Thrombophilia and Pregnancy

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13.1 Introduction

Thrombophilias, both hereditary and acquired, are frequently encountered by today's obstetricians. The complexity of the disorders makes both patient counseling and management challenging. Our knowledge of thrombophilias is expansive and evolving, causing both debate and frequent clinical practice changes over the past few decades. As new genetic risk factors for thrombosis have been discovered, the clinical implications are slowly being determined. The goal of this chapter is to discuss both hereditary and acquired thrombophilias, emphasizing the first and second trimesters of pregnancy. We will examine the evolving literature of each disorder and discuss current recommendations regarding screening and therapy.

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13.2 Pregnancy and Hemostasis

Pregnancy is a true test of the human coagulation system. From implantation through the puerperium, the maternal system must carefully balance between hypercoagulability and hemorrhage. Among the earliest challenges is the establishment of the maternal-fetal interface. The invading embryo's cytotrophoblasts access the maternal decidual vessels to establish early placental circulation. The endovascular trophoblasts invade the maternal spiral arteries, which after morphological conversion, provide the high-flow, low resistance blood supply necessary to support the rapidly growing gestation. Implantation provides a multitude of opportunities for both hemorrhage and thrombosis, either of which could initiate miscarriage or pathological placentation. Many of the poor obstetrical outcomes discussed later in this chapter are theorized products of a compromised maternal-fetal placental interface, including preeclampsia, intrauterine growth restriction, pregnancy loss, and abruption.

Delivery and the puerperium make up another serious challenge to the maternal coagulation system. The rapid transition from the 600 to 700 ml/min blood flow to a term placenta (approximately 80 % of uterine blood flow) to appropriate postpartum bleeding is critical [1].

Though much of the hemostatic burden is carried by myometrial contractions and vasospasm, a substantial amount is left to the maternal coagulation cascade to prevent life-threatening postpartum hemorrhaging. This

A. Malvasi et al. (eds.), *Management and Therapy of Early Pregnancy Complications*, DOI 10.1007/978-3-319-31377-1_13

responsibility leads to an increased risk for thrombotic complications, particularly in the setting of a concurrent clotting disorder. Venous thromboembolism (VTE) complications remain a leading cause of maternal death (Fig. 13.1), accounting for an estimated 9.3 % of maternal deaths in the United States from 2006 to 2010 [2]. Risk factors for maternal venous thromboembolism are presented in Table 13.1 [3–7].

Pregnancy has multiple physiological changes that make women susceptible to VTE. All three elements of Virchow's triad (Fig. 13.2) are present, including venous stasis, endothelial injury, and a hypercoagulable state. Hormone changes of pregnancy lead to lower extremity pooling and venous stasis secondary to vasodilation (Fig. 13.3). The uterine compression of the pelvic venous return further augments maternal lower extremity venous stasis (Fig. 13.4). Whether provider recommended or self-prescribed, decreased maternal activity can be an additional contributor to decreased lower extremity venous flow. Endothelial injury and thrombus formation (Figs. 13.5, 13.6, 13.7, 13.8, and 13.9) are present especially at time of delivery. The primary endothelial injury occurs at the uterine placental site, and the risk of VTE is enhanced by cesarean section and operative delivery [8].

There is also increased risk of VTE with infection, postpartum hemorrhage, and preeclampsia, all of which are associated with endothelial injury [9].

The physiology accounting for the hypercoagulability of pregnancy is complex and generated by a factor combination (Fig. 13.10). Many of the procoagulant factors of the clotting cascade are progressively increased throughout pregnancy including factors II, VII, VIII, and X (Fig. 13.11). Decreases

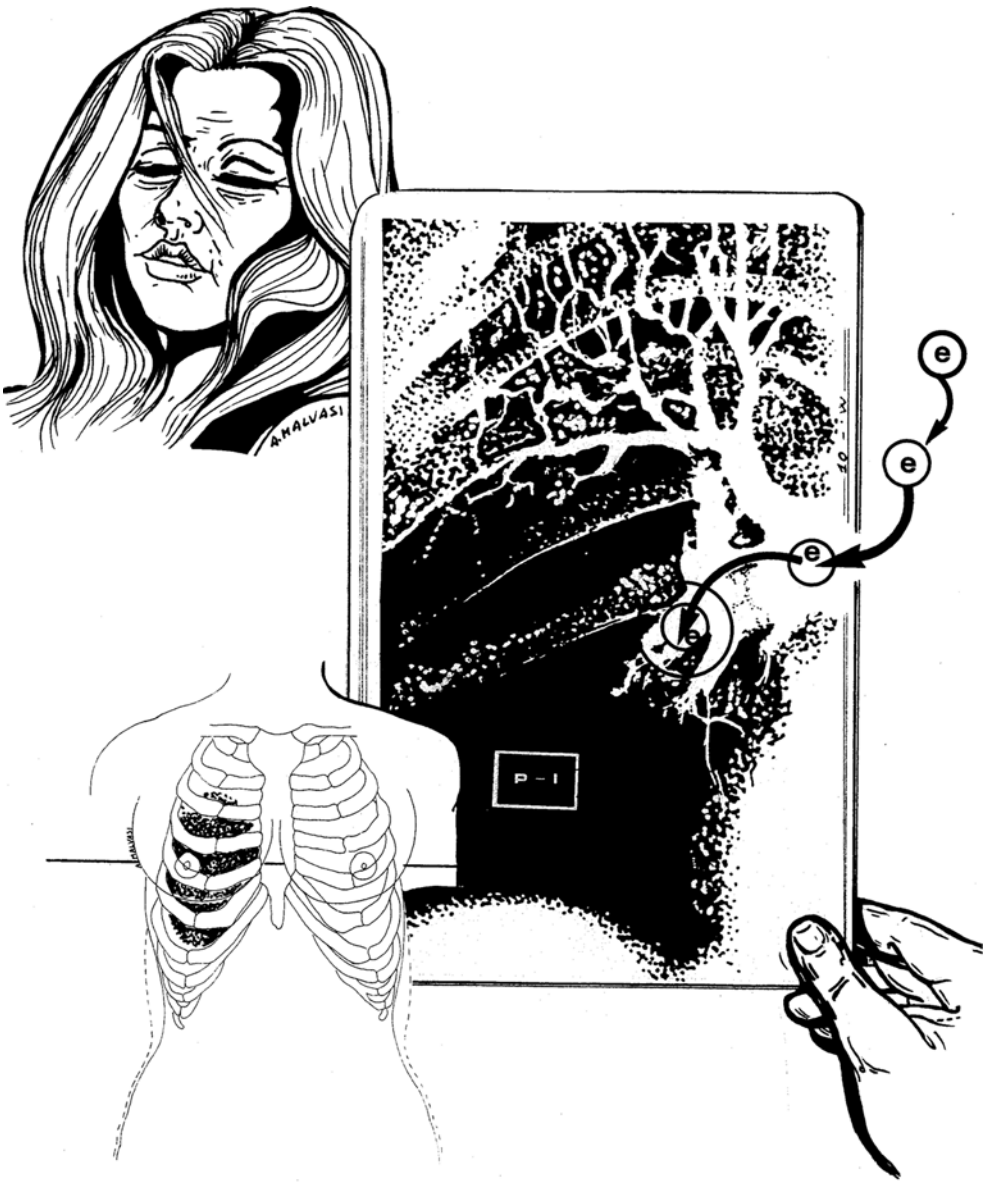

Fig. 13.1 A maternal death for venous thromboembolism (VTE) in pregnancy

Table 13.1 Antepartum and postpartum risk factors for VTE in pregnancy

Antepartum and Postpartum VTE	Odds ratio (95 % CI)
Thrombophilia [3]	51.8 (38.7–69.2)[a]
Previous VTE [3]	24.8 (17.1–36.0)
Family history of VTE [4]	3.9[b]
Superficial venous thrombosis [5]	10.0 (1.3–78.1)
BMI >25 kg/m^2[c] [6]	1.8 (1.3–2.4)
Antepartum immobilization [6]	7.7 (3.2–19.0)
BMI >25 kg/m^2[c] and antepartum immobilization [6]	62.3 (11.5–337.6)
Antepartum VTE [6]	
Assisted reproduction	4.3 (2.0–9.4)
Smoking	2.1 (1.3–3.4)
Postpartum VTE [6]	
Hemorrhage (without surgery)	4.1 (2.3–7.3)
Hemorrhage (with surgery)	12.1 (3.9–36.9)
Infection (vaginal)	20.2 (6.4–63.5)
Infection (cesarean)	6.2 (2.4–26.3)
IUGR	3.8 (1.4–10.2)
Preeclampsia	3.1 (1.8–5.3)
Preeclampsia and IUGR	5.8 (2.1–16.0)
Emergency cesarean delivery	2.7 (1.8–4.1)
Other possible risk factors	
Cesarean delivery [3]	2.1 (1.8–2.4)
Cesarean delivery [6]	1.3 (0.7–2.2)
Age [3]	2.1 (2.0–2.3)
Age [6]	0.8 (0.6–1.1)
Parity [5]	1.1 (0.9–1.4)
Parity [6]	1.7 (1.2–2.4)

Adapted from Bourjeily et al. [7]
VTE venous thromboembolism, *BMI* body mass index. *IUGR* intrauterine growth restriction, [ ] = reference
[a]Risk varies by type of thrombophilia
[b]95 % CI not reported; $p<0.05$
[c]BMI at the time of the first prenatal visit

in protein S and resistance to activated protein C also suppress fibrinolysis, further tilting the system toward coagulation [8].

The addition of a thrombophilia, to a varying extent depending on the specific dysfunction, makes the possibility of VTE substantially higher. The incidence of VTE in pregnancy is approximately 1 per 1500 pregnancies, a prevalence four to six times higher than the rate of women of childbearing ages outside of pregnancy [8, 11–13].

Though venous thromboembolism events can happen at anytime throughout pregnancy, it is generally thought 50 % occur before delivery and 50 % occur in the postpartum period. Data regarding specific trimester-related frequency of VTE is contradictory, but it is clear that the increased risk starts with conception, and the most recent data suggest that the thromboembolic risk is exponential as pregnancy proceeds, with the greatest risk in the peri-delivery period [8, 13–16].

Seventy to ninety percent of DVTs in pregnancy occur in the left leg (Fig. 13.12). This is explained anatomically due to the right iliac artery crossing the proximal left iliac vein, compressing the vessel. The prompt identification and treatment of thrombosis are important in decreasing mortality or complications of thrombotic disease in pregnancy.

13.3 Hereditary Thrombophilias

The inherited thrombophilias addressed in this chapter are all mutations affecting the coagulation cascade (Fig. 13.13). The multiple enzymes and cofactors required for effective hemostasis make opportunities for genetic variation (Fig. 13.11) [10].

The most common genetic prothrombotic mutations include heterozygous carriers of factor V Leiden (FVL) and prothrombin gene mutation (PGM) G20210A. Others we will address in this chapter are far less common including deficiencies in protein C, protein S, and antithrombin (Table 13.2) [18].

We will describe the available data regarding both VTE and adverse pregnancy outcomes (Table 13.3).

Treatment and management of these disorders will be reserved for the end of the chapter.

13.3.1 Factor V Leiden

The inherited thrombophilia most commonly encountered by obstetricians is factor V Leiden (FVL). It is a gene mutation named for the city in which it was first identified in 1994: Leiden, Netherlands [24]. On the procoagulant side of the clotting cascade, factor V is activated by prothrombin to factor Va, which is then a cofactor for the conversion of prothrombin to thrombin. On the anticoagulant side of the equation, factor Va is cleaved by activated protein C and acts as a cofactor for the negative feedback on factor VIII [25]. FVL results from a point mutation in the factor V gene on chromosome 1q23, which codes for an arginine to glutamine substitution at position 506 of the protein. This single amino acid change distorts activated protein C's cleavage site, impairing its ability cleave factor Va.

FVL is most prevalent in Caucasians of European descent with carrier frequencies estimated at 5–9 % of the population. It is less prevalent in those of Asian and African descent [26]. The rate of homozygosity is approximately of 1 % of those with the gene mutation, and they tend have to have a higher incidence of VTE [20, 27].

Screening for FVL can be performed by a second-generation APC resistance assay with confirmatory genetic testing for the FVL mutation. However, most providers go directly to genetic testing which is not affected by anticoagulation.

Retrospective data suggests heterozygous carriers of FVL have a five- to tenfold relative risk for VTE during pregnancy, and it is present in 43 % of pregnant women with their

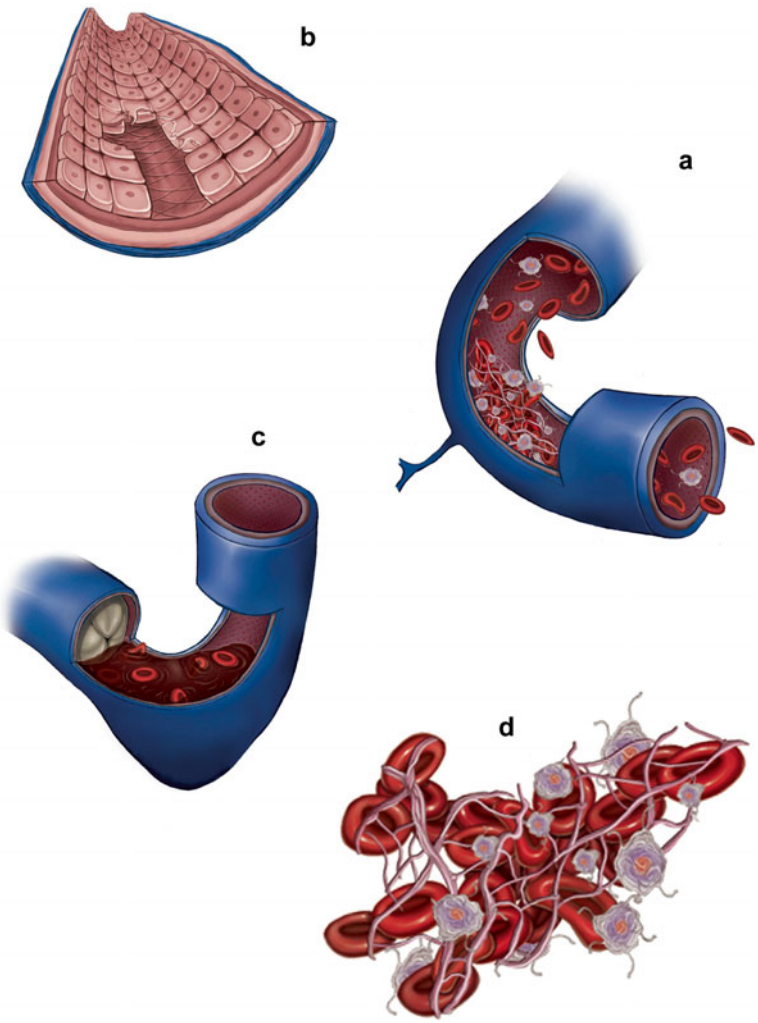

Fig. 13.2 The elements of Virchow's triad, (**a**) venous stasis, (**b**) endothelial damage, and (**c**) venous thrombus formation; (**d**) magnification of the thrombus

first thrombotic event [28–31]. It should be pointed out that the overall carrier rate is high and the overall thrombotic incidence is low. The risk of VTE is only 0.25 % in heterozygotes without a family or personal history of thrombosis. For patients with a family or personal history of VTE, the risk could be as high as 10 % [29]. One large multicenter prospective NICHD study looked at 4885 gravid patients without a personal history of thrombotic event. In the 134 FVL carriers found, there was no increase risk of VTE (0 %; 95 % CI, 0–2.7 %) [32].

Contradictory findings confound the association of FVL and spontaneous abortions. A 2003 meta-analysis looking at seven retrospective studies evaluating FVL and recurrent fetal loss before 13 weeks of gestation suggested an association (OR 2.01; 95 % CI, 1.13–3.58) [23]. Similar findings were found in a later systemic review (OR 1.91; 95 % CI 1.01–3.61) [20]. Contrary to this, Roque et al. found FVL to be protective from recurrent fetal losses prior to 10 weeks of gestation in a cohort of women with poor obstetrical outcomes (OR .229; 95 % CI, 0.07–.77) [33]. Another large case-controlled study of 3496 matched women found an association with fetal loss starting after the 10th week of gestation (OR 3.46; 95 % CI, 2.53–4.72) but not from the 3 to 9th week of gestation (OR 1; 95 % CI, 0.4–2.52) [34]. Overall, it appears FVL might be a small risk factor for first trimester loss, and this increased risk is likely limited to after 10 weeks of gestation.

Many studies have found FVL associated with second trimester fetal losses and stillbirth [23, 35–37]. One meta-analysis associates FVL with second and third trimester loss with a pooled OR 3.6 (95 % CI, 2.2–5.8). This risk increased with each prior fetal loss and with prior losses at later gestations [38]. Kocher et al. used a prospective case-controlled study of 5000 pregnancies and found a stillbirth association (OR 10.9; 95 % CI, 2.07–56.94) [39].

The protective association of FVL in the first trimester of pregnancy and the association with fetal loss later in pregnancy could be explained by the contrasting environments necessary at the placental interface during different stages of development. The partial pressures of oxygen are low in the

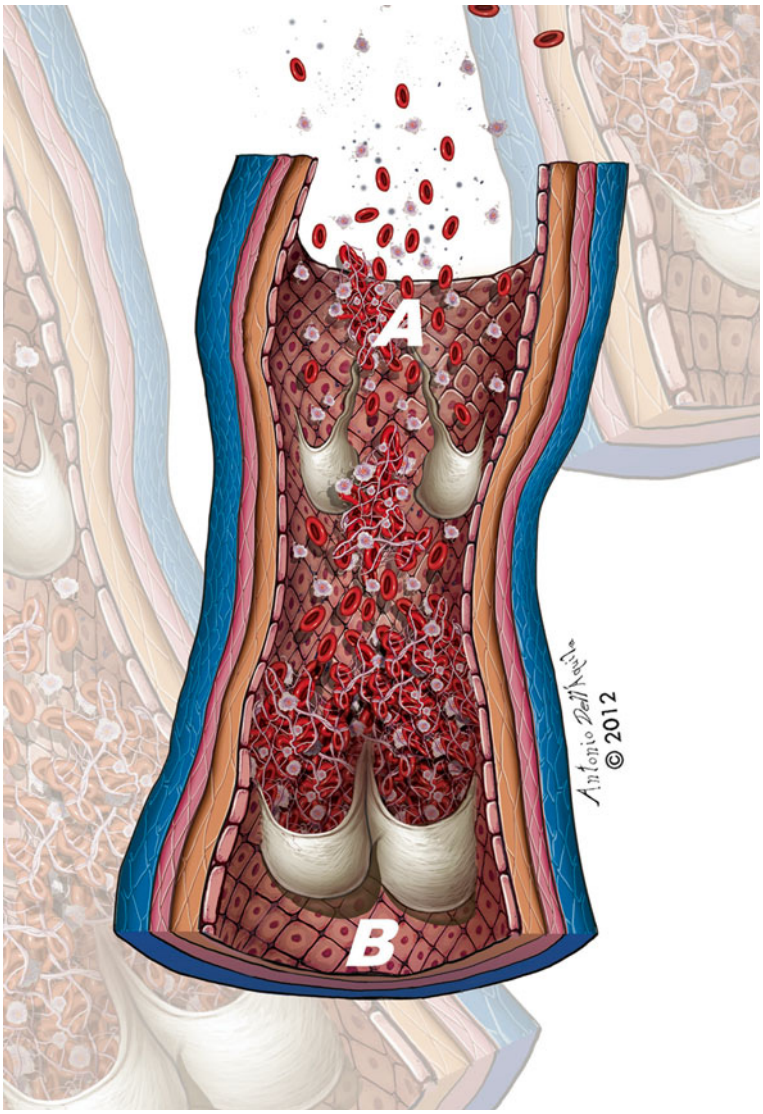

Fig. 13.3 Front section of saphenous vein: (**a**) incontinence of the venous valves and (**b**) thrombus formation

mid first trimester: 17 ± 6.9 mmHg at 8–10 weeks when compared to 60.7 ± 8.5 mmHg at 13 weeks [40]. This hypoxia prior to 10 weeks occurs when trophoblasts are invading and plugging the spiral arteries as evidenced by low Doppler blood flow found on ultrasound [41]. If the hypoxic environment persisted or occurred at later gestations, pregnancy loss would be more likely. This provides a plausible mechanism of how an increased clotting tendency would not affect pregnancy viability prior to 10 weeks but be associated with pregnancy loss when a more oxygen-rich milieu is necessary after the first trimester.

While early studies indicated FVL might be a risk factor for intrauterine growth restriction, most studies indicate that an association is not present. Facco et al. evaluated 12 retrospective case-control studies and four retrospective cohort studies in a systemic review [42]. When all studies are included, an association is suggested (OR 1.23; 95 % CI, 1.04–1.44). When the cohort studies were isolated, the pooled OR for the association did not reach statistical significance (OR 1.16; 95 % CI, 0.98–1.38) [42]. Others have found similar findings [19, 43, 44].

Some available evidence shows an association between the FVL gene mutation and preeclampsia. Lin et al. published a meta-analysis of 12 case-control studies showing an association with both preeclampsia (OR 1.81; 95 % CI, 1.14–2.87) and severe preeclampsia (OR 2.24; 95 % CI, 1.28–3.94) [45]. More recently, a nested case-controlled cohort study of the Danish National Birth Cohort took 519 cases of severe preeclampsia out of 91,661 women and found a positive association (OR 1.94; 95 % CI, 1.27–2.96) [46]. An interesting Italian prospective cohort study showed a higher risk of recurrent preeclampsia in women with FVL (59 %) compared to those without a thrombophilia (25.9 %) [47]. Other studies have failed to find an increased risk of preeclampsia

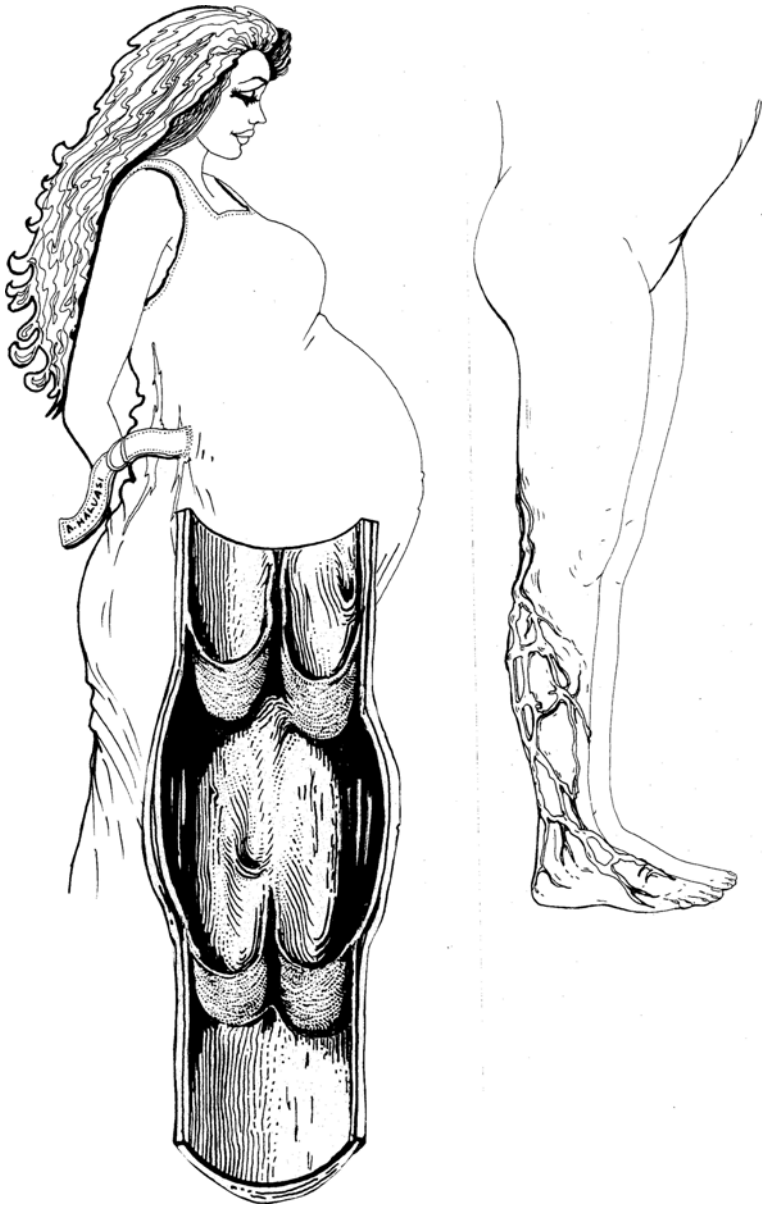

Fig. 13.4 The venous stasis secondary to vasodilation in pregnancy in combination with incontinence valve causes the formation of varicose veins in the legs

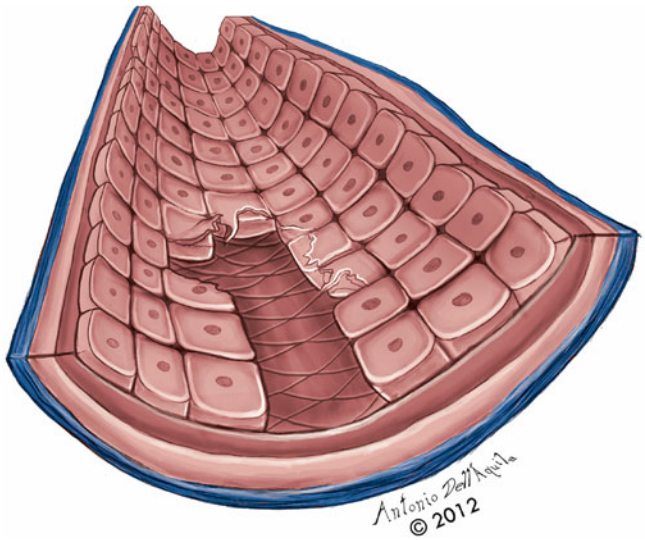

Fig. 13.5 Endothelial injury

with FVL carriers [32, 36, 48], including a meta-analysis of nine prospective cohort studies (OR 1.23; 95% CI 0.89–1.7) [19]. If an association with preeclampsia is present, it is likely not sufficiently significant to alter clinical practice.

Due to the relative infrequency of placental abruption, there are few and conflicting studies evaluating its relationship to FVL. Zdoukopoulos et al. found a positive association in five out of ten retrospective case-control studies. A meta-analysis of those ten studies showed an associative risk (OR 3.42; 95% CI, 1.42–8.25) [49]. The case–cohort study using the Danish Cohort showed a lower but present association (OR 1.87; 95% CI 1.25–2.81) among its 378 cases of placental abruption [46]. No association was found in a NICHD multicenter prospective cohort study in which 134 FVL mutation carriers were identified in a cohort of 4885 women. Nested carrier-control analysis found no association with placental abruption [32].

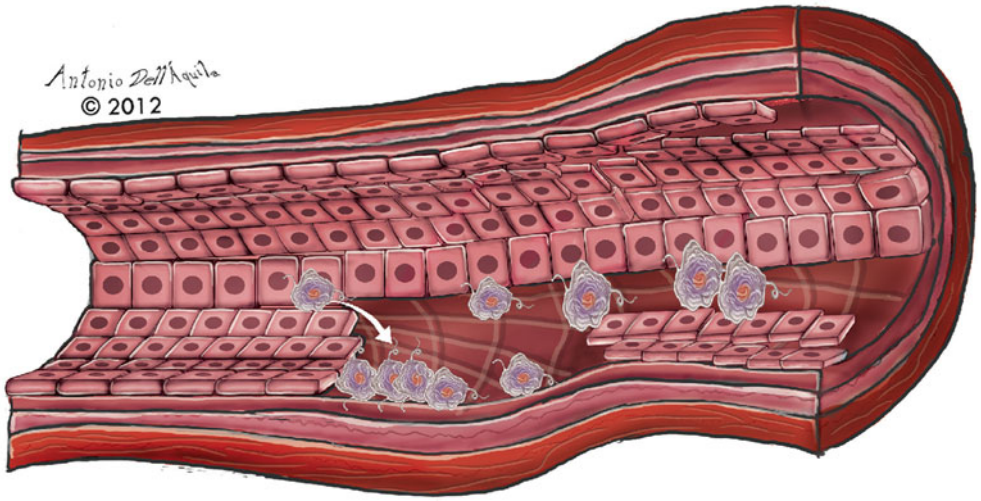

Fig. 13.6 Platelet adhesion to damaged endothelium

Currently, a consistent association between FVL and abruption has not been shown.

Overall, FVL carriers are at increased risk of VTE in pregnancy. FVL is also associated with fetal losses after 10 weeks and stillbirths. There is not enough evidence to strongly support FVL as a risk factor for preeclampsia, fetal growth restriction, or abruption.

13.3.2 Prothrombin Gene Mutation (PGM)

The second-most prevalent inherited thrombophilia results from a polymorphism in the untranslated 3′ region of the gene coding for prothrombin (factor II). A single guanine (G) to adenine (A) nucleotide point mutation, G20210A, leads to enhanced translation and gene expression. The result is elevated circulating prothrombin plasma levels. The carrier prevalence of PGM is 2–4 % in European Caucasians. Similar to FVL, PGM is much less common in those of Asian and African descent [26, 27]. Testing is performed by PCR for the specific G20210A mutation.

PGM is a risk factor for VTE, especially during pregnancy. Gerhardt et al. found that 17 % of 119 patients diagnosed with VTE in pregnancy were carriers of the mutation compared to 1.3 % of matched unaffected controls [28]. Other studies have shown a large variation in carrier percentages among patients with their first VTE related to pregnancy, from 31 % out of 42–3.8 % out of 313 [31, 50]. Like FVL, the overall probability of a thrombosis during pregnancy among PGM carriers without a personal or family history of VTE is as low as 0.37 %. The risk increases to over 10 % for those who have had a prior VTE. The probability appears to be higher for those who are homozygous for PGM mutation, but the available data is sparse [31]. The risk appears much higher for compound heterozygotes for both FVL and PGM, with a 4.6 % probability of a VTE during pregnancy and puerperium even without a prior history [28].

There is conflicting data regarding an association between early fetal loss and PGM carriers (Fig. 13.14). In a meta-analysis of four pooled retrospective studies, PGM carriers had increased risk of recurrent losses before 13 weeks (OR 2.32; 95 % CI, 1.12–4.79) [23]. A similar systemic review of six studies also showed an association with recurrent first trimester loss (OR 2.70; CI 1.37–5.34) [20].

Both of these pooled studies included multiple small retrospective case-control studies that are prone to bias. Subsequent prospective studies have failed to show an association. In one prospective cohort of 4872 pregnancies tested, 2.8 % were carriers for the PGM G20210A gene, and no association with early fetal loss was found (OR 0.74; 95 % CI 0.30–1.84) [39].

Most available data suggest G20210A gene mutation is not a strong risk factor for stillbirth. Korteweg et al. found in a pooled cohort of 1025 fetal deaths that the rate of PGM was no different than the normal population (2.4 % of mothers) [51]. Kocher's prospective cohort study of over 4872 women also found no evidence of PGM as risk factor for stillbirth [39]. In secondary analysis of a large prospective multicenter NICHD cohort study of 4167 women enrolled, no association was noted with pregnancy losses across all gestational ages (OR 0.98; 95 % CI 0.49–1.95) [52]. A 2003 systemic review including five case-controlled studies addressing nonrecurrent losses after 20 weeks suggests an association (OR 2.66; 95 % CI 1.28–5.53) [20]. A more recent meta-analysis of four prospective studies failed to show an association with pregnancy loss (OR 1.13; 95 % CI, 0.64–2.01) [19]. Overall, the association between both early pregnancy loss and stillborn is likely modest if present at all.

Studies regarding PGM and fetal growth restriction generally do not support an association. Lykke's nested case–cohort study of the Danish National Birth Cohort did not show an increased risk of growth restriction in PGM carriers (OR 0.82; 95 % CI 0.46–1.43) [46]. This was similar to prospective data from Silver et al. regarding PGM and for small

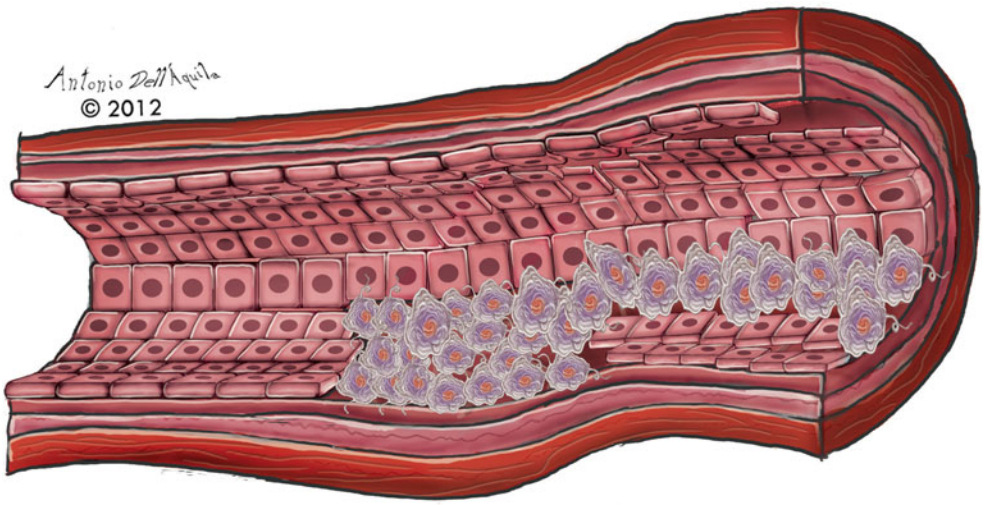

Fig. 13.7 Platelet aggregation on the damaged endothelium

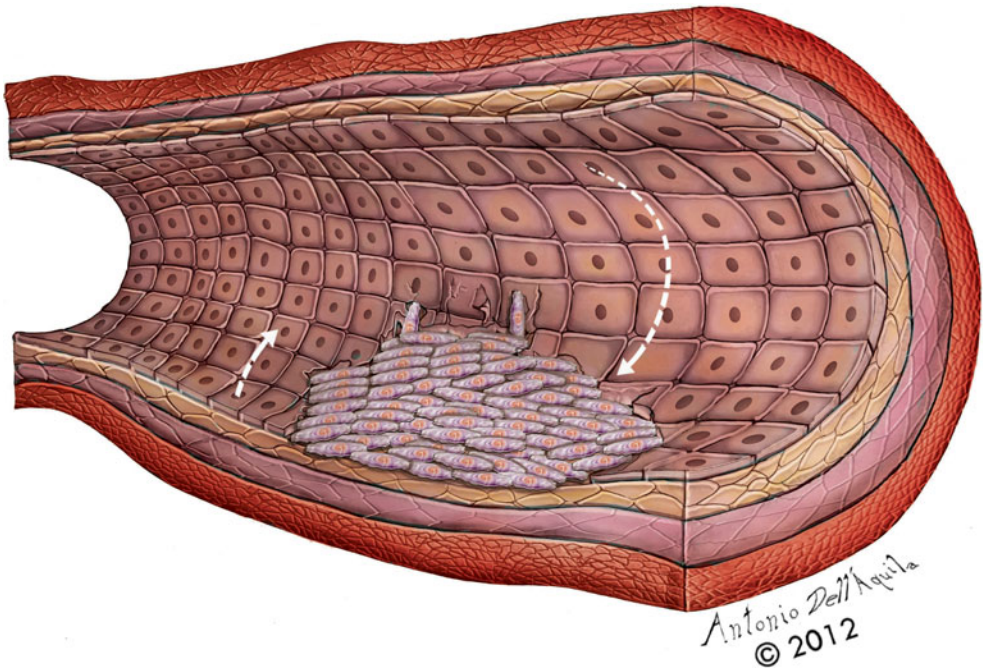

Fig. 13.8 Formation of the platelet plug

for gestational age less than 10 % (OR 1.34; 95 % CI; 0.8–2.25) and less than 5 % (OR 1.39; 95 % CI, 0.67–2.89) using sex- and race-specific growth curves [52]. Similar findings were made by others [19, 36, 39, 53, 54].

Studies showing an association between PGM and IUGR have been limited to case-control studies [37, 55].

Prothrombin gene mutation has not been linked to preeclampsia. In the nested case–cohort evaluation of Danish National Birth Cohort, no association between PGM and severe preeclampsia was found (OR 0.81; 95 % CI, 0.29–2.30) [46].

Rodger et al.'s meta-analysis of prospective studies, including 549 women with PGM, also failed to show an association with preeclampsia (OR 1.25; 95 % CI, 0.79–1.99) [19]. Multiple other studies have shown that PGM is not a risk factor for preeclampsia [36, 48, 52, 56, 57].

The association between PGM and placental abruption is difficult to assess due to the infrequency of abruption. A systemic review including three retrospective case-control studies found a positive association (OR 7.71; 95 % CI 3.01–19.76), but even when pooled, the number of PGM carriers was low ($n = 20$) [20].

In a prospective cohort of 2034 women, Said et al. found that PGM was an isolated risk factor for abruption (OR 12.15; 95 % CI, 2.45–60.39) [36]. The strongest study available comes from pooled prospective data in a 2010 meta-analysis, which failed to find a significant association (OR 2.02; 95 % CI, 0.81–5.02) [19].

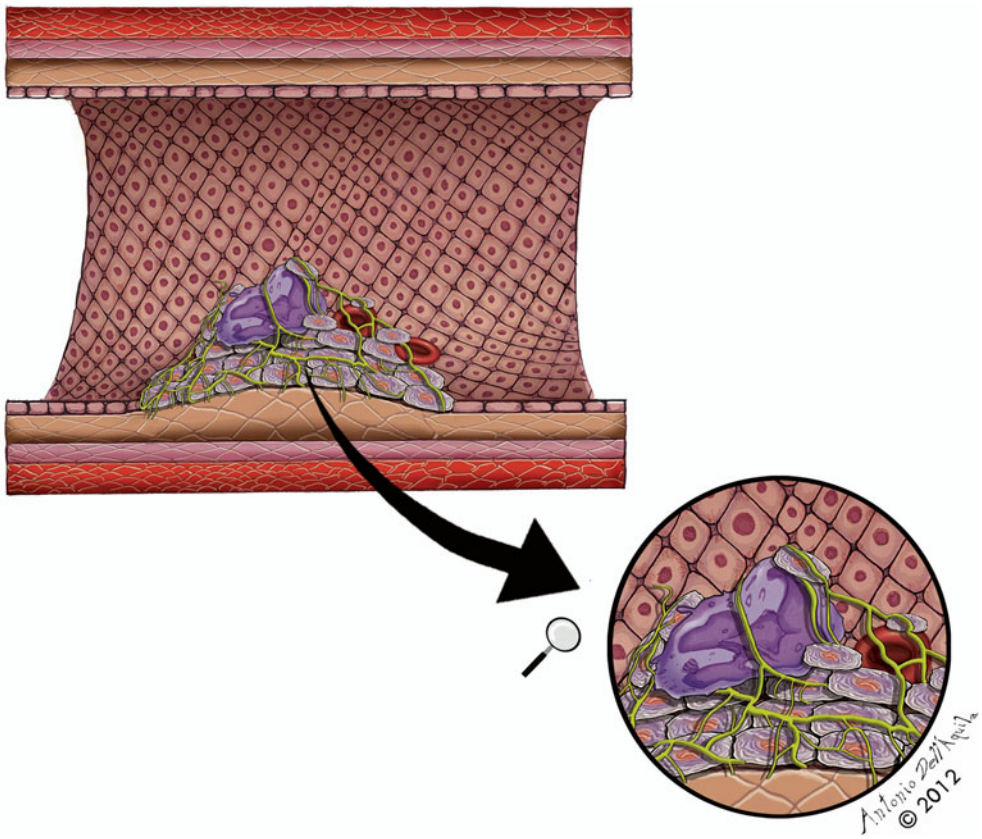

Fig. 13.9 Thrombus formation

In summary, the prothrombin gene mutation G20210A is a relatively common heritable risk factor for thrombosis especially in pregnancy. VTE risk appears higher in homozygotes and those with compound heterozygotes. There has been contradictory data regarding PGM's effect on first trimester losses, stillbirth, and abruption. If associations are present, they are likely weak. There is little evidence that preeclampsia and IUGR are associated with PGM.

13.3.3 Protein C Deficiency

Protein C is an anticoagulant responsible for the deactivation of factor Va and factor VIIIa. It is activated by thrombin to activated protein C (APC) which then degrades factors Va and VIIIa, inhibiting clot formation [27].

Protein S, a nonenzymatic cofactor for this action, will be discussed later in this chapter. Protein C's synthesis (Fig. 13.15a) or functional deficiency is found in 0.2–0.3 % of individuals of European descent. It appears more frequently in those of Asian and African descent [26]. The gene coding for protein C is located on chromosome 2. It is vitamin K dependent and is synthesized by the liver. Two major subtypes of APC deficiencies have been delineated. The more common phenotype, type I, has both reduced protein C levels and activity. Type II phenotypes have quantitatively normal levels of protein C but have compromised functional activity. Laboratory evaluation includes both protein C antigen levels and activity levels. Laboratories typically use activity levels of <50–60 % as abnormal. Testing is unreliable during an acute thrombosis or during anticoagulation therapy.

In regard to a thrombotic event risk in pregnancy, protein C deficiency is moderately pro-thrombogenic (Fig. 13.15b). The risk is likely proportional to the deficiency of substrate and/or function. Zotz et al. found the relative risk of a first VTE in pregnancy to be RR 3.0 (95 % CI: 1.4–6.5) if using a <73 % of normal protein C activity cutoff and RR 13.0 (95 % CI, 1.4–123) if using a <50 % cutoff in his case-control study of 173 women with VTE compared to 325 normal controls [29]. A 2006 systemic review of available retrospective case-controlled studies showed a modest risk of VTE (OR 4.76; 95 % CI, 2.15–10.57) in patients with hereditary protein C deficiency [20]. Because both DVT and protein C deficiency are rare, prospective studies regarding their association are unlikely.

Data regarding the association of protein C deficiency and poor obstetrical outcomes is sparse, and the studies available are underpowered. The diverse genetic variants and phenotypes make it difficult to make any conclusion regarding management strategies. Many studies that do include protein C deficiency pool data with protein S and antithrombin deficiency. Preston et al. found the risk of loss in the first or

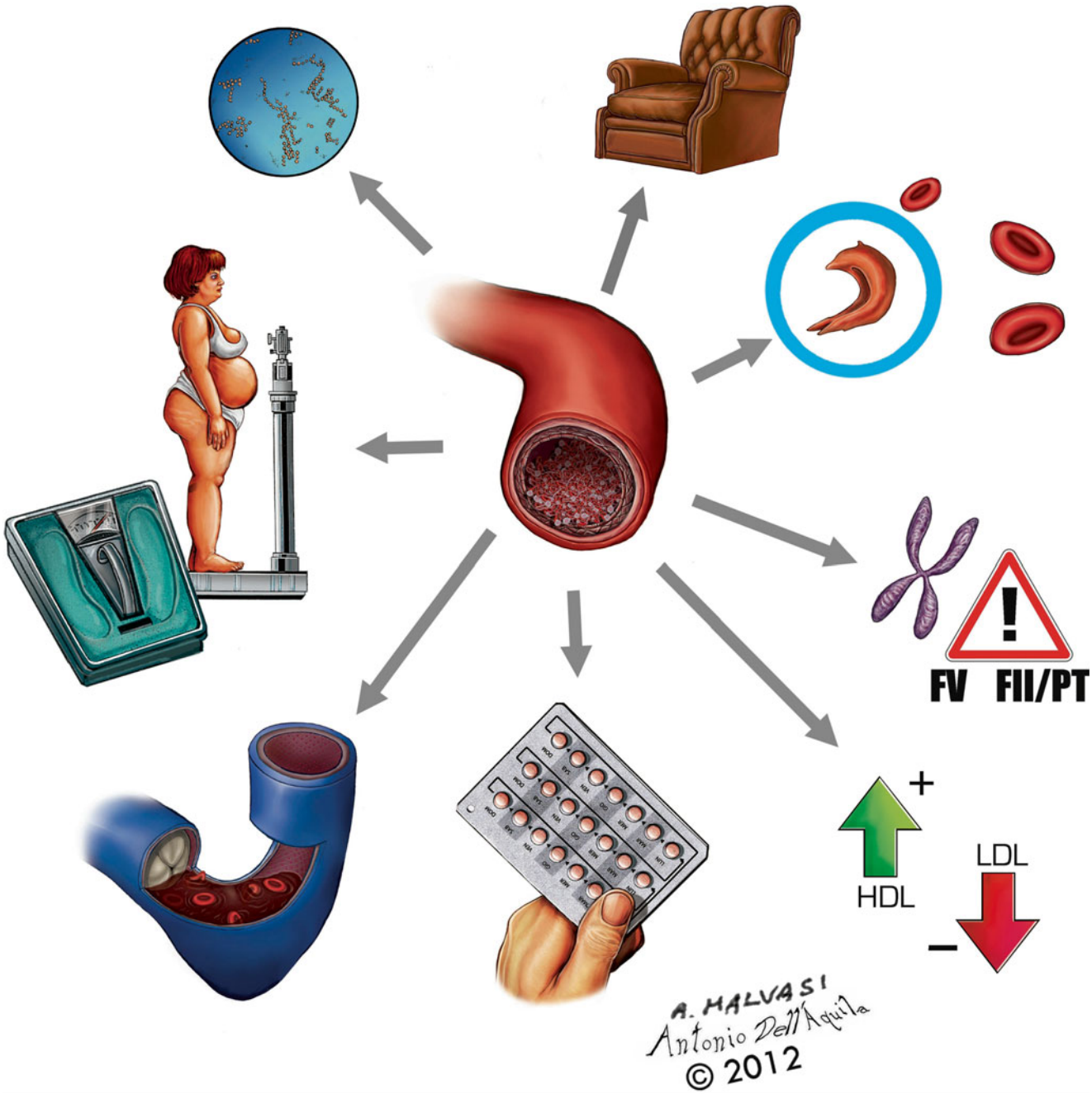

Fig. 13.10 A factor combination accounting for the hypercoagulability of pregnancy

second trimester to be OR 1.4 (95 % CI, 0.9–2.2) compared to a third trimester loss OR 2.3 (95 % CI, 0.6–8.3) [22]. Others have not been able to find associations between recurrent early pregnancy loss and protein C deficiency [58]. In systemic review of retrospective case-controlled studies, Alfirevic et al. found that protein C deficiency was not associated with stillbirth (OR 1; 95 % CI, 0.1–11.1) but was associated with preeclampsia (OR 21.5; 95 % CI, 1.1–414.4). All of the included studies were limited by small study size and large confidence intervals [21]. Our retrospective cohort found an association with preeclampsia (OR 6.85; 95 % CI, 1.09–43.21) and abruption (OR 13.86; 95 % CI, 2.21–86.94) but failed to show associations with the other poor pregnancy outcomes studied [33].

13.3.4 Protein S Deficiency

Protein S is a vitamin K-dependent anticoagulant cofactor in the clotting cascade. It accelerates activated protein C's dis-

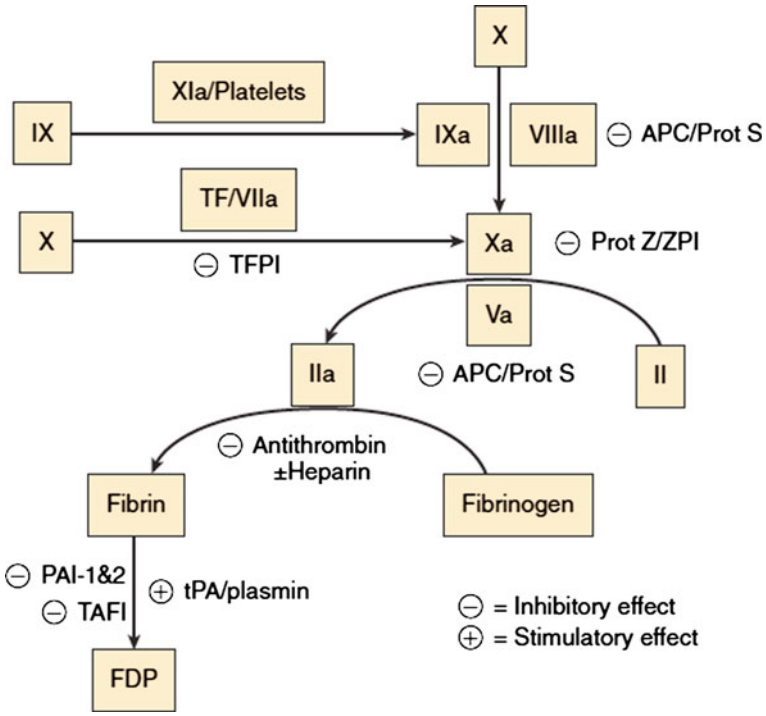

Fig. 13.11 Hemostatic, thrombotic, and fibrinolytic pathways. *FDP* fibrin degradation product. *TPA* tissue-type plasminogen activator (From Pettker and Lockwood [10])

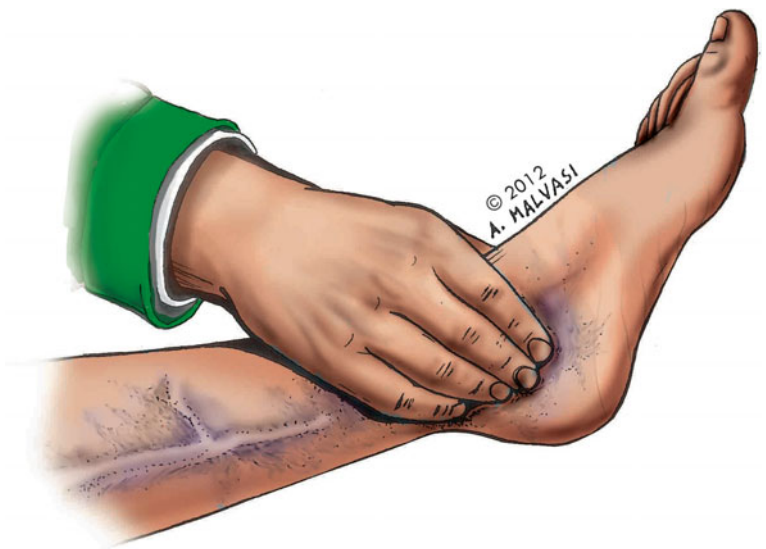

Fig. 13.12 Seventy to ninety percent of DVTs in pregnancy occur in the left leg

ruption of factor Va and factor VIIIa, ultimately suppressing thrombin formation. It is a less common thrombophilia with prevalence of 0.03–0.13 % in the Caucasian European population. The coding gene, PROS1, is located on chromosome 3. There have been over 130 mutations found to cause protein S deficiency with variable expression.

Deficiency of protein S has been divided into three major phenotypes. Type I disease has quantitatively low levels of protein S antigen, both free and total, and decreased function. Type II is characterized by normal free and total protein S levels but compromised functional activity. Type III disease has normal total antigen levels but low of free protein S antigen and activity levels. Protein S activity is variable secondary to fluctuating levels of complement 4B-binding protein, a regulator in the compliment system. Free levels fall throughout pregnancy due to increasing C4b-binding protein. We found in pregnancy free protein S levels substantially lower than nonpregnant values, with free levels of 38.9 ± 10.3 % in the second trimester and 31.2 ± 7.4 % in the third trimester [59]. When indicated, testing for the dysfunction is generally differed until 6-week postpartum to avoid confounding information. Laboratory evaluation is by free protein S antigen levels, which are not reliable in pregnancy, on anticoagulants, or with an active

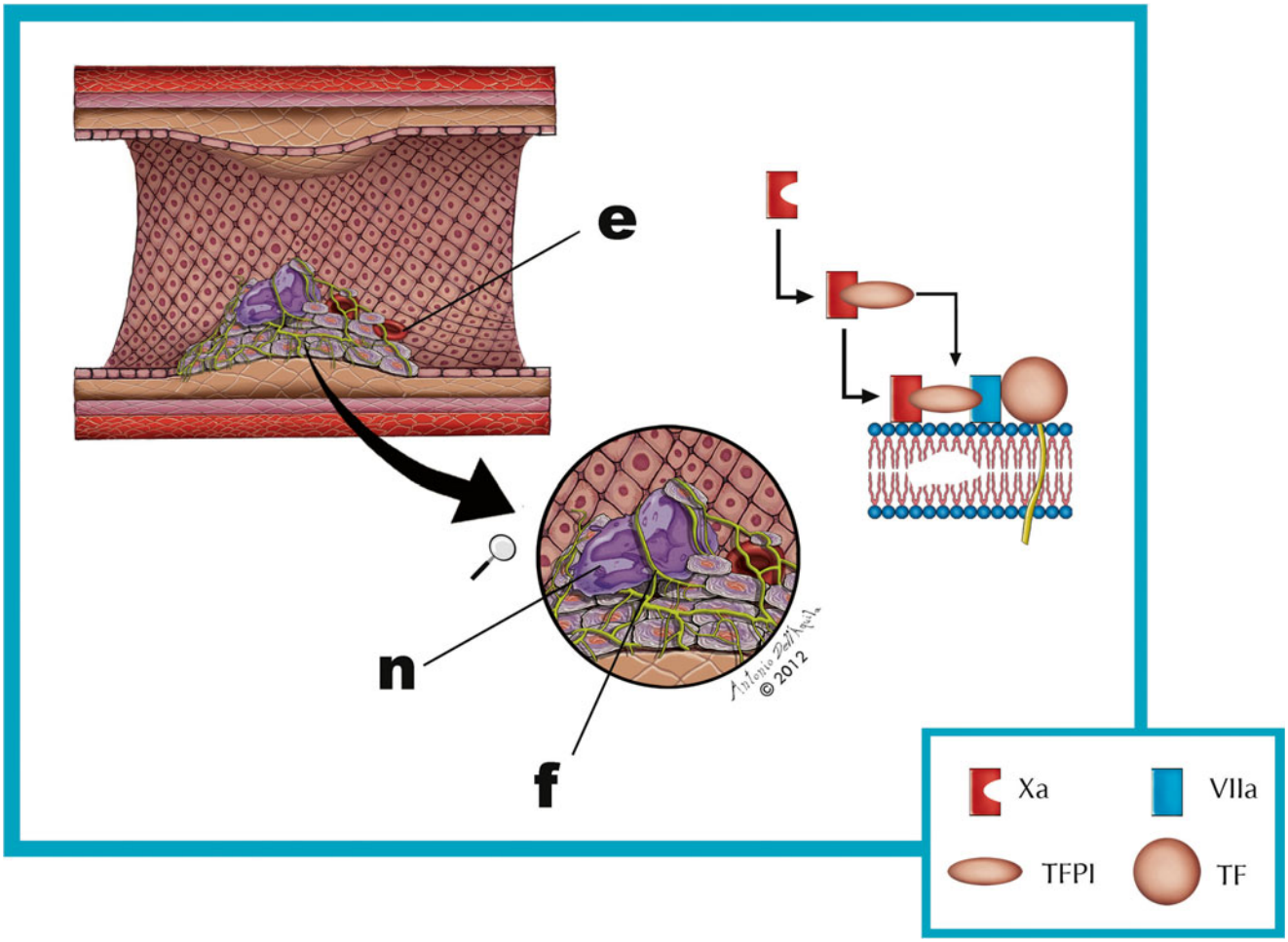

Fig. 13.13 Schematic description of how it is formed a vascular thrombus; at the bottom right, the factors of the coagulation cascade: (*e*) erythrocytes, (*n*) leukocytes, and (*f*) network of adhesion to endothelium

Table 13.2 The risk of venous thromboembolism in pregnant patient with selected thrombophilias

Condition	Prevalence in European populations	Prevalence in patients with VTE in pregnancy	Risk of VTE without prior history	Risk of VTE with prior history
Factor V Leiden (FVL)				
Heterozygous	5.3 %	44	0.26 %	>10 %
Homozygous	0.07 %	<1	1.50 %	>10 %
Prothrombin mutation (PGM)				
Heterozygous	2.90 %	17	0.37–0.5 %	>10 %
Homozygous	0.02 %	<1	2.8	>10 %
Compound FVL/PGM	0.17 %	<1		4.70 %
Protein C deficiency	0.2–0.3 %	<14	0.8–1.7 %	
Protein S deficiency	0.03–0.13 %	12	<1–6.6 %	
Antithrombin deficiency	0.02–1.1 %	1	11.6 % [17]	11–40 %

Adapted from Han et al. [18]

VTE. Free antigen levels below 60 % are considered abnormal, but a diagnosis of hereditary protein S deficiency cannot be made on the basis of protein S activity or free antigen levels when these levels are only determined in pregnancy. Protein S levels must be determined outside of pregnancy and the postpartum period, as well as in the absence of hormonal contraception to confirm the presence of a hereditary protein S deficiency.

Because of the relative infrequency of protein S deficiency, the number of studies regarding its risks

Table 13.3 Association between hereditary thrombophilias and selected pregnancy complications

	Preeclampsia	Pregnancy loss	IUGR	Abruption	Recurrent pregnancy loss	Late pregnancy loss[b]
FVL	1.23 (0.89–1.7) [19]	1.52 (1.06–2.19) [19]	1.0 (0.8–1.25) [19]	1.85 (0.92–3.7) [19]	1.91 (1.01–3.61) [20][a]	2.06 (1.1–3.86) [20]
PGM	1.25 (0.79–1.99) [19]	1.13 (0.64–2.01) [19]	1.25 (0.92–1.7) [19]	2.02 (0.81–5.02) [19]	2.70 (1.37–5.34) [20][a]	2.66 (1.2–5.53) [20]
Protein C deficiency	21.5 (1.1–414.4) [21]	1.4 (0.9–2.2) [22]	NA	5.93 (0.23–151.58) [20]	1.57 (0.23–10.54) [23]	2.3 (0.6–8.3) [22]
Protein S deficiency	2.83 (0.76–10.57) [20]	1.3 (0.8–2.1) [22]	10.2 (1.1–91) [21]	0.3 (0–70.1) [21]	14.72 (0.99–218.01) [23]	7.39 (1.28–42.83) [23]
Antithrombin deficiency	7.1 (0.4–117.4) [21]	2.1 (1.2–3.6) [22]	NA	4.1 (0.3–49.9) [21]	NA	5.2 (1.5–18.1) [22]

Resources: [19–23]
Data are odds ratio (confidence interval 95 %)
IUGR fetal growth restriction, [] = resource
[a]Only first trimester losses included
[b]Definition of late varied from >20 to >28 weeks of gestation depending on study

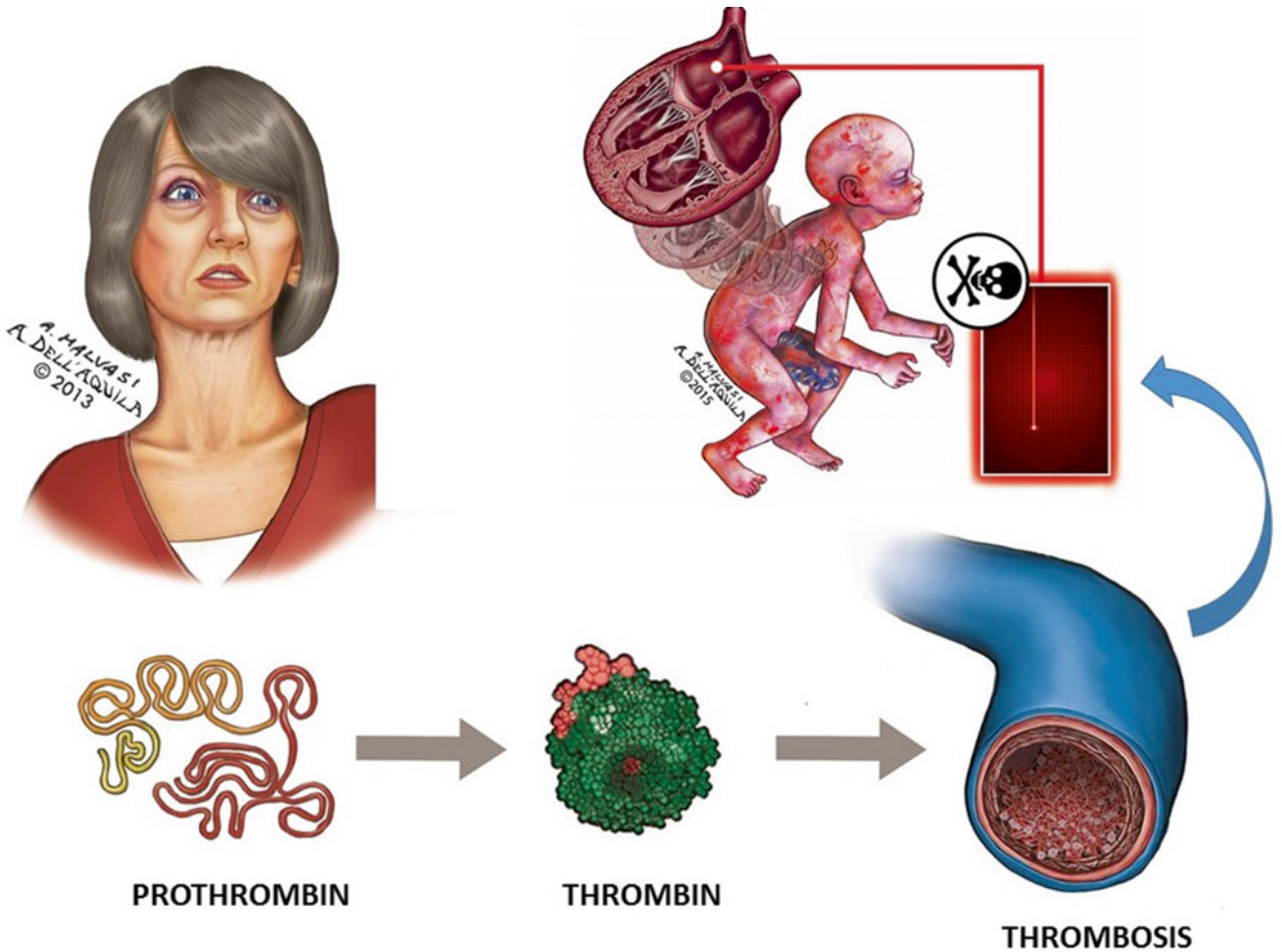

Fig. 13.14 The second-most prevalent inherited thrombophilia of the gene coding for prothrombin (factor II) is associated with early fetal loss

during pregnancy is limited. Robertson's systemic review of available case-controlled studies in 2006 showed an OR 3.19 (95 % CI 1.48–6.88) of VTE and pregnancy [20].

Conard et al.'s evaluation of 44 pregnancies in 17 patients with congenital protein S deficiency showed no thrombosis during pregnancies without anticoagulation but had 5 thrombotic events in the postpartum 17 % (95 % CI 3–31) [60].

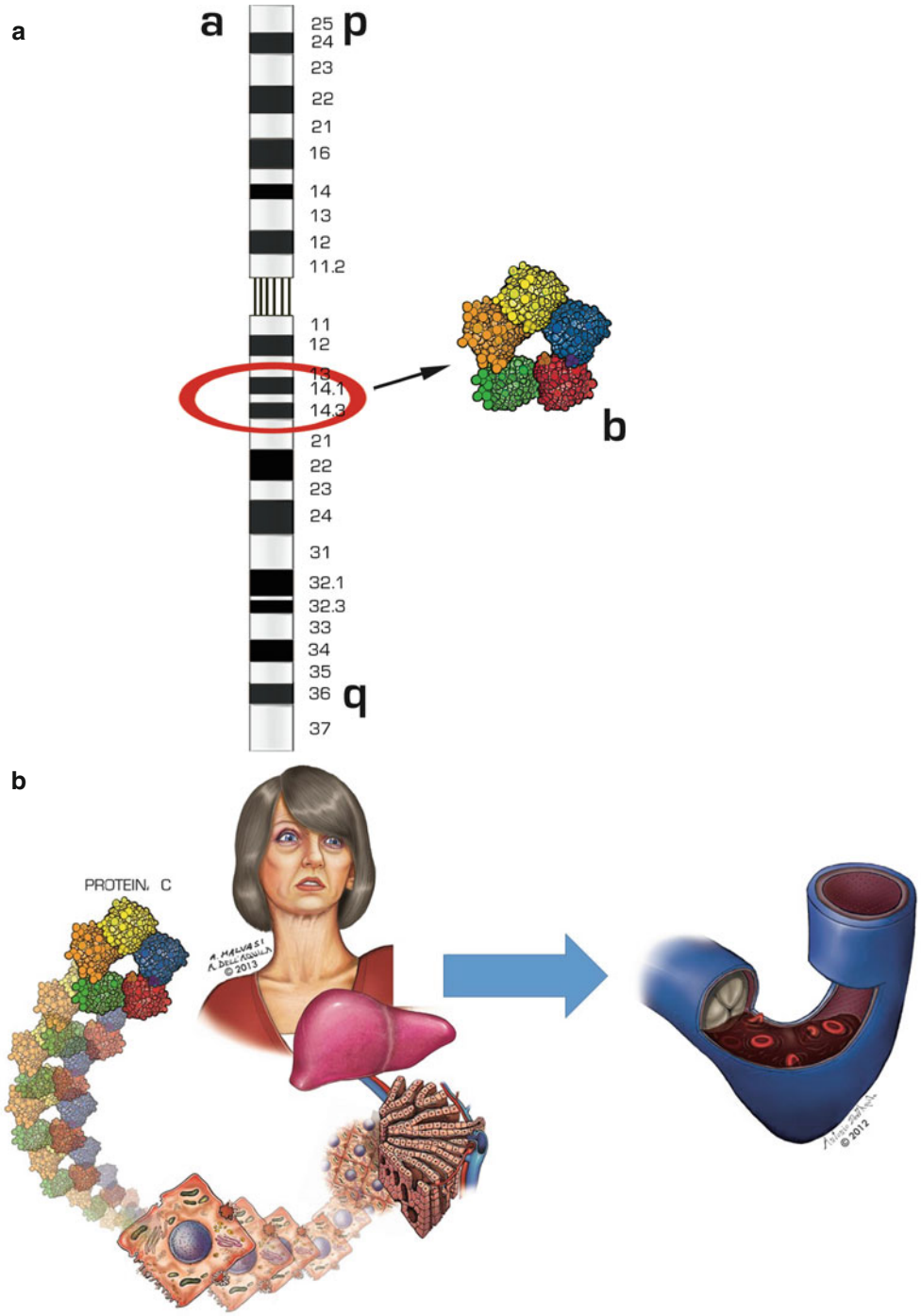

Fig. 13.15 Protein C's synthesis (**a**); protein C is an anticoagulant and its deficiency is moderately pro-thrombogenic factor (**b**)

The most compelling findings regarding protein S deficiency and pregnancy outcomes have been in regard to late fetal loss, although study sizes are small. A systemic review found a relatively strong association with stillbirth defined as unexplained fetal loss after 20 weeks with no fetal abnormalities (OR 16.2; 95 % CI, 5–52.3) [21]. Similar findings were published by Saade and McLintock, who found an association when looking at fetal losses after 28 weeks (OR 41; 95 % CI, 4.8–359) [61]. Although Alfirevic's group found associations with both preeclampsia (OR 12.7; 95 % CI, 4–39.7) and IUGR (OR 10.2; 95 % CI, 1.1–91.0) [21], others have failed to find associations with other poor obstetrical outcomes [20].

13.3.5 Antithrombin Deficiency

A less common but more thrombogenic hereditary dysfunction is caused by mutation in the serine protease inhibitor antithrombin (AT) gene. Sometimes referred to as antithrom-

bin III, AT inhibits active thrombin's conversion of fibrinogen to fibrin. It is also a known inhibitor of factors Xa and IXa, XIa, XIIa, trypsin, plasmin, and kallikrein. Besides its role as anticoagulant, AT has also been found to have anti-inflammatory characteristics [62].

Over 250 mutations have been identified at the AT gene loci which provide a wide spectrum of phenotypes. Type I disease infers a quantitative dysfunction. Type II is the qualitative class of dysfunction, which is further divided into subtypes. Type IIa is characterized by a defect in the reactive site of the protein and is generally more thrombogenic. Type IIb dysfunctions have a defect in the heparin-binding site and are less prone to thrombosis. Type IIc has defects in both binding sites. Type I makes up only 12 % of the total of cases of ATD, but it is much more thrombogenic, accounting for 80 % of symptomatic cases. The prevalence of ATD in Caucasian Europeans is estimated at 0.02–1.15 %. It has been found to be even more common in some Asian populations, with a prevalence of up to 2–5 % [26, 63].

The laboratory assay of choice is plasma AT activity, which, using heparin, measures how well AT inhibits thrombin or factor Xa. Activity <80 % is considered abnormal, but most patients with hereditary ATD have levels <60 %. Testing can be abnormal secondary to anticoagulation and acute thrombosis and should be delayed until after completing treatment.

The risk of VTE in pregnancy can be high with antithrombin deficiency, though as discussed previously there is large variability among phenotypes. A systemic review reported an OR 4.69 (95 % CI 1.30–16.96) regarding VTE and pregnancy [20]. A more recent systemic review which included 112 pregnancies with AT deficiency without a personal history of VTE, found the incidence risk of VTE to be 11.6 % in each pregnancy (OR 6.09; 95 % CI 1.58–24.43) [17].

Retrospective studies have however estimated the risk for the more thrombogenic type I disease (OR 282; 95 % CI, 31–2532) compared to a much smaller risk with type II disease (OR 28; 95 % CI, 5.5–142) [9, 64]. It is estimated that the lifetime risk of VTE in those with type I disease is 50 % [65]. One case series of 63 untreated women with type I ATD who went through pregnancy without anticoagulation found that 18 % had a thrombotic complication during pregnancy and another 33 % had a thrombotic complication postpartum [60].

Though it is the first inherited thrombophilia identified, the data regarding its association to poor obstetrical outcomes is less robust due to its rarity. Regarding early fetal loss, a retrospective cohort found a modest risk of a fetal loss <28 weeks in patients with ATD (OR 1.7; 95 % CI, 1–2.8) [22]. A meta-analysis did not find a significant increased risk of recurrent loss before 17 weeks OR 0.88 (95 % CI 0.17–4.48) or nonrecurrent loss at any gestational age 1.54 (95 % CI 0.97–2.45) [23].

Other studies have failed in demonstrating an association with ATD and early pregnancy loss [20, 33, 58, 66, 67].

Studies investigating the relationship between stillbirth and ATD are even more limited due the infrequency of both diagnoses. Prestin's retrospective cohort study found a significant association (OR 5.2; 95 % CI, 1.5–18.1) [22]. Other attempts to evaluate the risk have been limited by small numbers, but they have not identified a significant association [21, 23, 68].

We found an increased risk of IUGR (OR 12.93; 95 % CI, 2.72–61.45) and abruption (OR 60.01; 95 % CI, 12.02–300.46) in our retrospective cohort of 491 patients with poor pregnancy outcomes [33]. To the contrary, other small studies have failed to show a significant association [20, 21, 68].

The relationship between hereditary antithrombin deficiency and preeclampsia requires further refinement. Lariciprete et al. reported an association between hereditary antithrombin deficiency and preeclampsia in a case-controlled study including 12 patients with ATD (RR 0.88 95 %; CI 0.83–0.94) [68]. A systemic review, however, which included only one study by D'Ellia et al., was not able to identify a significant increased risk (OR 3.89; 95 % CI, 0.16–97.19) [20].

The relationship between ATD and preeclampsia is an intriguing subject. A gradual decline in AT activity during the late stage of pregnancy, namely, pregnancy-induced AT deficiency, has been reported in literature, in healthy parturients at term [62, 69]. Antithrombin activity levels appear to be decreased in pregnancies complicated by preeclampsia. Weiner et al. found mean antithrombin activity to be 60 % ± 15 % in women with preeclampsia compared to 85 % ± 15 % in normal pregnant controls. Using a cutoff ≥ 70 % of AT activity levels provides a negative predictive value of 89 % for preeclampsia. The positive predictive value using a < 70 % AT activity level is 80 % [70, 71]. Others have found falling AT activity levels in preeclampsia patients that was associated with worsening disease [72].

Antithrombin has a few properties that make it a potential pharmacologic therapy for preeclampsia. AT is a potent anticoagulant and anti-inflammatory agent [73]. Both plasma-derived and recombinant forms of AT are currently available for other indications in pregnancy [74]. Some promising studies have used plasma-derived AT to successfully prolong pregnancy in early onset preeclampsia [75–79]. Currently, a large prospective multicenter double-blinded trial is evaluating recombinant AT therapeutic benefits in patients with preterm preeclampsia between 23 and 30 weeks [74].

13.3.6 Methylenetetrahydrofolate Reductase Mutations

Methylenetetrahydrofolate reductase (MTHFR) is an enzyme involved in the folate metabolism pathway. It reduces 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is active in reducing homocysteine to methionine. Defects in the MTHFR gene can lead to elevated levels of

homocysteine, which is known to be prothrombotic. The well-studied MTHFR gene is located on chromosome 1p36.4, and two major mutations are common: C677T and A1298C [80].

The C677T allele (cysteine to thymine at nucleotide 677) is relatively common worldwide, with a carrier frequency ranging from 44 % in Italians to 7 % in sub-Saharan Africans. The activity of the enzyme for which it codes is thermolabile, making it less active at temperatures >37 °C. Homozygotes for the C677T allele can have elevated plasma homocysteine levels if they are folate deficient, but normal homocysteine levels are found in those with normal folate levels.

The second commonly discussed mutation is A1298C, which has a less drastic decrease in enzyme function. However, when present compounded with a C677T mutation, it can produce an elevated homocysteine similar to C677T homozygotes when folate deficient [80].

So while MTHFR gene mutations are relatively common, diet and food fortification with folic acid (Fig. 13.16) make hyperhomocysteinemia rare. Hyperhomocysteinemia has been associated with VTE OR 2.5 (95 % CI 1.8–3.5) [81]. MTHFR mutations in the absence of elevated homocysteine levels do not increase VTE risk in isolation regardless of pregnancy status [64, 82].

A recent large meta-analysis including 11,000 cases and 21,000 controls found those homozygous for MTHFR C677T were not at increased risked for VTE [83].

Though attempts have been made to link MTHFR and hyperhomocysteinemia to adverse pregnancy outcomes, evidence has been contradictory. One meta-analysis found a small association between fetal loss <16 weeks and hyperhomocysteinemia (OR 2.7; 95 % CI, 1.4–5.2) and even smaller with isolated MTHFR (OR 1.4; 95 % CI, 1.0–2.0) [84]. Another group studying homocysteine levels in 5883 woman and their 14,492 pregnancy outcomes found a tendency between elevated levels and stillbirth which did not reach statistical significance (OR 2.03; 95 % CI, 0.98–4.21) [85, 86]. Other more recent publications have failed to show a relationship between MTHFR and first trimester loss, early fetal loss, or stillbirth [20, 36].

Though some report the contrary, hyperhomocysteinemia or MTHFR do not appear to be associated with preeclampsia [87], abruption [88], or fetal growth restriction [42, 89]. If associations do exist, they are likely mild and overcome with folic acid fortification and standard supplementation. Because of the lack of strong evidence between MTFHR and the outcomes discussed above, screening is not recommended. In the often encountered scenario of a patient with a known MTHFR mutation presenting for pregnancy recommendations, folic acid supplementations should be encouraged. No other special care is necessary regarding MTHFR management during pregnancy.

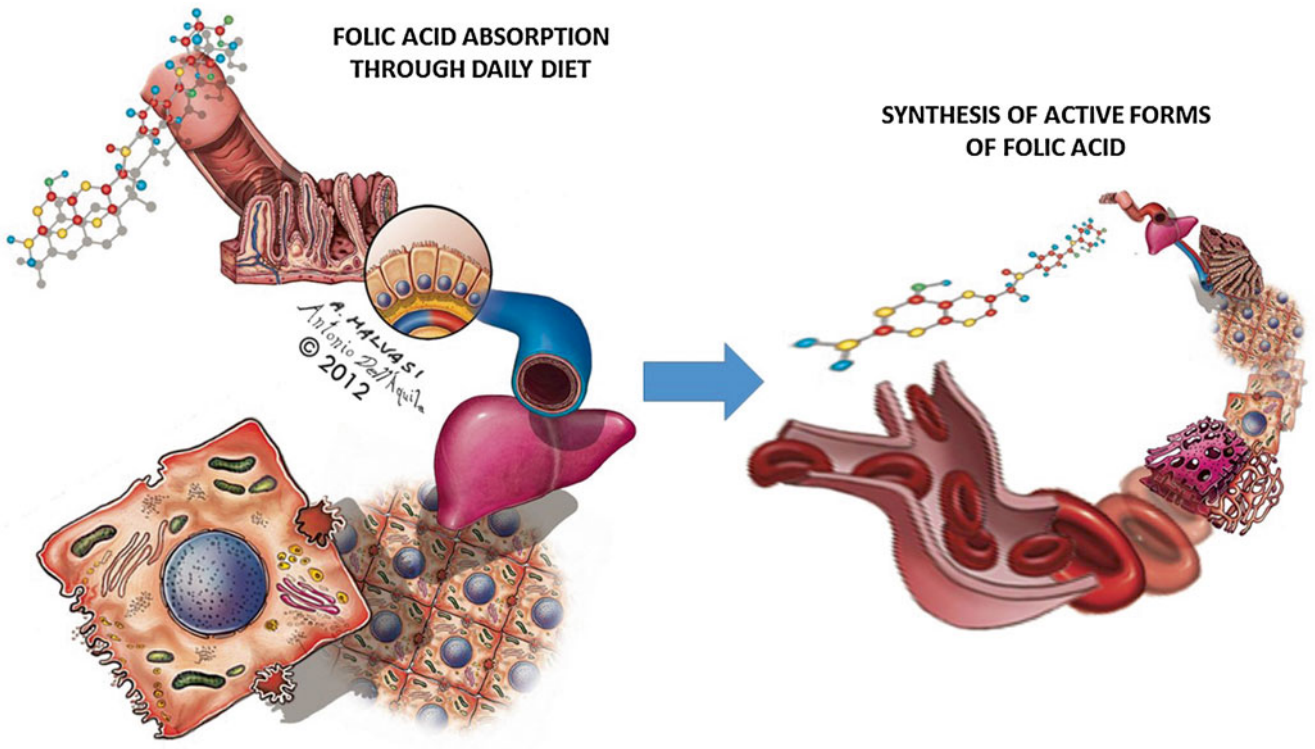

Fig. 13.16 On the *left*, folic acid adsorption by diet and food fortification; on the *right*, synthesis of active forms of folic acid, reducing homocysteinemia and risk of venous thromboembolism (VTE)

13.4 Acquired Thrombophilia

13.4.1 Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is the most common acquired thrombophilia faced by obstetricians. It has been well associated with both VTE and poor obstetrical outcomes, and it is an important disease for obstetrical providers to understand. APS is an autoimmune disorder in which antibodies are produced targeting endothelial cell membrane phospholipids including cardiolipin, β2-glycoprotein 1, and phosphatidylserine. The subsequent clinical consequences of these antibodies are thrombosis, both venous and arterial, and adverse pregnancy outcomes. These clinical outcomes make up a large part of the diagnosis criteria.

Fifty percent of patients affected by APS have an underlying disease making them at risk for developing the autoantibodies, most commonly systemic lupus erythematosus (SLE). APS was first identified in SLE patients with anticardiolipin antibodies that developed a clotting disorder. Lupus and related rheumatic diseases injure an intact endothelial membrane, exposing anionic phospholipids that bind specialized proteins. This process presents new antigens to an often already compromised immune system. Once the autoantibodies to the endothelial proteins are established, they inhibit endogenous anticoagulants (protein C, annexin V, antithrombin) and promote procoagulants (platelets, tissue factor, and compliment activation). The determination of the mechanism of these modulations is still ongoing [90–92].

Diagnosis of APS requires both specific clinical pathology and laboratory criteria as determined by an international consensus group in 2006 (see Table 13.4) [93, 94]. The first requirement is at least one of the listed clinical outcomes including a thrombotic event or poor obstetrical outcome. The second criterion is the presence of at least one of the listed laboratory abnormalities above the normal threshold, measured twice at least 12 weeks apart.

Antiphospholipid antibodies without the present clinical findings are found in 1–5 % of healthy individuals, many of which are transient [93]. This supports the diagnosis requirement of laboratory abnormality persistence for at least 12 weeks. Many of the studies regarding antiphospholipid antibodies and obstetrical outcomes do not use the strict criteria for APS, often lacking confirmatory lab work at least 12 weeks apart. Other studies were done prior to the establishment of the current diagnosis requirements. It is important to take these limitations into considerations when evaluating the available APS evidence.

APS accounts for 14 % of VTE events during pregnancy. The risk of thrombotic event is varied by the specific laboratory abnormalities. Lupus anticoagulant (LAC) reactivity is a sign of downstream alteration of prothrombin activation and evidence of active disease. Antibody presence alone without LAC abnormality is less likely to cause a thrombotic event. This is well demonstrated in a systemic review of 25 studies (non-obstetric) including 4184 patients and 3151 controls. They found that with lupus anticoagulant (LAC), the venous thrombotic OR was 4.1–16.2 and the arterial thrombosis OR

Table 13.4 Classification criteria for the antiphospholipid syndrome

Antiphospholipid syndrome is present if at least one of the clinical criteria and one of the laboratory criteria below are met
Clinical criteria
Vascular thrombosis
One or more episodes of arterial, venous, or small vessel thrombosis in any tissue or organ. Thrombosis must be confirmed by objective validated (unequivocal findings on appropriate imaging studies or histopathology). For histopathological confirmation, thrombosis should be present without evidence of inflammation in the vessel wall
Morbidity pregnancy
One or more unexplained death of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus
One or more premature birth of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe pre-eclampsia defined according to standard definitions, or recognized features of placental insufficiency
Three or more unexplained consecutive spontaneous miscarriages before the 10th week of gestation, with maternal anatomical or hormonal abnormalities excluded and paternal and maternal chromosomal caused excluded
Laboratory criteria
Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis
Medium or high titer (>40 lgG or lgM phospholipid unit (1 units is 1 μg of antibody), or >99th centile) of l gG or lgM anticardiolipin antibody in serum or plasma on two or more occasions, at least 12 weeks apart, measured by standardized enzyme-linked immunosorbent assay (ELISA).
Medium or high titer (>40 lgG or lgG or lgM phospholipid units, or >99th centile) of lgG or lgM anti-β_2 glycoprotein I antibody serum or plasma on two or more occasions, at least 12 weeks apart, measured by standardized ELISA, according to recommended procedures

Chart from Cohen et al. [93]
Original source: Miyakis et al. [94]

was 8.6–10.8. In the same study, anticardiolipin antibodies (ACA) were more associated with arterial events (OR 1–18) than venous events (OR 1–2.5). The data regarding anti-β2-glycoprotein 1 antibodies was less clear [95, 96]. Similar findings from a meta-analysis of nonpregnant APS patients with coexisting SLE showed an increased risk of primary VTE OR 6.32 (95 % CI, 3.7–10.8) and recurrent VTE OR 11.6 (95 % CI, 3.7–36.9) in LAC patients compared to ACA carriers primary VTE OR 2.5 (95 % CI, 1.5–4.1) and recurrent VTE OR 3.91 (95 % CI, 1.1–13.4) [97].

The association with APS and first trimester loss is controversial; nonetheless, three unexplained consecutive spontaneous abortions at ≤10-week gestation are part of the diagnostic criteria for APS [98]. Most available studies regarding APS and early pregnancy loss use 13 weeks as a cutoff and do not discriminate before and after 10 weeks. As discussed previously, the pathology of losses before 10 weeks and the rest of the third trimester weeks are different. Fifty percent of losses in patients confirmed to have APS are after 10 weeks of gestation [99].

In a study looking at recurrent miscarriage patients with APS, fetal cardiac activity was identified in 86 % of eventual pregnancy losses compared to 43 % in patients without APS ($P < 0.01$) [100].

An association between fetal loss after the first trimester and APS has been better described [58, 101, 102]. In a systemic review of 25 case-control studies, LAC was associated with recurrent pregnancy loss after 24 weeks (OR 7.79; 95 % CI, 2.30–26.45). Similar finding was found with moderate to high ACL IgG (OR 4.68; 95 % CI, 2.96–7.40) [103]. In a recent case-controlled study from the Stillbirth Collaborative Research Network (SCRN), 582 stillbirths diagnosed after 20 weeks were controlled with 1547 live births. They found associations with elevated ACL IgG (OR 3.43; 95 % CI 1.79–6.60) and anti-β2-glycoprotein 1 IgG (OR 3.17; 95 % CI 1.30–7.72). This study was limited by a lack of confirmatory laboratory evaluation 12 weeks apart and inconsistent assessment for lupus anticoagulant [104].

Though more often affecting pregnancies in third trimester, APS has been associated with second trimester placental-mediated obstetrical complications including IUGR and preeclampsia. When APS complicates second trimester pregnancies, the outcomes are often poor [98]. A meta-analysis of 28 studies by Abou-Nassar found LA associated with preeclampsia (OR 2.34; 95 % CI, 1.18–4.64) and IUGR 4.65 (95 % CI 1.29–16.71) in case-controlled studies but not significant with cohort studies [105]. A more recent prospective observational cohort study followed 280 women after a single <10-week embryonic demise with and without positive aPL antibodies and evaluated for their subsequent pregnancy. They found an association between LAC and IUGR (OR 10.27; 95 % CI, 2.37–44.52), ACL IgG and preeclampsia (OR 3.09; 95 % CI 1.13–8.48), and anti-β2-glycoprotein 1 IgG and preeclampsia (OR 4.61 95 % CI 1.53–13.88) [106].

A rare variant form of APS named catastrophic antiphospholipid syndrome (CAPS), also known as Asherson's syndrome, is an important consideration. It presents as multiple thrombosis (Fig. 13.17a, b) and multi-organ failure secondary to multiple small-vessel occlusions. Though most often associated with infection and trauma, it can be initiated with pregnancy. Of the 255 cases

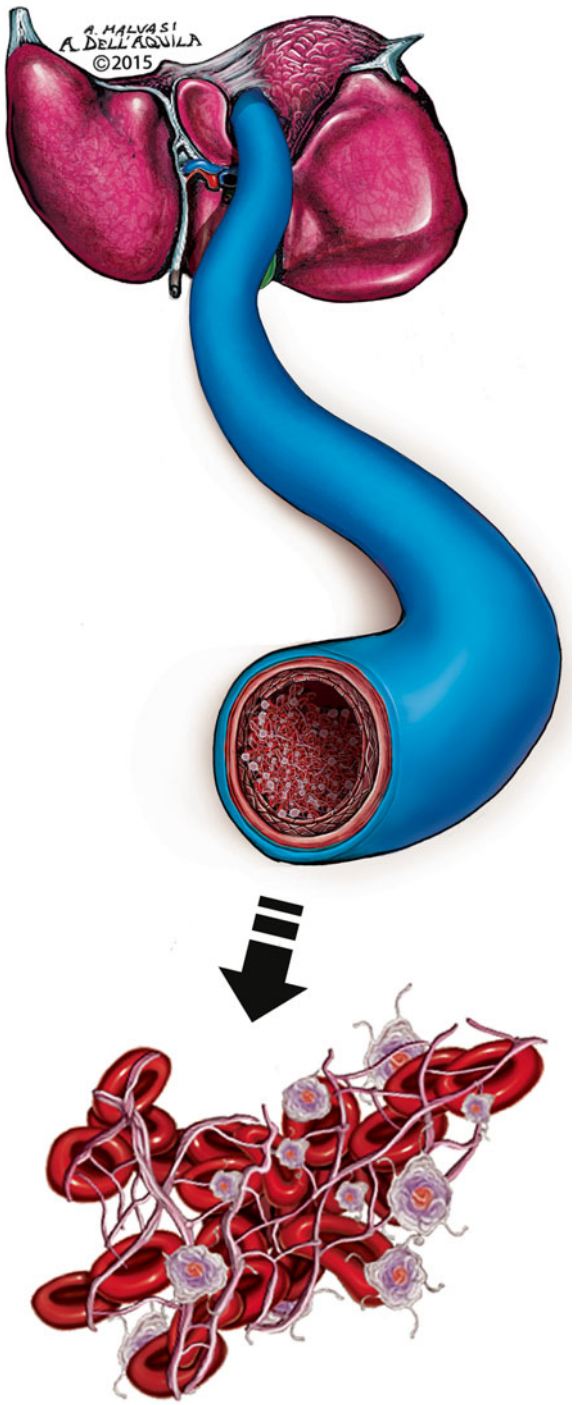

Fig. 13.17 (**a**) Hepatic vein thrombosis; (**b**) retinal thrombosis detected by retinal angiography

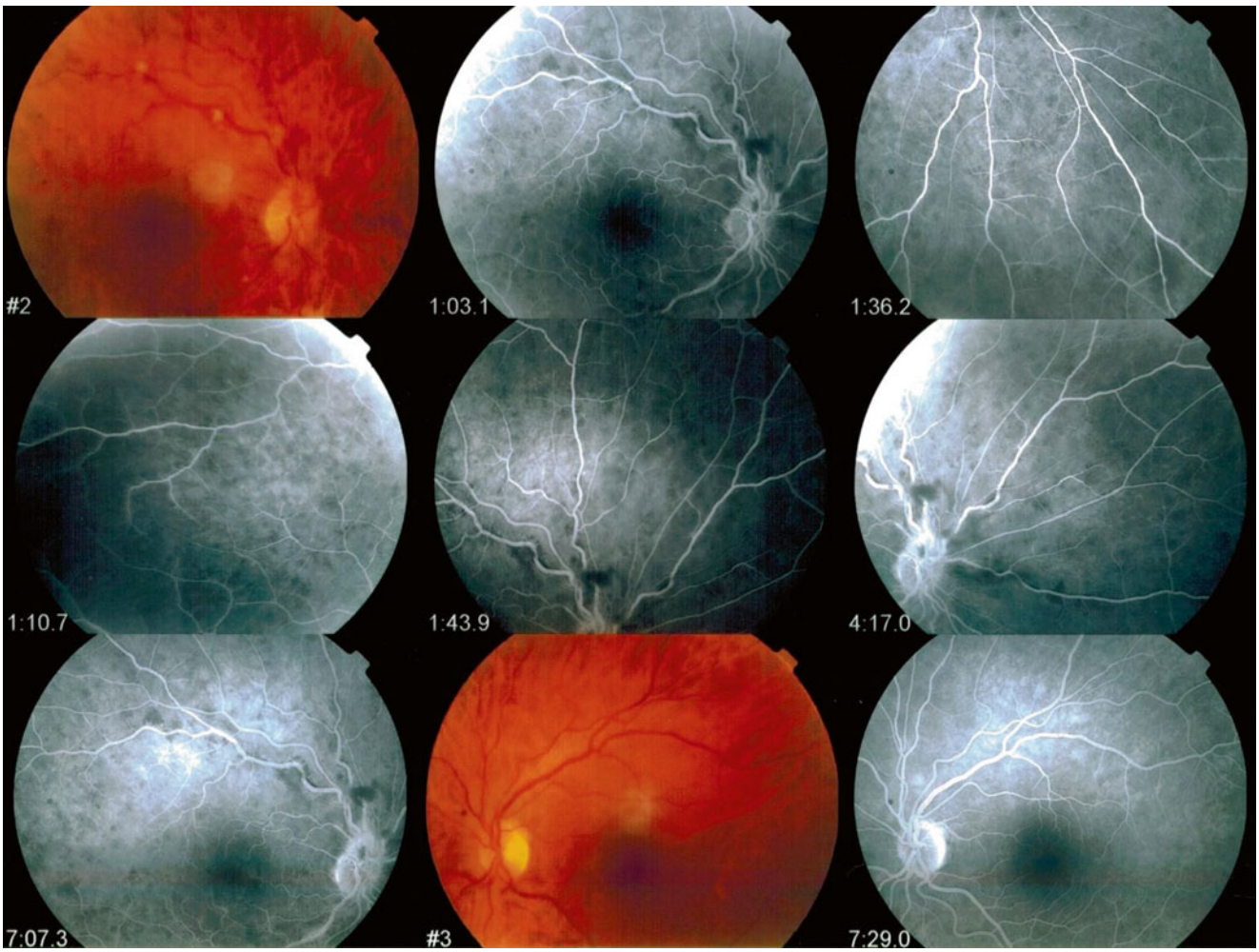

Fig.13.17 (continued)

in one international registry, 15 cases were associated with pregnancy. Of those pregnancy related, 50 % occurred during the antepartum, 43 % occurred during the puerperium, and one occurred 2 days after a D and E for an 18-week fetal demise. The mortality among the cases was 46 % [107]. A more recent study reviewed 13 patients with pregnancy-related CAPS in a French APS referral center. Twelve out of 13 patients held the diagnosis of HELLP syndrome prior to CAPS diagnosis at a mean gestational age of 26.6 weeks. Twelve out of 13 of their patients had postpartum CAPS. No maternal deaths were reported. Treatment combinations varied between patients but included heparin, aspirin, steroids, IVIG, cyclophosphamide, plasma exchange, and dialysis [108].

Another APS consequence to consider is neonatal antiphospholipid syndrome, a product of transplacental transmission of maternal aPL antibodies affecting the newborn. It is a rare entity which can lead to neonatal thrombosis, thrombocytopenia, livedo reticularis, and pericardial effusions [109].

While neonatal APS is rare, the transplacental transfer of maternal aPL antibodies is found in 5–16 % of APS pregnancies, the clinical significance of which is still being investigated [110, 111].

In summary, APS is associated with VTE and poor outcomes in pregnancy. Providers should use the current APS criteria when diagnosing patients. Management and treatment of APS will be described in the next section.

13.5 Thrombophilia Evaluation and Management

Obstetrical providers are often faced with prenatal management decisions in women with known or suspected thrombophilias. The management recommendations have been moving targets over the last three decades as more evidence has been published. In this section, we will discuss which patients should be tested for thrombophilias. We will finish the chapter discussing treatment options.

13.5.1 Thrombophilia Evaluation

Recommendations regarding testing for hereditary thrombophilias have been modified multiple times since their discoveries. Stillbirth, abruption, and recurrent pregnancy loss are among the most difficult conditions obstetrical providers must manage. Optimism for new treatments to potentially prevent such tragic outcomes led to the premature adoption of testing and treatment of hereditary thrombophilias with sparse evidence.

As larger prospective studies and meta-analysis have been published, the hereditary thrombophilias have been an overall disappointing therapy target for adverse outcomes. They may assist providers in the evaluation, management, and prevention of VTE associated with pregnancy.

The correct setting for testing for hereditary thrombophilia is a controversial subject. Most agree testing is appropriate for women with a personal history of VTE not associated with a nonrecurrent risk factor (e.g., surgery, immobilization, bone fracture). Testing is also recommended for patients with first-degree relatives diagnosed with high-risk thrombophilia regardless of the patients' personal VTE history including homozygous FVL and PGM, compound heterozygous FVL and PGM, and antithrombin deficiency. Testing for hereditary thrombophilias is not recommended as part of the evaluation for recurrent pregnancy loss, IUGR, abruption, or preeclampsia.

Thrombophilia evaluation in women experiencing a stillbirth should be limited to those cases where thrombophilia is plausible as an etiology of the stillbirth.

On the other hand, testing for antiphospholipid syndrome is a valuable part of the evaluation in a few obstetrical conditions. The outcomes which make up part of the APS diagnosis criteria are also indications for testing (vascular thrombosis, morphologically normal fetal loss after 10 weeks, three unexplained consecutive pregnancy losses prior to 10 weeks, or a prior delivery prior to 34 weeks for severe preeclampsia or placental insufficiency). See Table 13.4. It is critical that positive testing be repeated after 12 weeks have lapsed to avoid an incorrect diagnoses and unwarranted therapy.

Our screening protocol for inherited and acquired thrombophilia is provided in Table 13.5. The laboratory reliability varies under different clinical scenarios, and some testing should be performed after the anticoagulant course or 6-week postpartum, when using functional assays, not genetic screening tests.

Table 13.5 Screening for thrombophilia

Lupus anticoagulant[a]
Anticardiolipin IgG, IgM
Anti-β2-glycoprotein I IgG, IgM
Factor V Leiden (PCR)
Prothrombin gene mutation 20210A (PCR)
Protein C activity[a, b]
Protein S activity[c,a,b,d]
Antithrombin III activity[a,b]

[a]Not reliable on anticoagulation
[b]Not reliable with active thrombus
[c]Not reliable in pregnancy
[d]Use protein S free antigen in pregnancy

13.5.2 Pregnancy Management

Antenatal care for mothers with hereditary and acquired thrombophilia depends on the specific dysfunction and required therapy. Patients should be screened routinely for preeclampsia including BP, urine protein screening, and symptoms. Fetal growth should be routinely monitored by ultrasound in any patient receiving anticoagulation. In APS patients, we start weekly antenatal testing on patients at 36 weeks and deliver at 39 weeks if no complications warrant delivery earlier.

13.6 Anticoagulants in Pregnancy

Common dosing regimens for anticoagulation in pregnancy are reviewed in Table 13.6 [9, 15, 112, 113].

Unfractionated heparin (UFH) is an injectable or intravenous anticoagulant commonly used in the obstetrical population. UFH binds to antithrombin, inducing a conformational change that enhances antithrombin's ability to deactivate coagulation factors IIa and Xa. It is an attractive anticoagulant because it is not teratogenic, it does not cross the placenta, and it is reversible with protamine sulfate. Its side effects include hemorrhage, bone loss, and heparin-induced thrombocytopenia, all of which are rarely seen with prophylactic dosing. If UFH therapy is started, calcium supplementation and periodic platelet monitored should be started.

Low-molecular-weight heparins (LMWH) are a similar group of injectable anticoagulants also commonly used during pregnancy. They are often the preferred therapy over heparin due to ease of use and improved safety profile (Fig. 13.18). LMWH has a longer half-life, requiring less injections, and rarely causes heparin-induced thrombocytopenia. Because of the longer half-life, patients are typically transitioned to UFH at 36 weeks of gestation or earlier if preterm delivery is expected. This therapy conversion is typically performed to decrease the risk of neuraxial anesthesia and bleeding complications around the time of delivery (Fig. 13.19). However, a recent recommendation suggests continuation of LWMH until delivery [114].

LWMH is not teratogenic and it also does not cross the placenta. Protamine is less effective in reversing LMWH.

Table 13.6 Suggested anticoagulation doses

Prophylactic regimens	**First trimester**	**Second trimester**	**Third trimester**		
Unfractionated heparin (UFH)	5000 units twice daily	7500 units–10,000 units twice daily	10,000 units twice daily		
Low-molecular-weight heparin (LMWH)	**Weight based (initial prenatal weight)**				
	<50 kg	**50–90 kg**	**91–130 kg**	**131–170 kg**	**>170 kg**
Enoxaparin	20 mg daily	40 mg daily	60 mg daily[a]	80 mg daily[a]	0.6 mg/kg daily[a]
Dalteparin	2500 units daily	5000 units daily	7500 units daily[a]	10,000 units daily[a]	75 units/kg daily[a]
Tinzaparin	3500 units daily	4500 units daily	7000 units daily	9000 units daily	75 units/kg daily
Therapeutic regimens	**Initial dose**	**Adjusted target**			
Unfractionated heparin (UFH)	10,000 units twice daily	aPTT 1.5–2.5 6 h after injection			
Low-molecular-weight heparin (LMWH)		Twice daily dosing: antifactor Xa level 0.6–1 units/mL 4–6 h after dose[b] Once daily dosing: antifactor Xa level >1 units/mL 4–6 h after dose[b]			
Enoxaparin	1 mg/kg twice daily				
Dalteparin	200 units/kg daily[a]				
Tinzaparin	175 units/kg daily				
Warfarin (postpartum only)		Target INR 2.0–3.0			

Resources: [9, 15, 112, 113]
[a]May be given in two divided doses
[b]If anti-Xa level monitoring is indicated

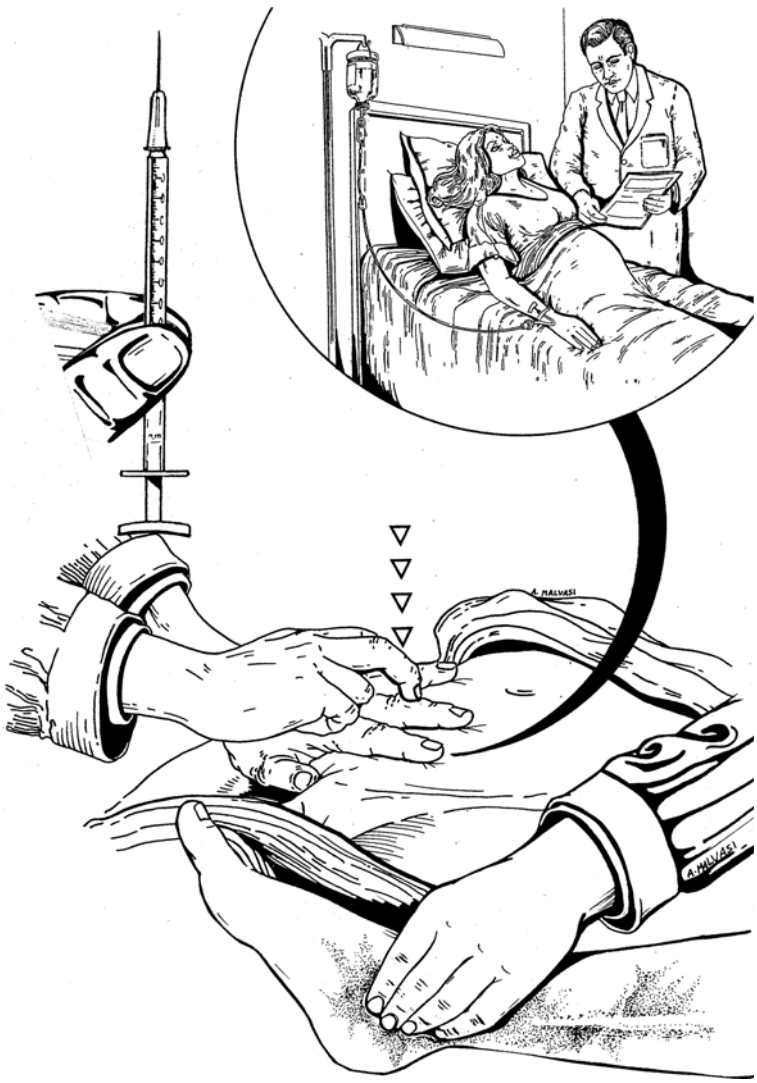

Fig. 13.18 On the *top*, pregnant patient, pregnant woman, pregnant to submit to scheduled cesarean section at risk for thrombophilia; on the *bottom*, patient under antithrombotic prophylaxis by low-molecular-weight heparins (LMWH) in puerperium

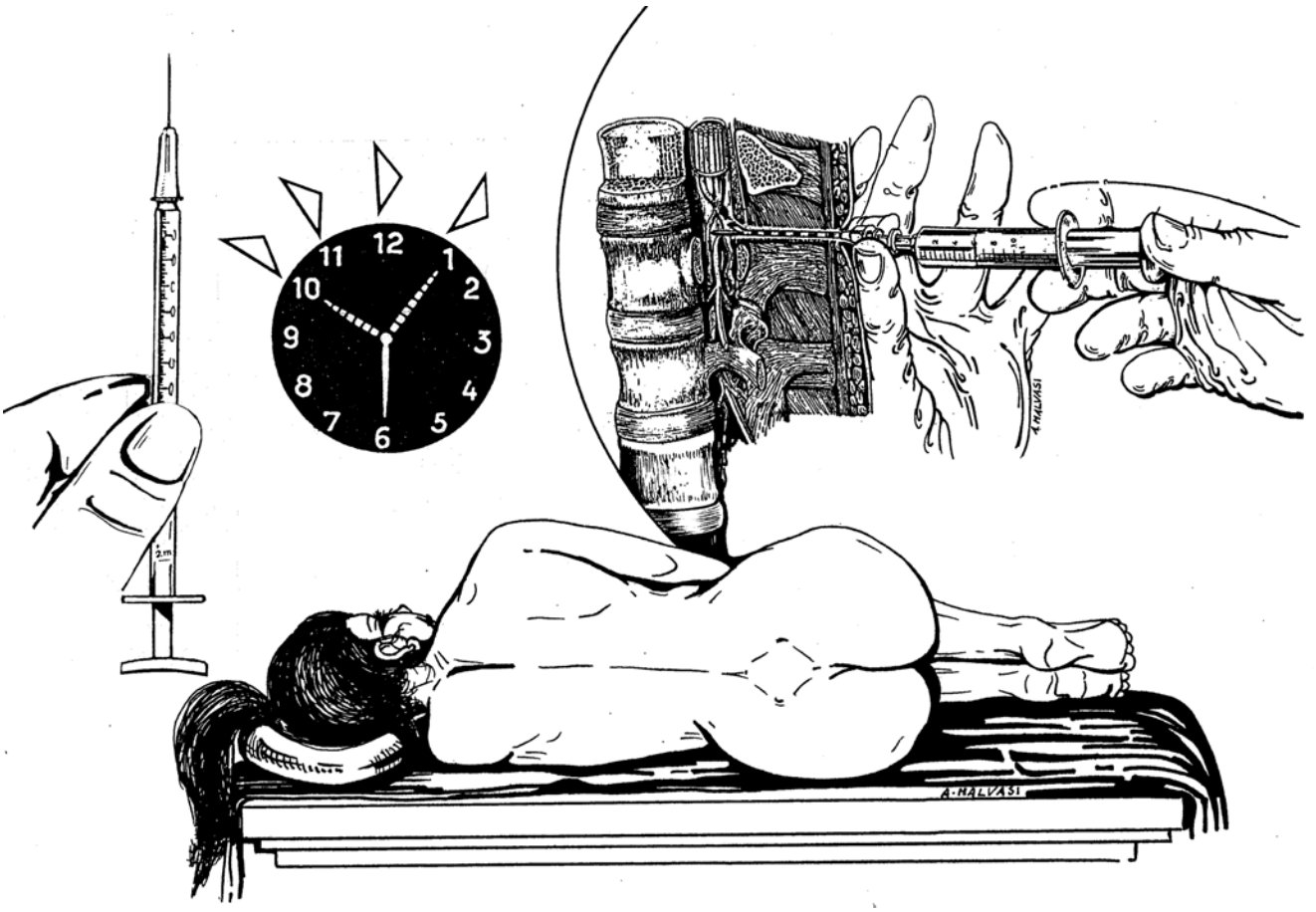

Fig. 13.19 A woman receiving regional anesthesia. See text for details

Fondaparinux is a synthetic pentasaccharide that binds antithrombin, effectively inhibiting factor Xa. Though its use in pregnancy is limited, there are some small patient series published showing its use in safely pregnancy [115]. It is a promising anticoagulant alternative for patients with heparin hypersensitivity or a history of HIT. Fondaparinux can cross the placenta causing a small but measurable amount antifactor Xa activity in umbilical cord blood samples. More studies are needed to thoroughly evaluate its safety in pregnancy, but its use might be appropriate in carefully selected patients [9, 116].

Warfarin in pregnancy is a more complicated matter. Warfarin is an oral vitamin K antagonist commonly used for anticoagulation in the nonpregnant population. For patients who conceive on warfarin, conversion to another anticoagulant (typically LMWH) should occur as early as possible once pregnancy is documented, around 5 weeks of gestation, due to its known teratogenic effects. One option is to convert patients from warfarin anticoagulation to LMWH anticoagulation prior to achieving pregnancy. The warfarin-associated embryopathy occurs with early fetal exposure and includes nasal and midface hypoplasia, CNS abnormalities, and skeletal malformations. Warfarin is also usually avoided later in pregnancy because it crosses the placenta, placing the fetus at risk for bleeding complications. The exceptions are in pregnancies complicated by mechanical heart valves, where it is suggested that warfarin is superior in preventing thrombotic complications.

13.7 Hereditary Thrombophilia Treatment

Recommendations regarding anticoagulation in women with hereditary thrombophilias are provided in Table 13.7 [9, 15, 112, 113].

In patients with risk factors requiring prophylactic antepartum anticoagulation, patients are started on subcutaneous LMWH dosing after a positive pregnancy test is confirmed. The patient is converted to subcutaneous UFH if any complications arise suggesting an early delivery or at 36 weeks of gestation. Because the risk of VTE continues into the postpartum period, we restart LMWH after delivery for 6 more weeks of prophylaxis. Patients and providers must have a high suspicion for any sign of DVT or PE, and

Table 13.7 VTE prophylaxis in pregnancy

Thrombophilia classification	History	Antepartum	Postpartum
High-risk thrombophilia	No VTE	P	P
Factor V Leiden (FVL) homozygous	Family VTE or risk factors	P	P
Prothrombin G20210A mutation (PGM) homozygous	One prior VTE	T	T or K
Antithrombin deficiency	Long-term anticoagulation	T	T or K
Compound heterozygote (FVL/PGM)			
Low-risk thrombophilia	No VTE	Vigilance	Vigilance
FVL heterozygous	Family VTE or risk factors	Vigilance	P
PGM heterozygous	Personal VTE	P	P
Protein C deficiency	Long-term anticoagulation	T	T or K
Protein S deficiency			
Acquired thrombophilia	No VTE	Vigilance	P
Antiphospholipid antibody syndrome	One prior VTE	T	T or K
	On long-term anticoagulation	T	T or K
No thrombophilia	One prior VTE associated with nonrecurrent condition	Vigilance	P
	One prior VTE in the absence of nonrecurring condition, or on OCPs, or in pregnancy	P	P
	Two prior VTE	T	T or K

Resources: [9, 15, 112, 113]

P prophylactic dose LMWH or UFH, *T* therapeutic dose LMWH or UFH, *K* vit K antagonist

patients should be evaluated promptly if any concerns arise. In patients on long-term anticoagulation planning for pregnancy, two options are available and management can be individualized. One option is to transition to therapeutic LMWH dosing prior to attempting conception. This approach eliminates the risk of warfarin-related embryopathy but is associated with longer treatment with LMWH. The second option is to maintain the patient on warfarin and transition to LMWH very early in pregnancy, once pregnancy is documented, ideally around 5-week gestation. This must be done understanding the risk of teratogenicity from 6 to 12 weeks of gestation and the implications of missing the conversion window. LMWH can be transitioned to UFH if early delivery becomes likely or at 36 weeks of gestation. Anticoagulation postpartum can be with LMWH or warfarin depending on patient preference. LMWH, UFH, and Coumadin are all compatible with breast-feeding [9]. Due to the highly thrombogenic nature of hereditary antithrombin deficiency, antithrombin replacement therapy is recommended to prevent thromboembolism in high-risk settings of delivery and surgery during pregnancy [117–119].

13.8 Antiphospholipid Antibody Syndrome Treatment

In patients with APS, treatment during pregnancy depends on which clinical criteria determined their diagnosis. For those with a history of VTE on lifelong anticoagulation, transitioning to therapeutic LMWH dosing prior to conception is appropriate. They can be transitioned back to warfarin postpartum. If the patient has a personal history of a VTE but is not on long-term anticoagulation, therapeutic dosing of LMWH should be started when pregnancy is diagnosed. If they also have APS-defining pregnancy morbidity, low-dose aspirin should be added in the antepartum.

The optimal treatment of APS patients diagnosed by obstetrical clinical criteria and no VTE history has not yet been determined. Most agree that prophylaxis with LMWH during the pregnancy and 6-week postpartum and clinical surveillance are both appropriate options. For those with a history of a fetal loss, low-dose aspirin in addition to prophylactic dosing LMWH has been found to decrease the risk of reoccurrence [99]. Low-dose aspirin alone or with LMWH can be used for patients that meet APS criteria with a history of a preterm delivery before 34 weeks due to preeclampsia, eclampsia, or placental insufficiency without a VTE history. There is no current evidence regarding isolated positive APS laboratory values in the absence of clinical criteria, though experts suggest low-dose aspirin would be a reasonable prophylaxis in the setting of SLE [93].

The management of pregnancy in rare cases of refractory adverse pregnancy outcomes secondary to APS can be particularly challenging. There are reports of successful use of hydroxychloroquine and corticosteroids in addition to the standard therapies for these rare scenarios, but more studies are needed to prove their efficacy [120].

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