation, that is an absolute indication to use an IVC filter. This is probably the most common reason for a pregnant woman to require an IVC filter. Even after a filter is placed, if she can tolerate it, further anticoagulation should be administered. There are more data accumulated demonstrating that retrievable filters work well in pregnancy, and they can be removed at least 6 weeks after delivery, if appropriate (Kawamata et al. 2005).

From the interventional radiologist's perspective (or whichever person is inserting the filter), jugular access for insertion of a filter is preferred. Another option would be a shielded pelvis (wrapped in a lead apron to protect the fetus). The preferred site to leave the IVC filter is in a suprarenal location. However, depending upon body habitus, infrarenal location is an option. A retrievable and/or repositional designed filter is also preferred as opposed to a permanent one.

Massive PE's that threaten the life of the mother have been treated with thrombolytic agents (Leonhardt et al. 2006). The risks of severe bleeding in pregnancy are the same as nonpregnant patients, at about 6 %. Fetal loss has occurred during thrombolytic therapy. Other indications besides large PE's, would include acute stroke, clots on heart valves, and particularly large DVT's affecting the ileofemoral veins (Leonhardt et al. 2006).

Anti-Phospholipid Antibodies

Anti-phospholipid antibodies (APLA) are autoantibodies directed against cell membrane phospholipids, which cause excessive blood clotting on both the arterial and venous sides of the circulation. Anti-phospholipid antibodies are a collection of antibodies directed against cardiolipin and β-2-glycoprotein. They are discussed in detail in the chapter on workup of the prolonged PTT. Indeed, these antiphospholipid antibodies are usually detected because the PTT is prolonged, and on inhibitor screening, there is immediate inhibition of the PTT test, as opposed to delayed inhibition as occurs with clotting factor inhibitors.

Pregnant individuals with anti-phospholipid antibodies suffer recurrent pregnancy loss (RPL), still births, preterm delivery, and preeclampsia. Some authors define the adverse pregnancy outcomes of anti-phospholipid antibodies to include three or more spontaneous miscarriages before 10 weeks gestation, one or more unexplained spontaneous miscarriage after 10 weeks, and premature birth (before 34 weeks) due to placental insufficiency or severe preeclampsia (Wilson et al. 1999; Miyakis et al. 2006). Some women with anti-phospholipid antibodies have VTE, in addition to RPL, and some just have RPL. There is a temporal importance to the occurrence of anti-phospholipid antibodies, because they should be documented on at least two separate occasions 12 weeks apart.

By just screening otherwise healthy pregnant women for anti-phospholipid antibodies, one

would find anywhere from 2 to 9 % positive. Therefore, it is recommended not to screen women who do not have a suggestive history. This variation depends on definitions of cutoffs for deciding when a woman is truly positive. If one screens women with RPL, one finds up to 20 % positive for APLA's. When one screens women who have pregnancy associated VTE, one may find up to 27 % positive for APLA's (Derksen et al. 2004).

If a woman with known APLA's is on coumadin for VTE and is contemplating pregnancy, she must be switched over to UFH or LMWH, and then conceive. At no time of the pregnancy should she be taking coumadin (see the debatable aspect of this above). If a woman has APLA's and has no history of thrombosis and is just being observed, it is advisable for her to start full dose UFH or LMWH once she knows she is pregnant. This is common obstetric practice, but the updated CHEST guidelines do not specifically comment on this (Bates et al. 2012). This should help prevent the risks to the fetus of this procoagulant state. Some authors might advise aspirin (Tincani et al. 2003) as opposed to UFH or LMWH if the titers of the APLA are low, and some advocate low-dose aspirin and prophylactic dose of UFH and LMWH. Once an asymptomatic APLA patient delivers, 6 weeks of postpartum coumadin is advised (again, after at least 5 days overlap UFH or LMWH so as to avoid warfarin-induced skin necrosis).

The current CHEST guidelines comment that when confronted with a woman with APLA's and three or more pregnancy losses, or a late pregnancy loss and no history of venous or arterial thrombosis, one should administer antepartum prophylactic or intermediate dose UFH or prophylactic LMWH combined with aspirin (Bates et al. 2012, and see Table 17.7).

If a woman has APLA plus other risk factors for VTE, such as FV Leiden, prothrombin gene mutation, low protein C or S, or hyperhomocysteinemia, and has a previous history of pregnancy loss or VTE, low-dose aspirin plus adjusted dose UFH or LMWH is advised. This is a common obstetric practice but, again, is not specifically commented upon in the current CHEST guideline.

Clinical Vignette 1: Neonatal Alloimmune Thrombocytopenia

A 34-year-old G3P2 female, currently 11 weeks pregnant, is referred to you for evaluation of neonatal alloimmune thrombocytopenia (NAIT). Her first pregnancy was without complications. However, she states that during her second pregnancy in September 2008, she was diagnosed with gestational diabetes and underwent induction at 39 weeks. Due to issues with bradycardia and fetal distress, she underwent emergency Caesarian section. She states that she noted scattered petechiae diffusely on the newborn baby. The following day, during lab testing, it was noted that the baby was oozing blood with excessive bleeding. This prompted a CBC which revealed a platelet count of 41,000/μl. The baby was treated with IVIgG on the same day, and repeat platelet count the following day demonstrated a rise to 142,000/μl. A repeat platelet count on the baby 1 week later was 395,000/μl. The baby did not have any further episodes of bleeding and is now 5 years old.

The woman is now pregnant with a third child. She and her partner underwent an evaluation which demonstrated that she is homozygous HPA-1b and has anti-HPA1a antibody, and the father of the baby is HPA-1a homozygous. The mother's platelet count is 244,000/μl.

Further analysis is as follows (Table 17.10):

Strong positive reactions detected in the mother's serum against HPA-1a positive platelets only. The platelet typing studies with the serologic results support a diagnosis of Neonatal Alloimmune Thrombocytopenia (NAIT) due to an incompatibility for HPA-1a in this family. Since the father is homozygous for the HPA-1a, subsequent pregnancies in this family are at extremely high risk (approaching 100 %) of being affected with NAIT. In the event future pregnancies

(continued)

Table 17.10 Platelet antibody identification

(a) Antigen capture ELISA II							
Class I HLA			*Pool Ib/IX*			*Pool IV*	
Negative			Negative			Negative	
(b) Modified antigen capture ELISA							
GPIIb/IIIa			*HPA 1a/1a–3a/3a*			*HPA 1b/1b–3b/3b*	
			Positive			Negative	
GPIa/IIa			*HPA 5a/5a*			*HPA 5b/5b*	
			Negative			Negative	
(c) Modified antigen capture ELISA crossmatch							
Father—IIb/IIIa							
Positive							
(d) Platelet antibody screen							
			IgG result			*IgM result*	
Target platelet 1			Positive			Negative	
Target platelet 2			Negative			Negative	
Mother's platelets			Negative			Negative	
Father's platelets			Positive			Negative	
(e) Platelet antigen typing—mother							
HPA-1	*HPA-2*	*HPA-3*	*HPA-4*	*HPA-5*	*HPA-6*	*HPA-9w*	*HPA-15*
HPA 1b/1a	HPA 2a/2b	HPA 3a/3b	HPA 4a/4a	HPA 5a/5a	HPA 6a/6a	HPA9a/9a	HPA 15a/15b
(f) Platelet antigen typing—father							
HPA-1	*HPA-2*	*HPA-3*	*HPA-4*	*HPA-5*	*HPA-6*	*HPA-9w*	*HPA-15*
HPA 1a/1a	HPA 2a/2a	HPA 3a/3b	HPA 4a/4a	HPA 5a/5a	HPA 6a/6a	HPA9a/9a	HPA 15a/15b

are contemplated, genetic counseling would be appropriate.

The genotype was determined from genomic DNA using PCR and fluorescent hydrolysis probes specific to the a and b alleles of the Human Platelet Antigen systems 1–6, 9, and 15. Analytical sensitivity is >99 %. Rare polymorphisms within primer or probe regions may interfere with detection of gene variants (Blood Center of Wisconsin).

Neonatal Alloimmune Thrombocytopenia

Neonatal alloimmune thrombocytopenia (NAIT) is that condition in which maternal antibodies against fetal platelet antigens cross the placenta and lead to premature destruction of fetal platelets. The baby is born with severe thrombocytopenia and can have ominous consequences, especially intracranial hemorrhage (ICH). NAIT occurs in 1:1,000 pregnancies. Severe NAIT is defined as a platelet count at birth of less than 50,000/μl.

Human platelet alloantibodies occur when a human platelet antigen (HPA) is found on the fetus' platelets but not on the mother's platelets. NAIT can occur in a primagravida, but more typically occurs in the second, third, or subsequent pregnancy.

In Caucasians, the two most important HPA's are HPA-1a and HPA-5b or the HPA-1 and HPA-5 systems. HPA alloantibodies can be either of the IgG or IgM class, but only the IgG can cross the placenta. One cannot predict, by laboratory testing, how low a neonate's platelet count will drop, though the severity of previous pregnancy outcomes can give one a sense of what might occur with subsequent pregnancies. If the father is heterozygous for the relevant HPA antigen, there is a 50 % chance that his child will be negative. If he is homozygous, there is almost certainty that the child will be born thrombocytopenic. One can determine the fetal HPA group in the first trimester using DNA amplification techniques of cells derived from amniocentesis from as early as 14 weeks gestation.

Babies affected by NAIT are born with petechiae and ecchymoses. ICH is rare, fortunately. The treating neonatologist must rule out other reasons for severe thrombocytopenia, such as disseminated intravascular coagulation (DIC), infections, or congenital anomalies. In a baby with NAIT, the platelet count can fall from the day of birth and nadir at Day 3–4 of life. Random donor platelet transfusions may help raise the platelet count, but antigen negative single donor platelets are preferred. The usual treatment involves giving the baby IVIgG until the platelet count improves. Once a woman is found to be at risk for delivering an infant with NAIT, she is treated with weekly IVIgG starting at 20 weeks gestation, at a dose of 1 g/kg. Steroids may also be of benefit.

Clinical Vignette 1 (Continued)
The mother starts weekly IVIgG at a dose of 1 g/kg weekly at 20 weeks gestation. Since she had gestational diabetes with her second child, the mother is reluctant to take steroids, though is convinced to take a low dose (10 mg daily), starting at 36 weeks.

She delivers a healthy baby, whose platelet count at birth is 210,000/μl.

Problems That Occur in Women for Which a Hematologist Will Be Consulted Later in Pregnancy

HELLP Syndrome, Preeclampsia, Eclampsia

Long awaited updated guidelines about the hypertensive disorders of pregnancy have just been published (Roberts et al. 2013). This document has new classifications of four types of hypertension in pregnancy (one of which is preeclampsia/eclampsia). The older definition of preeclampsia/eclampsia included proteinuria, which is not necessary according to these new guidelines. Therefore, physicians should not wait for the occurrence of proteinuria before invoking preeclampsia as a diagnosis – waiting for proteinuria can delay diagnosis and treatment. These three syndromes represent a spectrum of hypertensive disorders that occur during the last half of pregnancy, or even postpartum. In HELLP syndrome (Weinstein 1982), *h*emolysis, *e*levated *l*iver function tests, and *l*ow *p*latelets occur. There are many different scoring systems and criteria for labeling a woman with HELLP syndrome. The peripheral smear (see Fig. 17.1) must show an element of microangiopathic hemolytic anemia, platelets <100,000 μL, LDH >600 mg/dL, and indirect hyper-bilirubinemia and elevated SGOT (>70 μ/l) are seen on lab studies (U Tennessee Criteria) (Sibai 1990). In another set of criteria from the University of Mississippi (Martin et al. 1999), platelets have to be <150,000/μL, SGOT ≥40 U/l, or both, with an increased LDH >600 mg/dL and with evidence of hemolysis (increased LDH and progressive anemia), for a diagnosis of HELLP.

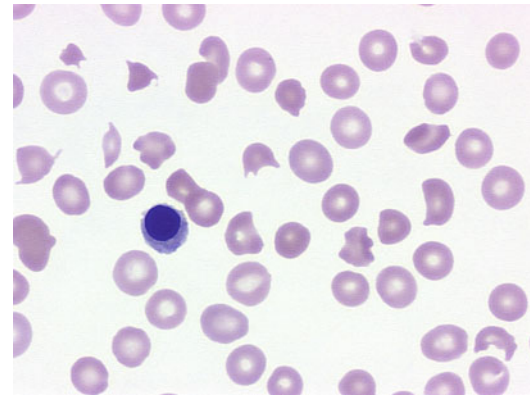

Fig. 17.1 Peripheral smear in a patient with HELLP syndrome, showing microangiopathic changes and low platelet count. Photomicrograph kindly provided by Dr. Karl Theil

Patients usually present with abdominal pain, typically epigastric. It is felt that this is due to progressive enlargement of the liver. In more full-blown preeclampsia or eclampsia, the liver can rupture and one can find evidence of supcapsular hematomas (Suarez et al. 2002). Women may present atypically with shoulder or back pain, upper body aching, headaches, nausea and vomiting. There can often be confusion as to whether a woman has HELLP syndrome, because there is a great deal of overlap with it and DIC, TTP, HUS, acute fatty liver of pregnancy (Ko and Yoshida 2006, and see below), a flare of systemic

lupus erythematosus, or preeclampsia. In these syndromes, other target organs are involved and renal failure may occur. Some women can have two of these disorders occurring simultaneously and treatments can differ for both.

The time course for certain of the elements of HELLP can give the examining obstetrician and hematologist clues as to what diagnosis is occurring. Usually, the platelet count drop occurs first, though if there is preexisting gestational thrombocytopenia, the drop in platelets can merge into the thrombocytopenia of HELLP subtly. LDH usually rises before transaminases. The implication is that hemolysis starts prior to liver injury. In acute fatty liver of pregnancy, transaminases are higher first, elevated bilirubin occurs early and may be more conjugated than unconjugated, PT and PTT rise, serum glucose falls, and then, usually, the platelets begin to fall. TTP differs from acute fatty liver of pregnancy and HELLP because both transaminases are not so prominently elevated in it, especially alanine aminotransferase (SGPT). Usually in HELLP, the magnitude of renal dysfunction mirrors the degree of hepatic dysfunction. IN HUS, however, the renal impairment is more paramount. If the examining physicians are convinced that TTP or HUS are occurring, plasma exchange is started. There is overlap in these syndromes, and it can be very difficult to distinguish them apart.

No one is certain as to the causation of HELLP, however, most theories contend that the placenta is at the root of causation (Zhou et al. 2002). Early on in the HELLP syndrome, activation of the coagulation cascade begins, and there is laying down of fibrin in small vessels (Widurer et al. 2007). The red cells are traumatized as they pass through this fibrin meshwork, leading to microangiopathy and the elevated LDH. Platelets are also consumed within these fibrin clots. Ischemia occurs downstream from these arterioles and capillaries which are full of cross-linked fibrin and the liver parenchyma in the periportal zones demonstrate necrotic changes (Gilbert et al. 2008). Distinguishing HELLP from DIC can be very difficult. If bleeding starts to occur from consumption of clotting factors, surgery, such as emergency C-section, can be very dangerous with massive blood loss.

The best treatment for HELLP syndrome is prompt delivery of the baby and removal of the placenta (Sibai 2007). Magnesium sulfate infusion may help forestall evolution to eclampsia and prevention of seizures or coma (Cahill et al. 2007). If there is a pattern of DIC, with elevated PT and PTT and a drop in fibrinogen, platelet count and red cell numbers, replacement with FFP, cryoprecipitate and platelet and red cell transfusions are necessary. Some clinicians use corticosteroids, though proof of their efficacy is lacking (Amorim et al. 1999). Antihypertensives, especially hydralazine and labetalol are helpful. Sodium nitroprusside is generally avoided because fetal cyanide toxicity has been observed.

Preeclampsia

More is written about causation of preeclampsia than HELLP. In preeclampsia, hypertension and proteinuria predominate (Samuel et al. 2011). Preeclampsia can begin as early as 20 weeks gestation, and can even start as late as 6 weeks postdelivery.

Epidemiology

Preeclampsia and, to a lesser degree, HELLP syndrome tend to occur in women who are pregnant for the first time, in younger mothers, and also older mothers. In women with a history of hypertension, diabetes, or kidney problems, prior to becoming pregnant, incidence of preeclampsia is higher. Also, women with a defined thrombophilia, like FV Leiden, have a greater chance of developing preeclampsia.

Women with a preexisting autoimmune disease, particularly SLE, have a higher risk for preeclampsia and HELLP. Women who have twins (or higher numbers of fetuses) also are at higher risk. The most significant risk factor is having had preeclampsia during a previous pregnancy (Hutcheon et al. 2011).

Preeclampsia Pathophysiology

A theory as to why preeclampsia occurs relates to how the placenta forms in the more superficial

wall of the uterus and becomes hypoxic. There may be an element of maternal immune reactivity against the placenta which leads to this shallow implantation. This leads to immunologically mediated release from the placenta of inflammatory mediators. A subsequent immune response against fetal and paternal antigens ensues. Placental abruption can occur during this process, and is often seen during hypertensive episodes in pregnancy. Evidence for this may be that there is a greater likelihood of finding fetal erythroblasts in the circulation of mothers with preeclampsia compared with mothers who do not develop it. It should be emphasized that tests to predict preeclampsia based on our current knowledge of its pathophysiology are not yet ready for clinical use.

Eclampsia

Eclampsia refers to pregnant women who develop neurologic sequelae to the previously mentioned hypertensive disorders of pregnancy. It is characterized by seizures, usually generalized tonic–clonic, blindness, often reversible, and coma. Eclampsia is not used as a diagnosis for women with a preexisting organic brain disorder. Eclampsia usually evolves from preeclampsia. Magnesium sulfate and diazepam are useful. Hematologically, and from a coagulation perspective, all issues discussed above pertaining to DIC management pertain here, especially FFP, cryoprecipitate, and platelet replacement. It can be very confusing if a woman in the latter stages of pregnancy presents with what appears to be TTP, who has seizures as a manifestation of the neurologic sequelae of TTP. To cover both the possibilities of eclampsia and TTP, evacuating the uterus and plasma exchange may need to be done concurrently.

DIC

DIC is the end result of an insult to the fine balance between clotting and bleeding. Activation of the clotting cascade(s) leads to intravascular thrombus formation with consumption of clotting factors and platelets, which results in bleeding, as well as activation of fibrinolysis. Some individuals with DIC present with bleeding excessively, some clot excessively, and some do both simultaneously. There are several conditions associated with pregnancy that lead to DIC. It is of historical interest that the first reports of DIC occurred in two pregnant women. One had a retained dead fetus and another had abruptio placenta. In the 1901 description of the clotting difficulties of these two patients, the author used the term for DIC as a "temporary hemophilia."

A pregnant woman with DIC is among the most challenging of obstetric presentations. If the fetus is alive, the decision to delay delivery while treating the mothers with transfusions, may threaten its viability. Proceeding with an emergency C-section, at a time when clotting parameters are not optimized, can cause fatal hemorrhage for the mother. Even in circumstances of fetal death, surgery on the mother can lead to fatal bleeding.

Abortion

Without getting into a political discussion of a controversial topic, it is imperative that hematologists are aware of the consultative issues that can arise in a woman who has had an abortion.

The term "septic abortion" refers to infection of the uterus that often occurred in this country before abortion became legal. After Roe vs. Wade was affirmed by the US Supreme Court, providers of abortion practiced in a more medically supervised environment, using sterile instruments, and providing proper postoperative supervision. When a woman has an abortion, infection can occur which can lead to DIC. These women need aggressive treatment with antibiotics and blood/blood product support. Excessive postabortion bleeding can lead to hypotension, consumption of clotting factors and platelets, and so the woman can enter into a DIC-state without having an infection. Even today, death occurs in this setting.

Other Obstetric Conditions Associated with DIC Are Found in Table 17.11

DIC is diagnosed both clinically and in the laboratory. Classically, the PT and PTT are prolonged, the peripheral smear has red cell trauma (schisto-

Table 17.11 Obstetric conditions associated with disseminated intravascular coagulation (DIC)

Septic abortion
Severe HELLP syndrome, or preeclampsia/eclampsia
Amniotic fluid embolism
Placenta previa
Abruptio placenta
Retained dead fetus
Acute fatty liver of pregnancy
Hemorrhage (associated with uterine atony postdelivery, placenta previa, or uterine rupture)

cytosis and polychromasia), fibrinogen is low and fibrin degradation products are elevated. DIC, as a syndrome, can exist along a time-continuum, meaning that one can see a woman early in a DIC state, and the PT might be slightly prolonged, PTT could be normal, platelet count might be normal, and the peripheral smear may be devoid of schistocytes, and the fibrinogen might be normal, or even high. The hematology consultant may confer with the obstetrician and state that right now, at this point, by strict laboratory numbers, the woman might not fit a preestablished criterion for DIC, but clinically, something is happening that is concerning both clinicians. If the woman becomes dyspneic, the BUN and creatinine start to rise, the fetus is showing signs of distress, there appears to be more vaginal bleeding than is normal or there is worrisome oozing from IV sites or the nose or GI tract, and vital signs are changing (hypotension, tachycardia), it is best to recheck DIC parameters quickly, because circumstances can change rapidly with pregnant women. The hematologist should think about the placenta as a separate organ, rich in tissue factor. If that tissue factor starts leaking into the maternal circulation due to any physical or biochemical endothelial damage, one can start along the DIC pathway. If that placenta starts seeing a lower head of pressure from the uterine arteries, its ischemia translates into further tissue factor and other thromboplastin-like substance release, exacerbating the DIC. So, if the first set of DIC numbers seemed reassuring, they should be checked again. If the PT or PTT rise at all, or the platelets or fibrinogen fall any, or the smear seems to be evolving towards RBC fragmentation, the hematologist has to communicate with the obstetrician about the fact that the maternal–fetal unit is heading into trouble and urgent action is needed.

There has been previous discussion in this chapter about DIC that occurs with HELLP, preeclampsia and eclampsia. The reader should refer back to those sections, realizing any of these conditions can rapidly merge into DIC. In acute fatty liver of pregnancy, there is the added feature that once DIC occurs, the liver is not able to compensate and produce more of the clotting factors that are being consumed.

Clinical Vignette 2

You are called by one of your obstetrics colleagues, who with a voice laced with panic asks you to come to the Labor and Delivery Suite immediately. There, you are confronted with a 40-year-old woman, who had three previous normal deliveries, who had an uncomplicated fourth pregnancy, and presented in a very routine way after rupturing her membranes 2 h ago. She was admitted, and had dilated to 4 cm, but suddenly complained of shortness of breath, and rapidly declined, with hypotension, and signs of fetal distress. Labs drawn on admission to the labor unit, which correspond to the time when she started complaining of shortness of breath, demonstrated a white blood count 15,500 with left shift, hemoglobin 9.7 g/dL, platelets 50 k/μL, PT 17 s, PTT 41 s, and fibrinogen 92 mg/dL. You review the smear and there are frequently found schistocytes, polychromasia, and rare nucleated red cells.

Amniotic Fluid Embolism

This catastrophic obstetric condition can occur during any pregnancy, or soon after delivery. It is characterized by the presence of fetal squamous cells in the pulmonary circulation of the mother. At autopsy, the fetal squamous cells can be found in all other organs, though the lungs seem to be the most affected. These squamous cells can be very hard to find. It occurs in 1 in 15,000 deliveries in the USA. In Europe it is 1 in 53,000. Suspected risk factors include rapid tumultuous

labor, trauma, multiparity, increased gestational age, and increased maternal age. Most amniotic fluid embolism (AFE) patients, however, have no clearly identified risk factors (Moore and Baldisseri 2005).

It is imperative to know that maternal death due to AFE can occur within 1 h of symptoms. Anywhere from 40 to 80 % of women with AFE will not survive, depending upon which source one reads. For fetuses still in the uterus at the time of onset, mortality rates are as high as 65 %. For survivors, there is a high risk of neurologic impairment, ranging from mild memory loss to complete anoxic brain injury. Infants may be affected by developmental delay, cerebral palsy, or limited brain function (Knight et al. 2010).

Women affected by AFE present with dyspnea, right heart failure, then left heart failure with hypotension, signs of fetal distress, seizures and DIC. Despite the most optimal resuscitative strategies, which can include recombinant VIIa for bleeding, proper RBC, FFP and platelet replacement for the DIC, ventricular assist devices, inhaled nitric oxide, cardiopulmonary bypass, and intraaortic balloon pump with extracorporeal membrane oxygenation, the outcome for both fetus and mother is usually poor (Gist et al. 2009).

Newer theories of causation suggest an immunologic causation for AFE. One theory suggests the mother suffers an anaphylactic reaction to fetal antigens that become displayed to the maternal immune system during labor. Another theory is that some event causes complement activation. When complement levels are measured in women in the midst of AFE, they are low in most series (Benson 2012).

Clinical Vignette 2 (Continued)

The obstetrician is concerned that the woman is suffering from amniotic fluid embolism, and the DIC numbers confirm his suspicion. He takes her to the operating room for an emergent C-section. The woman bleeds much more than a normal C-section, and is resuscitated with packed red cells, cryoprecipitate, platelets, and fresh frozen plasma. She continues to spiral downhill with intractable hypotension as the baby is delivered with low Apgar scores. In a desperate attempt to save the mother, it is decided to initiate recombinant factor VIIa, at a dose of 90 mcg/kg, and this is repeated every 2 h for the next 10 h. Her lowest platelet count is 10 k/μL. Anesthesiology and the intensivist services initiate inhaled nitric oxide, intraaortic balloon pump, and extracorporeal membrane oxygenation. Over the next 24 h, the bleeding abates. In total, she has been given 40 U of red cells, multiple units of cryoprecipitate, platelets, and plasma. Her DIC numbers get better, and by 36 h after delivery, her platelets are 100,000/μl, PT 12, PTT 36, and fibrinogen 210 mg/dL. The intensive resuscitation measures are withdrawn, and she shows steady and slow improvement. By 1 week after delivery, she is able to be transferred to a regular nursing floor, and with aggressive physical therapy, is able to walk within another week, though her memory and overall strength never recover to the level she was prior to giving birth (Ecker et al. 2012).

References

Amorim A, Santos LLC, Fundes A. Corticosteroid therapy for the prevention of respiratory distress syndrome in severe preeclampsia. Am J Obstet Gynecol. 1999; 180(5):1283–8.

Bates SM, Greer IA, Middeldorp S, Veenstra DL, Praboulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 Suppl):e691s–736.

Benson MD. Current concepts of immunology and diagnosis in amniotic fluid embolism. Clin Dev Immunol. 2012;Article ID 946576, 7 pages. doi:10.1155/2012/946576.

Bijsterveld NR, Middledorp S, Berends F, Büller HR. Monitoring therapy with vitamin K antagonists in patients with lupus anticoagulant: effect on different

tests for INR determination. J Thromb Thrombolysis. 2000;9(3):263–9.
Burrows RF, Ray JG, Burrows EA. Bleeding risk and reproductive capacity among patients with factor XIII deficiency: a case presentation and review of the literature. Obstet Gynecol Surv. 2000;55(20):103–8.
Cahill AG, Madones GA, Odigo AO, Stamilio DM. Magnesium for seizure prophylaxis in patients with mild preeclampsia. Obstet Gynecol. 2007;110(3): 601–7.
Chan YD, Valenti D, Mansfield HO, Stansby G. Warfarin induced skin necrosis. Br J Surg. 2000;87(3): 266–72.
de Boer K, ten Cate JW, Sturk A, Born JJ, Treffers PE. Enhanced thrombin generation in normal and hypertensive pregnancy. Am J Obstet Gynecol. 1989;160(1): 95–100.
Dempfle CE. Minor transplancental passage of fondaparinux in vivo. N Engl J Med. 2004;350:1914–5.
Dennis MW, Clough V, Tol CH. Unexpected presentation of type 2N von Willebrand disease in pregnancy. Haemophilia. 2000;6(6):696–7.
Derksen R, DeGroot PG, Nienwenhuis H, Christiaens G. How to treat women with antiphospholipid antibodies in pregnancy. Ann Rheum Dis. 2001;60(1):1–3.
Derksen RH, Khamashta MA, Branch DW. Management of the obstetric antiphospholipid syndrome. Arthritis Rheum. 2004;50(4):1028–39.
DiMinno G, Coppola A, DiMinno MND, Poon M-C. Glanzmann's thrombasthemia: proposals for management between evidence and open issues. Thromb Haemost. 2009;102:1157–64.
Dizon-Townson D, Miller C, Sibai B, et al. The relationship of the factor V leiden mutation and pregnancy outcomes for mother and fetus. Obstet Gynecol. 2005; 106:517–24.
Dossenbach-Glaninger A, van Trotsenburg M, Krugluger W, Dossengach JR, Oberkanins C, Huber J, Hopmeier P. Elevated coagulation factor VIII and the risk for recurrent early pregnancy loss. Thromb Haemost. 2004;91(4):694–9.
Dresang LT, Fontaine P, Leeman L, King VJ. Venous thromboembolism during pregnancy. Am Fam Physician. 2008;77(12):1709–16.
Ecker JL, Solt K, Fitzsimons MG, MacGillivray TE. Case 40-2012: a 43-year-old woman with cardiorespiratory arrest after a cesarean section. N Engl J Med. 2012;367(26):2528–37.
Faught W, Garner P, Jones G, Ivey G. Changes in protein C and protein S levels in normal pregnancy. Am J Obstet Gynecol. 1995;172(1):147–50.
Felbinger TW, Posner M, Eltzchig HK, Kodali BS. Laparoscopic splenectomy in a pregnancy patient with immune thrombocytopenic purpura. Int J Obstet Anesth. 2007;16(3):281–3.
Fraser DG, Moody AR, Morgan PS, et al. Diagnosis of lower-limb deep venous thrombosis: a prospective blinded study of magnetic resonance direct thrombus imaging. Ann Intern Med. 2002;136:89–98.
Gerhardt A, Scharf RE, Beckmann MW, et al. Prothrombin and factor V mutations in women with a history of thrombosis during pregnancy and the puerperium. N Engl J Med. 2000;342:374–80.
Gibson PS. Anticoagulants and pregnancy: when are they safe. Cleve Clin J Med. 2009;76(2):113–27.
Gilbert JS, Ryan MJ, LaMarca BB, Sedeek M, Murphy SR, Granger JP. Pathophysiology of hypertension during preeclampsia: linking placental ischemia with endothelial dysfunction. Am J Physiol Heart Circ Physiol. 2008;294:H541–50.
Gill KK, Kelton JG. Management of idiopathic thrombocytopenic purpura in pregnancy. Semin Hematol. 2000;37(3):275–89.
Ginsberg JS, Brill-Edwards P, Burrows RF, et al. Venous thrombosis during pregnancy: leg and trimester of presentation. Thromb Haemost. 1992;67:519–20.
Gist RS, Stafford IP, Leibowitz AB, Feilin Y. Amniotic fluid embolism. Anesth Analg. 2009;108(5):1599–602.
Glueck CJ, Pranikoff J, Khan N, Riaz K, Chavan K, Raj P, Aumar M, Wang P. High factor XI, recurrent pregnancy loss, enoxaparin. Fertil Steril. 2010;94(7):2828–31.
Greer I, Hunt BJ. Low molecular weight heparin in pregnancy: current issues. Br J Haematol. 2005;128: 593–601.
Greer IA, Nelson-Piercy C. Low molecular weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood. 2005;106:401–7.
Heit JA, Sobell JL, Li H, Sommer SS. The incidence of venous thromboembolism among factor V Leiden carriers: a community-based cohort study. J Thromb Haemost. 2005;3:305–11.
Hellgren M, Tangforn L, Abildgaard U. Pregnancy in women with congenital antithrombin III deficiency: experience of treatment with heparin and antithrombin. Gynecol Obstet Invest. 1982;14(2):127–41.
Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynecol. 2011;25(4):391–403.
Kawamata K, Chiba Y, Tanaka R, Higashi M, Nishigami K. Experience of temporary inferior vena cava filters inserted in the perinatal period to prevent pulmonary embolism in pregnant women with deep vein thrombosis. J Vasc Surg. 2005;41(4):652–6.
Kline JA, Williams GW, Hernancez-Nino J. D-dimer concentrations in normal pregnancy: new diagnostic thresholds are needed. Clin Chem. 2005;51:528–829.
Knight M, Tuffnell D, Brocklehurst P, Spark P, Kurinczu JJ, UK Obstetric Surveillance System. Incidence and risk factors for amniotic fluid embolism. Obstet Gynecol. 2010;115(5):910–7.
Ko HH, Yoshida E. Acute fatty liver of pregnancy. Can J Gastroenterol. 2006;20(1):25–30.
Kujovich JL. Von Willebrand disease and pregnancy. J Thromb Haemostast. 2005;3:245–53.
Lee CA, Chi C, Pavord SR, Bolton-Maggs PHB, Pollard D, Hinchcliff-Wood A, Kandir RA. The obstetric and

gynecological management of women with inherited bleeding disorders—review with guidelines produced by task force of UK Haemophilia Doctors' Organization. Haemophilia. 2006;12(4):301–36.
Leonhardt G, Gaul C, Nietsch NJ, Vuerke M, Schleussner E. Thrombolytic therapy in pregnancy. J Thromb Thrombolysis. 2006;21(3):271–6.
Levy JA, Murphy L. Thrombocytopenia in pregnancy. J Am Board Fam Prac. 2002;15(4):290–7.
Lindqvist PG, Svensson PJ, Marsaal K, et al. Activated protein C resistance (FV:Q506) and pregnancy. Thromb Haemost. 1999;81:532–7.
Mannucci PM. How I, treat patients with von Willebrand's disease. Blood. 2001;97(7):1915–9.
Martin Jr JN, Rinehart BK, May WL, Magann EF, Terrone DA, Blake PG. The spectrum of severe pre-eclampsia: comparative analysis by HELLP syndrome classification. Am J Obstet Gynecol. 1999;180(6 Pt 1): 1373–84.
Martin-Salces M, Jimenez-Yuste V, Alvarez MT, Quintana M, Hernandez-Navarro F. Review: factor XI deficiency: review and management in pregnant women. Clin Appl Thromb Hemost. 2010;16(2):209–13.
Meslovitz S, Many A, Landsberg JA, Varon D, Lessing J, Kupferminc M. The safety of low molecular weight heparin therapy during labor. J Matern Fetal Neonatal Med. 2005;17(1):39–43.
Miyakis S, Lockshin M, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite anti-phospholipid syndrome (APS). J Thromb Haemost. 2006;4(2):295–306.
Monte S, Lyons G. Peripartum management of a patient with Glanzmann's thrombasthemia using Thrombelastograph. Br J Anaesth. 2002;88:734–8.
Moore J, Baldisseri MR. Amniotic fluid embolism. Crit Care Med. 2005;33(10 Suppl):S279–85.
Myers B, Pavord S, Keen L, Hill M, Dolan G. Pregnancy outcome in factor XI deficiency: incidence of miscarriage, antenatal and postnatal hemorrhage in 33 women with factor XI deficiency. BJOG. 2007;114(5): 643–6.
Neunert C, Lim W, Crowther M, Cohen A, Solberg Jr L, Crowther MA. The American Society of Hematology 2011 evidence-based guideline for immune thrombocytopenia. Blood. 2011;117(16):4190–207.
Osinbowale O, Al Malki M, Schade A, Bartholomew JR. An algorithm for managing warfarin resistance. Cleve Clin J Med. 2009;76(12):724–30.
Pahade J, Litmanovich D, Pedrosa I, Romero J, Bankier A, Boiselle P. Imaging pregnant patients with suspected pulmonary embolism: what the radiologist needs to know. RadioGraphics. 2009;29:639–54.
Peaceman AM, Katz AR, Laville M. Bernard Soulier syndrome complicating pregnancy: a case report. Obstet Gynecol. 1989;73(3):457–9.
Phillips LE, McLintock C, Pollock W, Galt S, Popham P, Jankelowitz G, Ogle R, Cameron PA. Recombinant activated factor VII in obstetric hemorrhage: experiences from the Australian and New Zealand Haemostasis Registry. Anesth Analg. 2009;109(6):1908–15.
Poon M-C, D'Oiron R, Von Depka M, Khair K, Negrier C, Karafoulidou A, Huth-Khehne A, Morfina M. Prophylactic and therapeutic recombinant VIIa administration to patients with Glanzmann's thrombasthemia: results of an international survey. J Thromb Haemost. 2004;2:1096–103.
Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, Iotti M, Tormene D, Simioni P, Pagnan A. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with proximal deep vein thrombosis or pulmonary embolism. Haematologica. 2007;91:199–205.
Prandoni P, Piovella C, Spiezia L, Dalla Valle F, Pesquento R. Optimal duration of anticoagulation in patients with venous thromboembolism. Indian J Med Res. 2011; 134(1):15–21.
Rahini G, Rellecke S, Mallmann P, Nawroth F. Course of pregnancy and birth in a patient with Bernard Soulier syndrome—a case report. J Perinat Med. 2005;33: 264–6.
Ray JG. DDAVP use during pregnancy: an analysis of its safety for mother and child. Obstet Gynecol Surv. 1998;53:450–5.
Roberts JM, et al. Hypertension in pregnancy: Executive summary. Obstetrics and Gynecology. 2013;122(5): 1122–31.
Saade G, Hornsi R, Seoud M. Bernard-Soulier syndrome in pregnancy: a report of four pregnancies in one patient, and review of the literature. Eur J Obstet Gynecol Reprod Biol. 1991;40(2):149–52.
Samuel A, Lin C, Parviainen K, Jeyabalan A. Expectant management of preeclampsia superimposed on chronic hypertension. J Matern Fetal Neonatal Med. 2011;24(7):907–11.
Scarsbrook AF, Evans AL, Owen AR, Gleeson FV. Diagnosis of suspected venous thromboembolic disease in pregnancy. Clin Radiol. 2006;61:1–12.
Schindler D, Graham TP. Warfarin overdose in a breastfeeding woman. West J Emerg Med. 2011;12(2): 216–7.
Schulman S, Tengborn L. Treatment of venous thromboembolism in patients with congenital deficiency of antithrombin III. Thromb Haemost. 1992; 68(6):634.
Sibai BM. The HELLP syndrome: much ado about nothing? Am J Obstet Gynecol. 1990;162(2):311–6.
Sibai BM. Chap 33: Hypertension. In: Table SG, Niebyl JR, Simpson JL, editors. Obstetrics—normal and problem pregnancies. 5th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2007.
Sloan N, Durocher J, Aldrich T, Blum J, Winikoff B. What measured blood loss tell us about postpartum bleeding: a systematic review. BJOG. 2010;117: 788–800.
Spencer J, Rosengren S. Hermansky-Pudlak syndrome in pregnancy. Am J Perinatol. 2009;26(9):617–9.
Suarez B, Alves K, Senat MV, Fromageot J, Fischer C, Rosenberg P, Ville Y. Abdominal pain and preeclampsia. Sonographic findings in the maternal liver. J Ultrasound Med. 2002;21:1077–83.

Tincani A, Branch W, Lefy RA, Piette JC, Carp H, Rai RS, Khamashta M, Schoelfeld Y. Treatment of pregnant patients with antiphospholipid syndrome. Lupus. 2003;12(7):524–9.

Van Wersch JWJ, Ubachs JMH. Blood coagulation and fibrinolysis during normal pregnancy. Eur J Clin Chem Clin Biochem. 1991;29:45–50.

Varga EA, Sturm AC, Misita CP, Moll S. Homocysteine and MTHFR mutations. Circulation. 2005;11:e289–93.

Vitale N, DeFeo M, DeSanto LS, Pollice A, Tedesco N, Cotrufo M. Does-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. J Am Coll Cardiol. 1999;33(6):1637–41.

Webert KE, Mittal R, Sigouin C, Heddle NM, Kelton JG. A retrospective 11-year analysis of obstetric patients with immune thrombocytopenic purpura. Blood. 2003;102(13):4306–11.

Weinstein L. Syndrome of hemolysis, elevated liver enzymes, and low platelet count: a severe consequence of hypertension in pregnancy. Am J Obstet Gynecol. 1982;142(2):159–67.

White RH, Chan WS, Shou H, Ginsberg JS. Recurrent venous thromboembolism after pregnancy associated versus unprovoked thromboembolism. Thromb Haemost. 2008;100(2):246–52.

Widurer M, Villar J, Benigni A, Conde-Agudelot A, Karamanchi SA, Lindheimer M. Mapping the theories of preeclampsia and the role of angiogenic factors: a systematic review. Obstet Gynecol. 2007;109:168–80.

Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, Brey R, Derksen R, Harris EN, Hughes GR, Triplett DA, Khamashta MA. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum. 1999;42(7):1309–11.

Winer-Muram HT, Boone JM, Brown HL, et al. Pulmonary embolism in pregnant patients: fetal radiation dose with helical CT. Radiology. 2002;224:487–92.

Wysowski DK, Talarico L, Bacsanyi J, Botstein P. Spinal and epidural hematoma and low molecular weight heparin. N Engl J Med. 1998;338:1774–5.

Yamada T, Yamada H, Morikawa M, Kato EH, Kishida T, Ohnaka Y, Nikaido H, Ozawa T, Fujimoto S. Management of pregnancy with congenital antithrombin III deficiency: two case reports and a review of the literature. J Obstet Gynaecol Res. 2001;27(4):189–97.

Zhou Y, McMaster M, Woo K, Janatpour M, Perry J, Karpanen T, Alitalo K, Damsky C, Fisher SJ. Vascular endothelial growth factor ligands and receptors that regulate human cytotrophoblast survival are dysregulated in severe preeclampsia and hemolysis, elevated liver enzymes, and low platelets syndrome. Am J Pathol. 2002;160:1405–23.