

Thrombosis, Thrombophilia, and Thromboprophylaxis in Pregnancy

Andra H. James, MD, Leo R. Brancazio, MD, and Thomas L. Ortel, MD, PhD

Dr. James is Assistant Professor and Dr. Brancazio is Clinical Associate Professor in the Department of Obstetrics and Gynecology of the Duke University Medical Center in Durham, NC, where Dr. Ortel is Associate Professor in the Department of Medicine.

Address correspondence to:

Andra H. James, MD, Division of Maternal and Fetal Medicine, Box 3967, Duke University Medical Center, Durham, NC 27710; E-mail: andra.james@duke.edu.

Abstract: Normal pregnancy is accompanied by changes in coagulation that have likely evolved to protect women from the bleeding challenges of miscarriage and childbirth. Consequently, pregnant women are at an increased risk of thrombosis. The most important risk factors are thrombophilia and a history of thrombosis. Most thromboses in pregnancy occur in the left lower extremity, but pelvic vein thromboses are not uncommon. Thrombophilia increases not only the risk of maternal thrombosis but also the risk of poor pregnancy outcome. All pregnant women should be asked about a personal or family history of thrombosis and the details of their obstetrical history. Some women should undergo laboratory testing, particularly those with a personal history of thrombosis or a history of poor pregnancy outcome. The purpose of testing is to help determine which women should receive anticoagulation therapy, which is used not only to treat venous thromboembolism, but also to prevent thromboembolism and reduce the risk of poor pregnancy outcome in women with thrombophilia. Low-molecular-weight heparins are preferred over unfractionated heparin because they have a longer half-life and are presumed to have fewer side effects. Their longer half-life is a disadvantage around the time of delivery when unfractionated heparin, with its shorter half-life, is easier to manage. The risk of thrombosis is higher postpartum than during pregnancy, so anticoagulation therapy is usually continued for at least 6 weeks after delivery.

Women are 5 times more likely to suffer a thromboembolic event when pregnant than when not.¹ Venous events are 4 times more common than arterial events, and of these venous events, 79% are deep vein thromboses (DVT) and 21% are pulmonary emboli (PE).² The overall risk for venous thromboembolism (VTE) is 1.72 per 1,000 births.² VTE accounts for 1 death per 100,000 births.² Women are at risk not only for the immediate morbidity and mortality associated with DVT and PE, but also the long-term morbidity associated with post-thrombotic syndrome. In fact, the majority of these women ultimately develop sequelae that range from edema and skin changes to recurrent thromboses and ulceration.³⁻⁵

This predisposition to thrombosis results from the hypercoagulable state of pregnancy, which has likely evolved to protect women from hemorrhage during miscarriage and childbirth. Indeed, the leading cause of

Keywords

Anticoagulation, thrombophilia, thrombosis, pregnancy, thromboprophylaxis

maternal death in the developing world is hemorrhage,⁶ but in Western Europe and the United States, where hemorrhage is successfully treated or prevented, the leading cause of maternal death is embolic disease.⁷

Thrombophilia, an acquired or inherited tendency to develop thrombosis, in a pregnant woman increases the risk of thrombosis from 1.72 in 1,000 births to as high as 1 in 2.⁸⁻¹⁰ The utero-placental-fetal as well as the maternal circulation may be affected. Women with thrombophilia are more likely to experience placental abruption, preeclampsia, fetal growth restriction, stillbirth, and, possibly, recurrent miscarriage.¹¹⁻¹³ Thromboprophylaxis for pregnant women with thrombophilia has been shown to reduce maternal morbidity and mortality¹⁴ and improve pregnancy outcome in those with the antiphospholipid syndrome¹⁵ and those with inherited thrombophilia and a history of fetal loss.¹⁶ Thromboprophylaxis for the treatment or prevention of VTE in pregnancy, however, is not without risk, to both the mother and the fetus, especially with agents that cross the placenta barrier.

The purpose of this paper is to review the changes in coagulation during pregnancy, the risk factors for VTE, the maternal and fetal issues associated with thrombophilia, and the indications and strategies for anticoagulation during pregnancy and the postpartum period.

Virchow's Triad

The 19th century German pathologist Rudolf Virchow is credited with describing the 3 factors contributing to thrombosis: hypercoagulability, vascular injury, and stasis.¹⁷ Pregnant women are at an increased risk for venous stasis as a result of hormonally induced decreased venous capacitance and decreased venous outflow,^{18,19} possibly as a result of mechanical obstruction by the uterus²⁰ and, questionably, as a result of decreased mobility.²¹⁻²⁴ However, these factors, along with vascular injury,²⁰ appear to be less important during pregnancy than postpartum. During pregnancy, the important factor is hypercoagulability.

Changes in Coagulation During Normal Pregnancy

Normal pregnancy is accompanied by increased concentrations of factors VII, VIII, and X and von Willebrand factor and by pronounced increases in fibrinogen.²⁵ Factors II, V, and IX are relatively unchanged.²⁵ Free protein S, the active, unbound form, is decreased during pregnancy secondary to increased levels of its binding protein, the complement component C4b.²⁵ Plasminogen activator inhibitor type 1 (PAI-1) levels increase 5-fold.²⁵ All of these changes favor coagulation and may contribute to the hypercoagulable state of pregnancy. These changes begin with conception, as does the risk of thrombosis. In a meta-analysis by Ray et al,²⁶ 21.9% of events during pregnancy occurred during the first trimester. In our review of 53 cases of peripartum DVT, we found that 44% of events during pregnancy occurred in the first trimester.²⁷

The changes in the coagulation system do not return to baseline until more than 8 weeks postpartum.²⁵ Venous capacitance and venous outflow are only moderately improved at

Table 1. Risk Factors for Peripartum Venous Thromboembolism²

Risk Factor	Odds Ratio	Confidence Interval
Heart disease	7.1	6.2, 8.3
Thrombophilia (including a history of thrombosis and the antiphospholipid syndrome)	27.9	22.6, 34.3
Sickle cell disease	6.7	4.4, 10.1
Lupus	8.7	5.8, 13.0
Obesity	4.4	3.4, 5.7
Anemia	2.6	2.2, 2.9
Hyperemesis	2.5	2.0, 3.2
Fluid and electrolyte imbalance	4.9	4.1, 5.9
Antepartum hemorrhage	2.3	1.8, 2.8
Postpartum infection	4.1	2.9, 5.7
Transfusion	7.6	6.2, 9.4
Cesarean delivery	2.1	1.8, 2.4

6 weeks postpartum and are not significantly improved until 3 months postpartum. Compared to the risk during pregnancy, the risk of thrombosis is even higher after delivery. In the meta-analysis by Ray et al,²⁶ 34.5% of events occurred postpartum, as did 36% of events in our review of 53 cases.²⁷ Half of the postpartum cases occurred within the first 2 weeks after delivery, suggesting that the risk is highest immediately postpartum.

Risk Factors for Thrombosis During Pregnancy

In the same review of 53 cases of peripartum DVT, the 2 most important risk factors during pregnancy were diagnosed thrombophilia, present in 24% of cases, and a history of thrombosis, present in 15% of cases.²⁷ Other statistically significant medical risk factors for VTE during pregnancy from our analysis of 14,334 records from the Nationwide Inpatient Sample² were anemia, heart disease, sickle cell disease, lupus, and obesity. Pregnancy and delivery complications that increased the risk were hyperemesis, fluid and electrolyte imbalance, antepartum hemorrhage, cesarean delivery, postpartum infection, and transfusion. The relative risks for these factors are given in Table 1.²

Sites of VTE in Pregnancy

When DVT occurs, it is most likely to be proximal, massive,⁴ and occur in the left lower extremity. In their meta-analysis, Ray et al²⁶ reported that 82.2% of DVTs occurred in the left lower extremity. This left-sided predominance is associated with proximal thromboses.^{28,29} Although distal thromboses are as likely to occur on the right as on the left side, proximal thromboses occurring under the influence of estrogen^{27,28} are

Table 2. Odds Ratios for Venous Thromboembolism Among Women With Inherited Thrombophilia in Pregnancy

Reference	Risk Factors (95% Confidence Interval)		
	Factor V Leiden	Prothrombin Gene	MTHFR C677T
Grandone et al ³⁵	16.3 (4.8–54.9)	10.2 (4.0–25.9)	2.1 (1.0–4.5)
Gerhardt et al ³⁶	9.3 (5.1–16.9)	15.2 (4.2–52.6)	—
McCull et al ³⁷	4.5 (2.1–14.5)	4.4 (1.2–16)	0.45 (0.13–1.58)
Dilley et al ³⁸	18.3 (2.7–432)	—	1.3 (0.3–3.1)
Martinelli et al ³⁹	10.6 (5.6–20.4)	2.9 (1.0–8.6)	—

more likely to occur on the left side. The predominance of left-sided proximal or ileo-femoral thromboses is thought to be due to a relative stenosis of the left common iliac vein where it lies between the lumbar vertebral body and the right common iliac artery,³⁰ but the mechanism is unknown.³¹

Pelvic vein thrombosis, a rare event outside of pregnancy or pelvic surgery, accounted for 11% of cases among pregnant or postpartum patients in our review²⁷ but less than 1% of all cases of DVT in a large multicenter registry.³²

Diagnosis of DVT and PE in Pregnancy

The 2 most common initial symptoms of peripartum DVT, present in more than 80% of cases, are pain and swelling.²⁷ When DVT is suspected, the first test recommended is compression ultrasonography of the proximal veins.³³ When results are equivocal or an iliac vein thrombosis is suspected, magnetic resonance venography (MRV) may be used.³⁴ MRV does not carry the radiation risk of contrast venography. The diagnosis of PE in pregnant patients is similar to that in nonpregnant patients. Ventilation/perfusion scanning gives relatively low radiation exposure to the fetus.³⁴ In the case of indeterminate results in a woman without DVT, a confirmatory test such as angiography or spiral computed tomography (CT) is necessary to prevent unnecessary exposure to anticoagulants during pregnancy, at delivery, or in future pregnancies.³⁴

Thrombophilia and Maternal Thrombosis

Both acquired and inherited thrombophilia increase the risk of maternal thrombosis. Several studies have compared the prevalence of inherited thrombophilia in women who experienced VTE in pregnancy versus those who did not.^{35–39} The odds ratios for these studies are listed in Table 2. Factor V Leiden and the prothrombin gene mutation each confer an approximately 10-fold increased risk of VTE in pregnancy. Combined they confer a risk increased by approximately 100-fold,³⁶ similar to the risk associated with homozygosity of factor V Leiden.⁴⁰

The risk of VTE during pregnancy in women with antithrombin, protein C, and protein S deficiency is hard to quantify. There are few studies and the definition of deficiency varies from study to study. Gerhardt et al,³⁶ using cutoffs of 75% activity for protein C, 65% for protein S, and 80% for antithrombin, analyzed them together and found a risk increased by only 13.1 (5.0–34.5) times. McCull et al,³⁷ on the other hand, using a

cutoff of 50% activity for antithrombin, found an increased risk of 28 (5.5–142) times for type I deficiency (a quantitative defect with reduced activity and reduced antigen) and an increased risk of 282 (31–2,532) times for type II deficiency (a qualitative defect with reduced activity and normal antigen). The absolute risk to the untreated woman with antithrombin deficiency has been reported to be as high as 40–68%.^{8–10} The absolute risk to the untreated woman with protein C or S deficiency has been reported to range from 0% to 22%.⁴¹ Homozygosity, let alone heterozygosity, for the methylenetetra-hydrofolate reductase (MTHFR) C677T polymorphism does not appear to confer any increased risk of VTE in pregnancy. The odds ratios for VTE in women with inherited thrombophilia are summarized in Table 2.

The risk of VTE in pregnancy in women with the antiphospholipid syndrome has been reported to be 30%.⁴² There is some controversy as to whether women who have not had a thrombosis and are diagnosed solely on the basis of poor pregnancy outcome are at the same risk. Evidence suggesting that they are was reported by Erkan et al,⁴³ who found an event rate of 7.4 per 100 patient-years in women who did not receive thromboprophylaxis after delivery.

Thrombophilia and Pregnancy Outcome

The relationship between antiphospholipid antibodies and poor pregnancy outcome has been recognized since the late 1980s. The antiphospholipid syndrome has been associated with recurrent miscarriage, abruption of the placenta, stillbirth, fetal growth restriction, and preeclampsia. In 1995, Dekker et al⁴⁴ reported a study of 85 women with severe preeclampsia who were tested for both acquired and inherited thrombophilias. A high prevalence of defects was noted. Subsequently, in 1996, using data from the European Prospective Cohort on Thrombophilia (EPCOT), Preston et al⁴⁵ reported on the association between inherited thrombophilia and fetal loss. Data were obtained retrospectively, by questionnaire, from 571 cases and 541 controls. Fetal loss was greater among women with thrombophilia. The odds ratio for stillbirth (3.6) was higher than that for miscarriage (1.27). The highest odds ratio for stillbirth was in women with combined defects (14.3).

Since these first studies, multiple others demonstrating—as well as others refuting—the association between poor pregnancy outcome and thrombophilia have been published. Alfirevic et al¹² reviewed the association between maternal thrombophilia

Table 3. Pooled Odds Ratios With 95% Confidence Intervals for Thrombophilia and Poor Pregnancy Outcome¹²

Maternal Risk Factors	Pregnancy Outcome			
	Abruption (4 studies) ¹¹⁰⁻¹¹³	Stillbirth (4 studies) ^{110,114-116}	IUGR (3 studies) ^{110,115,117}	Preeclampsia (18 studies) ^{44,115,117-130}
Factor V Leiden homozygote	16.9 (2–141.9)	—	—	3.7 (0.9–15.6)
Factor V Leiden heterozygote	6.7 (2–21.6)	6.1 (2.8–13.2)	0.8 (0.3–2.3)	1.6 (1.2–2.2)
Prothrombin gene mutation	28.9 (3.5–236.7)	0.6 (0.2–2.4)	5.7 (1.2–27.4)	—
MTHFR C677T homozygote	2.2 (0.4–11.6)	1.4 (0.9–2.1)	5 (1.8–13.8)	2.4 (1.2–4.7)
MTHFR C677T heterozygote	—	1 (0.7–1.3)	—	1.2 (0.9–1.6)
Homocysteinemia	3.5 (1.5–8.1)	—	—	2.2 (0.9–5.2)
Antithrombin deficiency	4.1 (0.3–49.9)	—	—	7.1 (0.4–117.4)
Protein C deficiency	—	1 (0.1–11.1)	—	21.5 (1.1–414)
Protein S deficiency	0.3 (0–70.1)	16.2 (5–52.3)	10.2 (1.1–91)	12.7 (4–39.7)
Activated protein C resistance	6.6 (2.3–19)	5 (2–12.4)	—	4.6 (2.8–7.6)
Anticardiolipin antibody IgG	20.8 (2.5–175.8)	5.6 (2.6–11.7)	33.9 (1.6–736)	4 (0.4–44.5)
Anticardiolipin antibody IgM	—	—	—	—
Lupus anticoagulant	—	3.2 (1.2–9)	—	0.1 (0–6.8)

IUGR = intrauterine growth restriction.

and adverse pregnancy outcome. Controlled and cohort studies were included that tested for antithrombin deficiency, protein C deficiency, protein S deficiency, activated protein C resistance, anticardiolipin immunoglobulin (Ig) G, anticardiolipin IgM, the lupus anticoagulant, factor V Leiden, the prothrombin G20210A polymorphism, the MTHFR C677T polymorphism, or homocysteinemia. The systematic review is summarized in Table 3. With the exception of the MTHFR C677T polymorphism, inherited thrombophilias, as well as antiphospholipid antibodies, were associated with abruption, stillbirth (fetal death in the second and third trimesters), intrauterine growth restriction (IUGR), and preeclampsia. Subsequent to the review, studies have been published confirming the association between thrombophilia and abruption⁴⁶ and between thrombophilia and IUGR⁴⁷; however, 2 other published studies did not find an association between thrombophilia and IUGR.^{48,49} A large multicenter study sponsored by the US Centers for Disease Control and Prevention's Division of Hereditary Blood Disorders is currently underway to further investigate the relationship between thrombophilia and IUGR.

There is also a strong association between the presence of antiphospholipid antibodies and recurrent miscarriage. Fifteen percent of women with recurrent miscarriage have either the lupus anticoagulant (9.1%) or anticardiolipin antibodies (5.5%)⁵⁰ compared to 2% in the general obstetric population.^{51,52} Among women with these antibodies, up to 90% of conceptions may be miscarried.⁵⁰

Although there is evidence for an association between abruption, stillbirth, IUGR, preeclampsia and inherited thrombophilia, as well as for an association between the

antiphospholipid syndrome and early recurrent first trimester loss, the evidence for an association between inherited thrombophilia and first trimester loss is inconclusive.¹³ Two meta-analyses found a positive association between inherited thrombophilia and recurrent fetal loss, but both included first and second trimester losses.^{53,54} Among the studies included in the 2 meta-analyses that examined the relationship between inherited thrombophilia and recurrent first trimester loss, 2 found evidence of an association,⁵⁵ but 5 did not.⁵⁶⁻⁶¹

Screening for Thrombophilia

Because of the increased risk of maternal thrombosis or poor pregnancy outcome, particularly after the first trimester, every pregnant woman or woman planning a pregnancy should be screened for thrombophilia. Information about the patient's personal or family history of thrombosis and details of her obstetrical history should be gathered. Some women should undergo laboratory testing, particularly those with a personal history of thrombosis or a history of poor pregnancy outcome. Figure 1 illustrates an algorithm we use at our institution to decide which patients to test.

Screening should include assays for both acquired and inherited thrombophilia. Since protein S activity falls during pregnancy, a cutoff of 35% activity is suggested.¹³ Activated protein C resistance (APC-R), independent of factor V Leiden, has been associated with thrombosis and poor pregnancy outcome, so testing for APC-R is recommended. Hyperhomocysteinemia is associated with thrombosis and possibly with poor pregnancy outcome; therefore, the recommended treatment is folic acid,

vitamin B₁₂, and vitamin B₆.¹³ Homozygosity for the MTHFR C677T polymorphism may or may not be associated with thrombosis or poor pregnancy outcome, but again the recommended treatment is folic acid, vitamin B₁₂, and vitamin B₆.¹³ We do not test for hyperhomocysteinemia or the MTHFR polymorphism, as we prescribe prenatal vitamins that include folic acid and the B vitamins. The 4G/5G PAI-1 polymorphism, specifically homozygosity for 4G, was associated with poor pregnancy outcome in 1 retrospective study⁶² but has not been studied sufficiently to be included in testing.

We recommend testing for:

- lupus anticoagulant
- anticardiolipin antibodies
- activated protein C resistance with factor V Leiden if abnormal
- prothrombin G20210A polymorphism
- protein C activity
- protein S activity
- antithrombin activity.

Anticoagulation Therapy

The purpose of screening is to determine who requires anticoagulation. The purpose of anticoagulation, besides treatment of DVT or PE, is to reduce the risk of maternal thrombosis in women at risk and to improve the outcome of pregnancy. Unique aspects of anticoagulation in pregnancy include both maternal and fetal issues. During pregnancy, there is an increase in blood volume of 40–50%¹⁸ and an increase in the volume of distribution. An increase in glomerular filtration¹⁸ results in increased renal excretion. Additionally, there is an increase in protein binding of heparin.

Fetal and neonatal issues include unintended pregnancies. The critical period for organogenesis is from the fourth week to the eighth week after conception.⁶³ Since 45% of pregnancies are unintended,⁶⁴ many women do not realize that they are pregnant. Warfarin taken during this period carries up to a 30% risk of congenital anomalies.⁶⁵⁻⁷¹ Placental transfer of warfarin later in pregnancy can result in fetal bleeding^{71,72} or stillbirth.^{66,68,69,73} Even thrombolytics that do not cross the placental barrier, such as urokinase, streptokinase, and recombinant tissue plasminogen activator, can potentially jeopardize the fetus if bleeding occurs in the retroplacental space⁷⁴ or results in hypovolemia or maternal death.⁷⁵

The preferred agents for anticoagulation in pregnancy are heparin compounds.⁷⁶ The main advantage of heparin compounds is that there is no transplacental passage.^{77,78} Disadvantages of unfractionated heparin include the necessity of parenteral administration, a 2% risk of major bleeding,⁷⁹ osteoporosis with a 17–36% reduction in bone density,^{80,81} a 2% risk of vertebral fracture,⁸² and a risk of heparin-induced thrombocytopenia (HIT).⁷⁶ While the risk of HIT is low in pregnancy, and may be lower than in nonpregnant patients,⁸³ the actual risk is unknown.⁷⁶

There are no large comparative studies in pregnant women, but in nonpregnant patients, low–molecular-weight heparins (LMWHs) have been associated with fewer side effects than

unfractionated heparin.⁷⁶ While parenteral administration is still required, potential advantages of LMWHs over unfractionated heparin are less bleeding, less bone loss, a more predictable response, a lower risk of HIT, and a longer half-life.⁷⁶ A disadvantage is that LMWHs are more expensive. Also, their longer half-life may be a problem at the time of delivery.

Treatment during pregnancy with a full-dose (adjusted dose) heparin compound is recommended for women with^{76,84}:

- current thrombosis
- a need for life-long anticoagulation
- antiphospholipid syndrome with a history of thrombosis.

Full-dose (adjusted dose) heparin or an intermediate or moderate dose is suggested for women with^{76,84}:

- antithrombin deficiency
- homozygosity for factor V Leiden, prothrombin G20210A polymorphism, or compound heterozygosity for these polymorphisms.

Thromboprophylaxis with low-dose anticoagulation is recommended for women with a history of^{13,76}:

- unprovoked thrombosis
- antiphospholipid syndrome with poor pregnancy outcome as the only clinical criteria
- thrombophilia and poor pregnancy outcome.

Close observation is recommended for women with a history of:

- thrombosis in the setting of transient risk factors⁷⁶
- thrombophilia with no history of thrombosis.

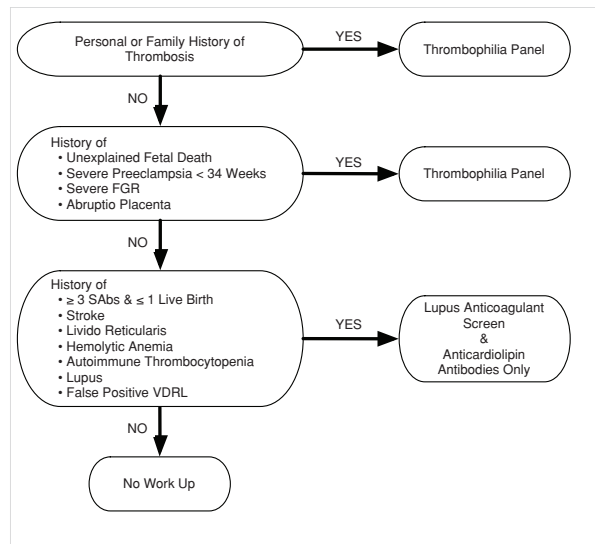


Figure 1. An algorithm to decide which patients to test for thrombophilia.

FGR = fetal growth restriction; SAb = spontaneous abortion; VDRL = venereal disease research laboratory.

Anticoagulation during pregnancy is accomplished with unfractionated heparin or LMWH; enoxaparin is the LMWH that has been studied and prescribed most in pregnancy. A Medline search of LMWHs in pregnancy revealed 5 articles about reviparin, 9 about tinzaparin, 14 about nadroparin, 37 about dalteparin, and 61 about enoxaparin. Neither heparin^{85,77,78} nor LMWH^{77,78} crosses the placental barrier, and both are considered safe in pregnancy.^{79,86}

The recommendations from the 7th American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy⁷⁶ as well as the protocol from our institution are included in Table 4. Our protocol reflects the increasing requirements for both heparin and LMWH as pregnancy progresses.⁸⁷⁻⁹⁰

Other anticoagulants are used in special circumstances. The indications, route of administration, placental transfer, and fetal effects of these other anticoagulants are summarized in Table 5.

Initiating Anticoagulation

Heparin administration is begun in the early first trimester after ultrasound demonstrates a live embryo and is continued throughout pregnancy and usually the first 6 weeks postpartum. It is debated whether full anticoagulation is required in the antiphospholipid syndrome if poor pregnancy outcome is the only clinical criteria. In a study of women without a history of thrombosis, low doses of anticoagulants were associated with a 71% live-birth rate.⁹¹ Low-dose aspirin is usually used in con-

junction with heparin,⁹² which is not required in cases of low levels of anticardiolipin antibodies as these are of questionable significance.⁹³ Because in 1 study aspirin alone was shown to compare favorably with aspirin plus LMWH in the treatment of women with the antiphospholipid syndrome (a 72% versus a 78% live birth rate—not a statistically significant difference),⁹⁴ low-dose aspirin alone may be an acceptable alternative for women who have no history of thrombosis or poor pregnancy outcome but who have lupus, the lupus anticoagulant, or moderate to high levels of anticardiolipin antibodies.

Until very recently, there were only case reports and case series demonstrating the efficacy of heparin in the improvement of pregnancy outcome in inherited thrombophilia, but a recent report from Gris et al¹⁶ found improved outcomes in women with inherited thrombophilia and a history of a single fetal loss at greater than 10 weeks gestation. Sixty-nine out of 80 women who took enoxaparin (Lovenox, Aventis) 40 mg per day had a healthy live birth, compared with 23 out of 80 who took low-dose aspirin. Although some experts would recommend thromboprophylaxis for all pregnant women with inherited thrombophilia, we do not routinely recommend anticoagulation for women with inherited thrombophilia and no history of thrombosis or poor pregnancy outcome (except those with antithrombin deficiency, homozygosity for factor V Leiden, the prothrombin G20210A polymorphism, or compound heterozygosity for these 2 polymorphisms); in these women, we believe the unknown benefits of anticoagulation are outweighed by the risks.

Table 4. Protocols for Thromboprophylaxis in Pregnancy

	ACCP Protocol ⁷⁶	Duke Protocol
Unfractionated Heparin		
Mini-dose “low dose”	• 5,000 U SC every 12 hr	• 5,000 U SC every 12 hr <8 wk • 7,500 U SC every 12 hr 8–28 wk • 10,000 U SC every 12 hr >28 wk
Moderate-dose “low dose”	• Every 12 hr to target antifactor Xa level of 0.1–0.3 U/mL	
Adjusted dose “full dose”	• Every 12 hr to target mid-interval aPTT in therapeutic range	• Every 8 or 12 hr to target mid-interval aPTT in therapeutic range
Low-Molecular-Weight Heparin		
Prophylactic dose “low dose”	• Enoxaparin 40 mg daily • Dalteparin 5,000 U daily • Tinzaparin 4,500 U daily	• Enoxaparin 40 mg daily or 30 mg twice-daily before 28 wk, then enoxaparin 40 mg twice-daily after 28 wk
Intermediate dose	• Enoxaparin 40 mg every 12 hr • Dalteparin 5,000 U every 12 hr	
Weight-adjusted dose “full dose”	• Enoxaparin 1 mg/kg twice-daily or 1.5 mg/kg daily • Dalteparin 100 U/kg every 12 hr or 200 U/kg every 24 hr • Tinzaparin 175 mg U/kg daily	• Enoxaparin 1 mg/kg twice-daily with target of antifactor Xa level of 0.5–1.0

ACCP = American College of Chest Physicians; SC = subcutaneously; aPTT = activated partial thromboplastin time.

Table 5. Anticoagulants Used in Pregnancy

Agent	Indication	Route of Administration	Placental Transfer	Fetal Outcome
Warfarin	Mechanical heart valves ⁷⁶	Oral	Yes	Miscarriage: 14.6–56% ^{66-69,73,131} Stillbirth: 5–33% ^{66,68,69,73} Congenital anomalies: 0–30% ⁶⁵⁻⁷¹ Fetal or neonatal intracranial hemorrhage: 2% ^{71,72} Adverse neurological outcome: 14% ¹³² Low IQ: 4% ¹³²
Unfractionated heparin	Treatment or prophylaxis ⁷⁶	Intravenous or subcutaneous	None ^{85,77,78}	No increase in adverse fetal outcome in 100 pregnancies ⁷⁹
Low-molecular-weight heparins	Treatment or prophylaxis ⁷⁶	Subcutaneous	None ^{77,78,133,134}	No increase in adverse fetal outcome in 624 pregnancies ⁸⁶
Danaparoid	Heparin allergy ¹³⁵⁻¹³⁸ or HIT ^{99-102,136}	Subcutaneous	Low placental permeability ¹⁰¹ No evidence of anti-Xa activity in placental blood ¹³⁹	No adverse fetal outcome reported in numerous cases; not available in the United States
Recombinant hirudin	Heparin allergy ¹⁰⁴ or HIT ^{101,103}	Intravenous or subcutaneous	Low placental transfer in dogs ¹⁴⁰ <2% of maternal levels detected in plasma of fetal rabbits ¹³⁹	No adverse fetal outcome in 2/2 cases ^{103,104}
Fondaparinux	Heparin allergy ^{105,141} or HIT ¹⁴¹	Subcutaneous	No transfer in in-vitro placental model ^{142,143} 10% of maternal levels detected in umbilical cord blood ¹⁰⁵	No adverse fetal outcome in 5/5 cases ¹⁰⁵
Low-dose aspirin	Supplemental therapy in women with mechanical heart valves ¹⁴⁴ or women with the antiphospholipid syndrome ⁹²	Oral	Yes	No adverse fetal outcome in meta-analyses of large randomized trials ^{145,146}
Other antiplatelet agents	History of myocardial infarction or risk factor for arterial thrombosis including supplemental therapy in women with mechanical heart valves	Oral	No data for dipyridamole, clopidogrel, or ticlopidine. A small amount of abciximab was detected on the fetal side of an in vitro placental model	No adverse fetal outcome with dipyridamole in numerous cases; no adverse fetal outcome with clopidogrel in 2/2 cases ^{147,148} ; no adverse fetal outcome with ticlopidine in 2/2 cases ^{148,149} ; no adverse fetal outcome with abciximab in 1 case ¹⁴⁸
Thrombolytics	Life-threatening thromboembolism	Intravenous	No	Fetal loss: 5.8% ⁷⁵ Hemorrhage: 8.1% ⁷⁵ Maternal mortality: 1.2% ⁷⁵ Reports of subchorionic hematomas, ⁷⁴ abruptio placentae ¹⁵⁰

IQ = intelligence quotient; HIT = heparin-induced thrombocytopenia.

Women on life-long anticoagulation may be converted from warfarin to LMWH before pregnancy or as soon as possible after conception. The problem with conversion prior to pregnancy is the inconvenience and discomfort of parenteral administration of heparin or LMWH and the risks associated with their long-term use. The problem with conversion after conception is that the half-life of warfarin is 36–42 hours⁹⁵ and it may remain in the maternal circulation for several days, increasing the risk of miscarriage and congenital anomalies. Only a few women, including patients with mechanical heart valves and certain other unusual conditions, are candidates for warfarin rather than heparin therapy during pregnancy.

Women who are not on life-long anticoagulation but who are candidates for thromboprophylaxis in pregnancy should start soon after conception. An exception is women who will be undergoing ovulation induction. Because hormone therapy, including clomiphene, increases the risk of thrombosis,⁹⁶ these women should begin anticoagulation at the time they start ovulation induction.

Since HIT manifests within the first 5–15 days of exposure,⁹⁷ platelet counts may be monitored for the first 2–3 weeks after initiation of therapy. Although platelet counts usually drop by 10% in pregnancy and thrombocytopenia affects up to 10% of all pregnancies,⁹⁸ HIT must be considered in women who develop thrombocytopenia while taking heparin or LMWHs. If the diagnosis is confirmed, there are little data to guide treatment. Danaparoid has been used most commonly to treat HIT in pregnancy,^{99–102} but it is not available in the United States. The use of recombinant hirudin has been reported in 1 case of HIT¹⁰³ and 1 case of heparin allergy in pregnancy,¹⁰⁴ and the use of fondaparinux has been reported in 5 cases of heparin allergy in pregnancy¹⁰⁵; the use of argatroban (Encysive) in pregnancy has not been reported and there are no published data on placental transfer or fetal effects.

Peripartum Management

We convert patients to unfractionated heparin at 36–37 weeks of gestation or sooner if there is preterm labor, preeclampsia, fetal (or intrauterine) growth restriction, oligohydramnios, or other evidence of imminent delivery. The purpose of converting women to the shorter-acting unfractionated heparin has less to do with any risk of bleeding at the time of delivery than with the rare possibility of an epidural or spinal hematoma with regional anesthesia.¹⁰⁶ Due to this possibility, our anesthesiologists will not place a regional anesthetic if a woman has received LMWH within 24 hours. Because of the benefits of regional analgesia and anesthesia over other analgesia and anesthesia for labor and delivery,¹⁰⁶ we make every effort to ensure that women have not received LMWH within 24 hours of requiring regional anesthesia. Because women with a history of VTE or thrombophilia are at increased risk of poor pregnancy outcome, it is our practice, unless the woman has already delivered, to schedule delivery at 39 weeks. Depending on the risk of thrombosis, we withhold the unfractionated heparin for 6–24 hours prior to delivery. Should the woman go into labor while taking unfractionated heparin, the heparin should clear within 4–6 hours. Although the benefit of pneumatic compression devices for the preven-

tion of peripartum thrombosis has not been studied, we have extrapolated from perioperative data¹⁰⁷ and order the placement of pneumatic compression devices after epidural administration in labor or prior to cesarean delivery.

Postpartum Management

The pneumatic compression devices are left in place until the patient is ambulatory and until anticoagulation is restarted after delivery. To minimize bleeding complications, we wait to restart anticoagulation until 12 hours after vaginal delivery, 12 hours after epidural removal, or 24 hours after cesarean delivery. Unless a woman prefers to remain on unfractionated heparin or LMWH, she is bridged to warfarin for 6 weeks postpartum. Women who had a thrombotic event during pregnancy will be continued on warfarin for at least 3–6 months. Women on life-long anticoagulation will be continued indefinitely. Although warfarin is contraindicated during pregnancy, it is not contraindicated during breastfeeding. In a study of the transfer of warfarin into breast milk, less than 25 ng of warfarin was detected per milliliter.¹⁰⁸ The American Academy of Pediatrics' Committee on Drugs supports breastfeeding in women who take warfarin.¹⁰⁹

References

1. Prevention of venous thrombosis and pulmonary embolism. NIH Consensus Development. *JAMA*. 1986;256(6):744-749.
2. James A, Brancaccio L, Jamison M, Myers E. Peripartum thromboembolism in the United States 2000-2001: incidence, mortality and risk factors. *Am J Obstet Gynecol*. 2004;191(6):90S.
3. Bergqvist A, Bergqvist D, Lindhagen A, Matzsch T. Late symptoms after pregnancy-related deep vein thrombosis. *Br J Obstet Gynaecol*. 1990;97(4):338-341.
4. Ulander VM, Lehtola A, Kaaja R. Long-term outcome of deep venous thrombosis during pregnancy treated with unfractionated heparin or low molecular weight heparin. *Thrombosis Res*. 2003;111(4-5):239-242.
5. Rosfors S, Noren A, Hjertberg R, Persson L, Lillthors K, Torngren S. A 16-year haemodynamic follow-up of women with pregnancy-related medically treated ilio-femoral deep venous thrombosis. *Eur J Vasc Endovasc Surg*. 2001;22(5):448-455.
6. Maternal mortality in 2000: estimates developed by WHO, UNICEF and UNFPA: WHO; 2004.
7. Chang J, Elam-Evans LD, Berg CJ, et al. Pregnancy-related mortality surveillance-United States, 1991-1999. *MMWR Surveill Summ*. 2003;52(2):1-8.
8. Pabinger I, Schneider B. Thrombotic risk in hereditary antithrombin III, protein C, or protein S deficiency. A cooperative, retrospective study. Gesellschaft für Thrombose- und Hamostaseforschung (GTH) Study Group on Natural Inhibitors. *Arterioscler Thromb Vasc Biol*. 1996;16(6):742-748.
9. Conard J, Horellou MH, Van Dreden P, Lecompte T, Samama M. Thrombosis and pregnancy in congenital deficiencies in AT III, protein C or protein S: study of 78 women. *Thromb Haemost*. 1990;63(2):319-320.
10. Hellgren M, Tengborn L, Abildgaard U. Pregnancy in women with congenital antithrombin III deficiency: experience of treatment with heparin and antithrombin. *Gynecol Obstet Invest*. 1982;14(2):127-141.
11. Management of early recurrent pregnancy loss: ACOG; 2001.
12. Alfirevic Z, Roberts D, Martlew V. How strong is the association between maternal thrombophilia and adverse pregnancy outcome? A systematic review. *Eur J Obstet Gynecol Reprod Biol*. 2002;101(1):6-14.
13. Lockwood CJ. Inherited thrombophilias in pregnant patients: detection and treatment paradigm. *Obstet Gynecol*. 2002;99(2):333-341.
14. Brill-Edwards P, Ginsberg JS, Gent M, et al. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. Recurrence of Clot in This Pregnancy Study Group. *N Engl J Med*. 2000;343(20):1439-1444.
15. Branch DW, Rodgers GM. Recombinant activated factor VII: a new weapon in the fight against hemorrhage. *Obstet Gynecol*. 2003;101(6):1155-1156.

16. Gris JC, Mercier E, Quere I, et al. Low-molecular-weight heparin versus low-dose aspirin in women with one fetal loss and a constitutional thrombophilic disorder. *Blood*. 2004;103(10):3695-3699.
17. Dickson B. Venous thrombosis: on the history of Virchow's Triad. *Univ Toronto Med J*. 2004;81(3):166-171.
18. Gordon M. Maternal physiology in pregnancy. In: Gabbe S, Niebyl J, Simpson J, eds. *Normal and problem pregnancies*. 4th ed. New York: Churchill Livingstone; 2002:63-92.
19. Macklon NS, Greer IA, Bowman AW. An ultrasound study of gestational and postural changes in the deep venous system of the leg in pregnancy. *Br J Obstet Gynaecol*. 1997;104(2):191-197.
20. Whitty J, Dombrowski M. Respiratory diseases in pregnancy. In: Gabbe S, Niebyl J, Simpson J, eds. *Normal and Problem Pregnancies*. 4th ed. New York: Churchill Livingstone; 2002:1033-1064.
21. Danilenko-Dixon DR, Heit JA, Silverstein MD, et al. Risk factors for deep vein thrombosis and pulmonary embolism during pregnancy or post partum: a population-based, case-control study. *Am J Obstet Gynecol*. 2001;184(2):104-110.
22. Sikovanyecz J, Orvos H, Pal A, et al. Leiden mutation, bed rest and infection: simultaneous triggers for maternal deep-vein thrombosis and neonatal intracranial hemorrhage? *Fetal Diagnosis Therapy*. 2004;19(3):275-277.
23. Kovacevich GJ, Gaich SA, Lavin JB, et al. The prevalence of thromboembolic events among women with extended bed rest prescribed as part of the treatment for premature labor or preterm premature rupture of membranes. *Am J Obstet Gynecol*. 1989;182(5):1089-1092.
24. Carr MH, Towers CV, Eastenson AR, Pircon RA, Iriye BK, Adashek JA. Prolonged bedrest during pregnancy: does the risk of deep vein thrombosis warrant the use of routine heparin prophylaxis? *J Matern Fetal Med*. 1997;6(5):264-267.
25. Bremme KA. Haemostatic changes in pregnancy. *Best Pract Res Clin Haematol*. 2003;16(2):153-168.
26. Ray JG, Chan WS. Deep vein thrombosis during pregnancy and the puerperium: a meta-analysis of the period of risk and the leg of presentation. *Obstet Gynecol Surv*. Apr 1999;54(4):265-271.
27. James A, Tapson V, Goldhaber S. Thrombosis during pregnancy and the postpartum period. *Am J Obstet Gynecol*. 2005;192. In press.
28. Kierkegaard A. Side and site of deep vein thrombosis in women using oral contraceptives. *Acta Obstet Gynecol Scand*. 1985;64(5):399-402.
29. Kierkegaard A. Deep vein thrombosis and the oestrogen content in oral contraceptives. An epidemiological analysis. *Contraception*. 1985;31(1):29-41.
30. Cockett FB, Thomas ML. The iliac compression syndrome. *Br J Surg*. 1965;52(10):816-821.
31. Ginsberg JS, Brill-Edwards P, Burrows RF, et al. Venous thrombosis during pregnancy: leg and trimester of presentation. *Thromb Haemost*. 1992;67(5):519-520.
32. Goldhaber SZ, Tapson VF. A prospective registry of 5,451 patients with ultrasound-confirmed deep vein thrombosis. *Am J Cardiol*. 2004;93(2):259-262.
33. Bates SM, Ginsberg JS. How we manage venous thromboembolism during pregnancy. *Blood*. 2002;100(10):3470-3478.
34. Schafer AI, Levine MN, Konkle BA, Kearon C. Thrombotic disorders: diagnosis and treatment. *Hematology (Am Soc Hematol Educ Program)*. 2003;520-539.
35. Grandone E, Margaglione M, Colaizzo D, et al. Genetic susceptibility to pregnancy-related venous thromboembolism: roles of factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase C677T mutations. *Am J Obstet Gynecol*. 1998;179(5):1324-1328.
36. 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(6):374-380.
37. McColl MD, Ellison J, Reid F, Tait RC, Walker ID, Greer IA. Prothrombin 20210 G-->A, MTHFR C677T mutations in women with venous thromboembolism associated with pregnancy. *BJOG*. 2000;107(4):565-569.
38. Dilley A, Austin H, El-Jamil M, et al. Genetic factors associated with thrombosis in pregnancy in a United States population. *Am J Obstet Gynecol*. 2000;183(5):1271-1277.
39. Martinelli I, De Stefano V, Taioli E, Paciaroni K, Rossi E, Mannucci PM. Inherited thrombophilia and first venous thromboembolism during pregnancy and puerperium. *Thromb Haemost*. 2002;87(5):791-795.
40. Rosendaal F, Koster T, Vandenbroucke J, Reitsma P. High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance). *Blood*. 1995;85(6):1504-1508.
41. Girling J, de Swiet M. Inherited thrombophilia and pregnancy. *Curr Opin Obstet Gynecol*. 1998;10(2):135-144.
42. Krnic-Barrie S, O'Connor CR, Looney SW, Pierangeli SS, Harris EN. A retrospective review of 61 patients with antiphospholipid syndrome. Analysis of factors influencing recurrent thrombosis. *Arch Intern Med*. 1997;157(18):2101-2108.
43. Erkan D, Merrill JT, Yazici Y, Sammaritano L, Buyon JB, Lockshin MD. High thrombosis rate after fetal loss in antiphospholipid syndrome: effective prophylaxis with aspirin. *Arthritis Rheum*. 2001;44(6):1466-1467.
44. Dekker GA, de Vries JI, Doelitzsch PM, et al. Underlying disorders associated with severe early-onset preeclampsia. *Am J Obstet Gynecol*. 1995;173(4):1042-1048.
45. Preston FE, Rosendaal FR, Walker ID, et al. Increased fetal loss in women with heritable thrombophilia. *Lancet*. 1996;348(9032):913-916.
46. Prochazka M, Happach C, Marsal K, Dahlback B, Lindqvist PG. Factor V Leiden in pregnancies complicated by placental abruption. *BJOG*. 2003;110(5):462-466.
47. Martinelli P, Grandone E, Colaizzo D, et al. Familial thrombophilia and the occurrence of fetal growth restriction. *Haematologica*. 2001;86(4):428-431.
48. McCowan LM, Craigie S, Taylor RS, Ward C, McLintock C, North RA. Inherited thrombophilias are not increased in "idiopathic" small-for-gestational-age pregnancies. *Am J Obstet Gynecol*. 2003;188(4):981-985.
49. Infante-Rivard C, Rivard GE, Yotov WV, et al. Absence of association of thrombophilia polymorphisms with intrauterine growth restriction. *N Engl J Med*. 2002;347(1):19-25.
50. Rai R, Regan L, Clifford K, et al. Antiphospholipid antibodies and beta 2-glycoprotein-I in 500 women with recurrent miscarriage: results of a comprehensive screening approach. *Hum Reprod*. 1995;10(8):2001-2005.
51. Lockwood CJ, Romero R, Feinberg RF, Clyne LP, Coster B, Hobbins JC. The prevalence and biologic significance of lupus anticoagulant and anticardiolipin antibodies in a general obstetric population. *Am J Obstet Gynecol*. 1989;161(2):369-373.
52. Pattison NS, Chamley LW, McKay EJ, Liggins GC, Butler WS. Antiphospholipid antibodies in pregnancy: prevalence and clinical associations. *Br J Obstet Gynaecol*. 1993;100(10):909-913.
53. Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: a meta-analysis. *Lancet*. 2003;361(9361):901-908.
54. Kovalevsky G, Gracia CR, Berlin JA, Sammel MD, Barnhart KT. Evaluation of the association between hereditary thrombophilias and recurrent pregnancy loss: a meta-analysis. *Arch Intern Med*. 2004;164(5):558-563.
55. Reznikoff-Etievant MF, Cayol V, Carbonne B, Robert A, Coulet F, Milliez J. Factor V Leiden and G20210A prothrombin mutations are risk factors for very early recurrent miscarriage. *BJOG*. 2001;108(12):1251-1254.
56. Balasch J, Reverter JC, Fabregues F, et al. First-trimester repeated abortion is not associated with activated protein C resistance. *Hum Reprod*. 1997;12(5):1094-1097.
57. Rai R, Shlebak A, Cohen H, et al. Factor V Leiden and acquired activated protein C resistance among 1000 women with recurrent miscarriage. *Hum Reprod*. 2001;16(5):961-965.
58. Grandone E, Margaglione M, Colaizzo D, et al. Factor V Leiden is associated with repeated and recurrent unexplained fetal losses. *Thromb Haemost*. 1997;77(5):822-824.
59. Hashimoto K, Shizusawa Y, Shimoya K, et al. The factor V Leiden mutation in Japanese couples with recurrent spontaneous abortion. *Hum Reprod*. 1999;14(7):1872-1874.
60. Holmes ZR, Regan L, Chilcott I, Cohen H. The C677T MTHFR gene mutation is not predictive of risk for recurrent fetal loss. *Br J Haematol*. 1999;105(1):98-101.
61. Pickering W, Marriott K, Regan L. G20210A prothrombin gene mutation: prevalence in a recurrent miscarriage population. *Clin Appl Thromb Hemost*. 2001;7(1):25-28.
62. Glueck CJ, Phillips H, Cameron D, et al. The 4G/4G polymorphism of the hypofibrinolytic plasminogen activator inhibitor type 1 gene: an independent risk factor for serious pregnancy complications. *Metabolism*. 2000;49(7):845-852.
63. Moore K. Organogenetic Period: The Fourth to Eighth Weeks. The developing human: clinically oriented embryology, 6th ed. Philadelphia: WB Saunders Company; 1998:83-106.
64. Naimi TS, Lipscomb LE, Brewer RD, Gilbert BC. Binge drinking in the pre-conception period and the risk of unintended pregnancy: implications for women and their children. *Pediatrics*. 2003;111(5 Part 2):1136-1141.
65. Iturbe-Alessio I, Fonseca MC, Mutchinik O, Santos MA, Zajarias A, Salazar E. Risks of anticoagulant therapy in pregnant women with artificial heart valves. *N Engl J Med*. 1986;315(22):1390-1393.
66. Sadler L, McCowan L, White H, Stewart A, Bracken M, North R. Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and

- homograft valves. *BJOG*. 2000;107(2):245-253.
67. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. *Arch Intern Med*. 2000;160(2):191-196.
 68. Nassar AH, Hobeika EM, Abd Essamad HM, Taher A, Khalil AM, Usta IM. Pregnancy outcome in women with prosthetic heart valves. *Am J Obstet Gynecol*. 2004;191(3):1009-1013.
 69. Blickstein D, Blickstein I. The risk of fetal loss associated with Warfarin anticoagulation. *Int J Gynaecol Obstet*. 2002;78(3):221-225.
 70. Srivastava AK, Gupta AK, Singh AV, Husain T. Effect of oral anticoagulant during pregnancy with prosthetic heart valve. *Asian Cardiovasc Thorac Ann*. 2002;10(4):306-309.
 71. Meschengieser SS, Fondevila CG, Santarelli MT, Lazzari MA. Anticoagulation in pregnant women with mechanical heart valve prostheses. *Heart*. 1999;82(1):23-26.
 72. Chen WW, Chan CS, Lee PK, Wang RY, Wong VC. Pregnancy in patients with prosthetic heart valves: an experience with 45 pregnancies. *Q J Med*. 1982;51(203):358-365.
 73. Cotrufo M, De Feo M, De Santo LS, et al. Risk of warfarin during pregnancy with mechanical valve prostheses. *Obstet Gynecol*. 2002;99(1):35-40.
 74. Usta IM, Abdallah M, El-Hajj M, Nassar AH. Massive subchorionic hematomas following thrombolytic therapy in pregnancy. *Obstet Gynecol*. 2004;103(5 Pt 2):1079-1082.
 75. Turrentine MA, Braems G, Ramirez MM. Use of thrombolytics for the treatment of thromboembolic disease during pregnancy. *Obstet Gynecol Surv*. 1995;50(7):534-541.
 76. Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(3 Suppl):627S-644S.
 77. Harenberg J, Schneider D, Heilmann L, Wolf H. Lack of anti-factor Xa activity in umbilical cord vein samples after subcutaneous administration of heparin or low molecular mass heparin in pregnant women. *Haemostasis*. 1993;23(6):314-320.
 78. Schneider D, Heilmann L, Harenberg J. [Placental transfer of low-molecular weight heparin]. *Geburtshilfe Frauenheilkd*. 1995;55(2):93-98.
 79. Ginsberg JS, Kowalchuk G, Hirsh J, Brill-Edwards P, Burrows R. Heparin therapy during pregnancy. Risks to the fetus and mother. *Arch Intern Med*. 1989;149(10):2233-2236.
 80. Dahlman T, Sjöberg H, Ringertz H. Bone mineral density during long-term prophylaxis with heparin during pregnancy. *Am J Obstet Gynecol*. 1994;170:221-228.
 81. Barbour L, Kick S, Steiner J, et al. A prospective study of heparin-induced osteoporosis in pregnancy using bone densitometry. *Am J Obstet Gynecol*. 1994;170:862-869.
 82. Dahlman TC. Osteoporotic fractures and the recurrence of thromboembolism during pregnancy and the puerperium in 184 women undergoing thromboprophylaxis with heparin. *Am J Obstet Gynecol*. 1993;168(4):1265-1270.
 83. Fausett MB, Vogtlander M, Lee RM, et al. Heparin-induced thrombocytopenia is rare in pregnancy. *Am J Obstet Gynecol*. 2001;185(1):148-152.
 84. Thromboembolism in pregnancy: American College of Obstetrician and Gynecologists; August 2000. 19.
 85. Flessa HC, Kapstrom AB, Glueck HI, Will JJ. Placental transport of heparin. *Am J Obstet Gynecol*. 1965;93(4):570-573.
 86. Lepercq J, Conard J, Borel-Derlon A, et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. *BJOG*. 2001;108(11):1134-1140.
 87. Barbour LA, Smith JM, Marlar RA. Heparin levels to guide thromboembolism prophylaxis during pregnancy. *Am J Obstet Gynecol*. 1995;173(6):1869-1873.
 88. Brancazio LR, Roperti KA, Stierer R, Laifer SA. Pharmacokinetics and pharmacodynamics of subcutaneous heparin during the early third trimester of pregnancy. *Am J Obstet Gynecol*. 1995;173(4):1240-1245.
 89. Casele HL, Laifer SA, Woelkers DA, Venkataraman R. Changes in the pharmacokinetics of the low-molecular-weight heparin enoxaparin sodium during pregnancy. *Am J Obstet Gynecol*. 1999;181(5 Pt 1):1113-1117.
 90. Laifer SA, Casele HL. Puerperal thromboprophylaxis: comparison of the anti-Xa activity of enoxaparin and unfractionated heparin. *Br J Obstet Gynaecol*. 1999;106(6):614-615.
 91. Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ*. 1997;314(7076):253-257.
 92. Branch DW, Khamashta MA. Antiphospholipid syndrome: obstetric diagnosis, management, and controversies. *Obstet Gynecol*. 2003;101(6):1333-1344.
 93. Pattison NS, Chamley LW, Birdsall M, Zanderigo AM, Liddell HS, McDougall J. Does aspirin have a role in improving pregnancy outcome for women with the antiphospholipid syndrome? A randomized controlled trial. *Am J Obstet Gynecol*. 2000;183(4):1008-1012.
 94. Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. *Obstet Gynecol*. 2002;100(3):408-413.
 95. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(3 Suppl):204S-233S.
 96. Stewart JA, Hamilton PJ, Murdoch AP. Thromboembolic disease associated with ovarian stimulation and assisted conception techniques. *Hum Reprod*. 1997;12(10):2167-2173.
 97. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med*. 1995;332(20):1330-1335.
 98. McCrae KR, Bussel JB, Mannucci PM, Remuzzi G, Cines DB. Platelets: an update on diagnosis and management of thrombocytopenic disorders. *Hematology (Am Soc Hematol Educ Program)*. 2001:282-305.
 99. Macchi L, Sarfati R, Guicheteau M, et al. Thromboembolic prophylaxis with danaparoid (Orgaran) in a high-thrombosis-risk pregnant woman with a history of heparin-induced thrombocytopenia (HIT) and Widal's disease. *Clin Appl Thromb Hemost*. 2000;6(4):187-189.
 100. Woo YL, Allard S, Cohen H, Letsky E, de Swiet M. Danaparoid thromboprophylaxis in pregnant women with heparin-induced thrombocytopenia. *BJOG*. 2002;109(4):466-468.
 101. Lindhoff-Last E, Bauersachs R. Heparin-induced thrombocytopenia-alternative anticoagulation in pregnancy and lactation. *Semin Thromb Hemost*. 2002;28(5):439-446.
 102. Gill J, Kovacs MJ. Successful use of danaparoid in treatment of heparin-induced thrombocytopenia during twin pregnancy. *Obstet Gynecol*. 1997;90(4 Pt 2):648-650.
 103. Huhle G, Geberth M, Hoffmann U, Heene DL, Harenberg J. Management of heparin-associated thrombocytopenia in pregnancy with subcutaneous r-hirudin. *Gynecol Obstet Invest*. 2000;49(1):67-69.
 104. Aijaz A, Nelson J, Naseer N. Management of heparin allergy in pregnancy. *Am J Hematol*. 2001;67(4):268-269.
 105. Dempfle CE. Minor transplacental passage of fondaparinux in vivo. *N Engl J Med*. 2004;350(18):1914-1915.
 106. Horlocker TT. Low molecular weight heparin and neuraxial anesthesia. *Thromb Res*. 2001;101(1):V141-154.
 107. Baker WH, Mahler DK, Földes MS, et al. Pneumatic compression devices for prophylaxis of deep venous thrombosis (DVT). *Am Surg*. 1986;52(7):371-373.
 108. Orme ML, Lewis PJ, de Swiet M, et al. May mothers given warfarin breast-feed their infants? *Br Med J*. 1977;1(6076):1564-1565.
 109. Transfer of drugs and other chemicals into human milk. *Pediatrics*. 2001;108(3):776-789.
 110. de Vries JI, Dekker GA, Huijgens PC, Jakobs C, Blomberg BM, van Geijn HP. Hyperhomocysteinemia and protein S deficiency in complicated pregnancies. *Br J Obstet Gynaecol*. 1997;104(11):1248-1254.
 111. Goddijn-Wessel TA, Wouters MG, van de Molen EF, et al. Hyperhomocysteinemia: a risk factor for placental abruption or infarction. *Eur J Obstet Gynecol Reprod Biol*. 1996;66(1):23-29.
 112. Wiener-Megnagi Z, Ben-Shlomo I, Goldberg Y, Shalev E. Resistance to activated protein C and the leiden mutation: high prevalence in patients with abruptio placentae. *Am J Obstet Gynecol*. 1998;179(6 Pt 1):1565-1567.
 113. van der Spuy ZM, Bird AR, Lindow SW, Bruce C. The prevalence of antiphospholipid antibodies in women with reproductive failure or major abruptio placentae. *S Afr Med J*. 1993;83(5):319-321.
 114. Gris JC, Quere I, Monpeyroux F, et al. Case-control study of the frequency of thrombophilic disorders in couples with late foetal loss and no thrombotic antecedent—the Nimes Obstetricians and Haematologists Study5 (NOHA5). *Thromb Haemost*. 1999;81(6):891-899.
 115. Kupfermanc MJ, Eldor A, Steinman N, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. *N Engl J Med*. 1999;340(1):9-13.
 116. Rothbart H, Ohel G, Younis J, Lanir N, Brenner B. High prevalence of activated protein C resistance due to factor V leiden mutation in cases of intrauterine fetal death. *J Matern Fetal Med*. 1999;8(5):228-230.

117. Leeda M, Riyazi N, de Vries JI, Jakobs C, van Geijn HP, Dekker GA. Effects of folic acid and vitamin B6 supplementation on women with hyperhomocysteinemia and a history of preeclampsia or fetal growth restriction. *Am J Obstet Gynecol.* 1998;179(1):135-139.
118. Chikosi AB, Moodley J, Pegoraro RJ, Lanning PA, Rom L. 5,10-methylenetetrahydrofolate reductase polymorphism in black South African women with pre-eclampsia. *Br J Obstet Gynaecol.* 1999;106(11):1219-1220.
119. Dizon-Townson D, Nelson L, Easton K, Ward K. The factor V Leiden mutation may predispose women to severe preeclampsia. *Am J Obstet Gynecol.* 1996;175(4 Pt 1):902-905.
120. Grandone E, Margaglione M, Colaizzo D, et al. Prothrombotic genetic risk factors and the occurrence of gestational hypertension with or without proteinuria. *Thromb Haemost.* 1999;81(3):349-352.
121. Krauss T, Augustin HG, Osmer R, Meden H, Unterhalt M, Kuhn W. Activated protein C resistance and factor V Leiden in patients with hemolysis, elevated liver enzymes, low platelets syndrome. *Obstet Gynecol.* 1998;92(3):457-460.
122. Lindoff C, Ingemarsson I, Martinsson G, Segelmark M, Thysell H, Astedt B. Preeclampsia is associated with a reduced response to activated protein C. *Am J Obstet Gynecol.* 1997;176(2):457-460.
123. Nagy B, Toth T, Rigo J, Jr., Karadi I, Romics L, Papp Z. Detection of factor V Leiden mutation in severe pre-eclamptic Hungarian women. *Clin Genet.* 1998;53(6):478-481.
124. O'Shaughnessy KM, Fu B, Ferraro F, Lewis I, Downing S, Morris NH. Factor V Leiden and thermolabile methylenetetrahydrofolate reductase gene variants in an East Anglian preeclampsia cohort. *Hypertension.* 1999;33(6):1338-1341.
125. van Pampus MG, Dekker GA, Wolf H, et al. High prevalence of hemostatic abnormalities in women with a history of severe preeclampsia. *Am J Obstet Gynecol.* 1999;180(5):1146-1150.
126. Horstkotte D. Prosthetic valves or tissue valves—a vote for mechanical prostheses. *Z Kardiol.* 1985;74 Suppl 6:19-37.
127. De Groot CJ, Bloemenkamp KW, Duvekot EJ, et al. Preeclampsia and genetic risk factors for thrombosis: a case-control study. *Am J Obstet Gynecol.* 1999;181(4):975-980.
128. Mello G, Parretti E, Martini E, et al. Usefulness of screening for congenital or acquired hemostatic abnormalities in women with previous complicated pregnancies. *Haemostasis.* 1999;29(4):197-203.
129. Powers RW, Minich LA, Lykins DL, Ness RB, Crombleholme WR, Roberts JM. Methylenetetrahydrofolate reductase polymorphism, folate, and susceptibility to preeclampsia. *J Soc Gynecol Investig.* 1999;6(2):74-79.
130. Sohda S, Arinami T, Hamada H, Yamada N, Hamaguchi H, Kubo T. Methylenetetrahydrofolate reductase polymorphism and pre-eclampsia. *J Med Genet.* 1997;34(6):525-526.
131. Vural KM, Ozatik MA, Uncu H, et al. Pregnancy after mechanical mitral valve replacement. *J Heart Valve Dis.* 2003;12(3):370-376.
132. Wesseling J, Van Driel D, Heymans HS, et al. Coumarins during pregnancy: long-term effects on growth and development of school-age children. *Thromb Haemost.* 2001;85(4):609-613.
133. Dimitrakakis C, Papageorgiou P, Papageorgiou I, Antzaklis A, Sakarelou N, Michalas S. Absence of transplacental passage of the low molecular weight heparin enoxaparin. *Haemostasis.* 2000;30(5):243-248.
134. Melissari E, Parker CJ, Wilson NV, et al. Use of low molecular weight heparin in pregnancy. *Thromb Haemost.* 1992;68(6):652-656.
135. Harrison P. Progress in the assessment of platelet function. *Br J Haematol.* 2000;111(3):733-744.
136. de Saint-Blanquat L, Simon L, Toubas MF, Hamza J. [Treatment with danaparoid during pregnancy for a woman with a cutaneous allergy to low-molecular-weight heparin]. *Ann Fr Anesth Reanim.* 2000;19(10):751-754.
137. Myers B, Westby J, Strong J. Prophylactic use of danaparoid in high-risk pregnancy with heparin-induced thrombocytopenia-positive skin reaction. *Blood Coagul Fibrinolysis.* 2003;14(5):485-487.
138. Taylor AA. Successful use of heparinoids in a pregnancy complicated by allergy to heparin. *BJOG.* 2001;108(9):1011-1012.
139. Dager WE, White RH. Treatment of heparin-induced thrombocytopenia. *Ann Pharmacother.* 2002;36(3):489-503.
140. Markwardt F, Fink G, Kaiser B, et al. Pharmacological survey of recombinant hirudin. *Pharmazie.* 1988;43(3):202-207.
141. Parody R, Oliver A, Souto JC, Fontcuberta J. Fondaparinux (ARIXTRA) as an alternative anti-thrombotic prophylaxis when there is hypersensitivity to low molecular weight and unfractionated heparins. *Haematologica.* 2003;88(11): ECR32.
142. Lagrange F, Brun JL, Vergnes MC, et al. Fondaparinux sodium does not cross the placental barrier: study using the in-vitro human dually perfused cotyledon model. *Clin Pharmacokinet.* 2002;41(Suppl 2):47-49.
143. Lagrange F, Vergnes C, Brun JL, et al. Absence of placental transfer of pentasaccharide (Fondaparinux, Arixtra) in the dually perfused human cotyledon in vitro. *Thromb Haemost.* 2002;87(5):831-835.
144. Rowan JA, McCowan LM, Raudkivi PJ, North RA. Enoxaparin treatment in women with mechanical heart valves during pregnancy. *Am J Obstet Gynecol.* 2001;185(3):633-637.
145. Duley L, Henderson-Smart D, Knight M, King J. Antiplatelet drugs for prevention of pre-eclampsia and its consequences: systematic review. *BMJ.* 2001;322(7282):329-333.
146. Coomarasamy A, Honest H, Papaioannou S, Gee H, Khan KS. Aspirin for prevention of preeclampsia in women with historical risk factors: a systematic review. *Obstet Gynecol.* 2003;101(6):1319-1332.
147. Klinzing P, Markert UR, Liesaus K, Peiker G. Case report: successful pregnancy and delivery after myocardial infarction and essential thrombocythemia treated with clopidogrel. *Clin Exp Obstet Gynecol.* 2001;28(4):215-216.
148. Martin M, Romero E, Moris C. [Acute myocardial infarction during pregnancy. Treatment with clopidogrel]. *Med Clin (Barc).* 2003;121(7):278-279.
149. Ueno M, Masuda H, Nakamura K, Sakata R. Antiplatelet therapy for a pregnant woman with a mechanical aortic valve: report of a case. *Surg Today.* 2001;31(11):1002-1004.
150. Schumacher B, Belfort MA, Card RJ. Successful treatment of acute myocardial infarction during pregnancy with tissue plasminogen activator. *Am J Obstet Gynecol.* 1997;176(3):716-719.