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Thrombophilia and Recurrent Pregnancy Loss

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1. Introduction

Recurrent pregnancy loss (RPL) is usually defined as the loss of three or more consecutive pregnancies before 20 weeks of gestation. Within this definition is a large and heterogeneous group of patients with many different causes of miscarriage. RPL is a common clinical problem that occurs in approximately 1 % of reproductive-aged women. However, this frequency increases up to 5% when clinicians define RPL as two or more losses of pregnancy. In addition, epidemiological investigations have demonstrated that the frequency of subsequent pregnancy loss is 24% after two pregnancy losses, 30% after three and 40% after four successive pregnancy losses. In many cases, the etiology is unknown, but several hypotheses have been proposed, including chromosomal and uterine anatomic abnormalities, endometrial infections, endocrine abnormalities, antiphospholipid syndrome, inherited thrombophilias, alloimmune causes, genetic factors, exposure to environmental factors and unexplained causes. Recently, it has become clear that prothrombotic changes are associated with a substantial proportion of these fetal losses. Therefore, the role of thrombophilias in RPL has generated a great deal of interest. This heterogeneous group of disorders results in increased venous and arterial thrombosis. Although some thrombophilic states in RPL may be acquired such as antiphospholipid antibody syndrome (APAS), most are heritable such as hyperhomocysteinemia, activated protein C resistance, deficiencies in proteins C and S, mutations in prothrombin, and mutations in antithrombin III.

Data suggest that women with thrombophilia have an increased risk of pregnancy loss and other serious obstetric complications, including placental abruption, pre-eclampsia, intrauterine growth restriction and intrauterine fetal death. Recent attention has focused on thrombophilic factors that might be associated with pregnancy complications, including early pregnancy loss. Additionally pregnancy complications including idiopathic fetal loss are thought to result from placental under perfusion due to occlusive events, including thrombosis of placental vessels. Thrombosis of placental vessels is multicausal in nature and may involve both acquired and inherited risk factors, leading to RPL. It has been reported that genetic tendencies to thrombosis may also be associated with recurrent pregnancy loss. The three most common genetic markers for thrombophilia which are known to predispose to venous thrombosis are; factor V Leiden (FVL), methylenetetrahydrofolate reductase mutation (MTHFR, C677T) and prothrombin gene mutation (FII, G20210). In this chapter, we discuss the association of thrombophilia and RPL; these include important roles in management and treatment that appear to be required for normal pregnancy.

2. Recurrent pregnancy loss

Recurrent pregnancy loss (RPL) is usually defined as the loss of three or more consecutive pregnancies before 20 weeks of gestation or with fetal weights less than 500 grams. Within this definition is a large and heterogeneous group of patients with many different causes of miscarriage. RPL affects approximately 1 % of couples (1). However, this frequency increases up to 5% when clinicians define RPL as two or more losses of pregnancy (2) In addition, epidemiological investigations have demonstrated that the frequency of subsequent pregnancy loss is 24% after two pregnancy losses, 30% after three and 40% after four successive pregnancy losses (3). Additionally, recurrent risk for RPL may increase up to 50 percent even after six losses (4). Remarkably, the maternal and paternal age may approach the risk of pregnancy loss (Table 1) (5). Maternal age at conception and previous reproductive history are strong and independent risk factors for RPL. The chance of successful pregnancy in a woman aged 40 years or more and a man aged 40 years or more is poor. In many cases, the etiology is unknown, but several hypotheses have been proposed, including chromosomal and uterine anatomic abnormalities, endometrial infections, endocrine abnormalities, antiphospholipid syndrome, inherited thrombophilias, alloimmune causes, genetic factors, exposure to environmental factors and unexplained causes (Table 2) (6). The normal coagulation pathway is pivotal for the pregnancy outcomes (Table 3). Also any kind of disorder in coagulation pathway may cause thrombophilia that may be the reason of plasental insufficiency and PL (7). Recently, it has become clear that prothrombotic changes are associated with a substantial proportion of these fetal losses. Therefore, the role of thrombophilias in RPL has generated a great deal of interest. This heterogeneous group of disorders results in increased venous and arterial thrombosis. Although some thrombophilic states in RPL may be acquired such as antiphospholipid antibody syndrome (APAS), most are heritable such as hyperhomocysteinemia, activated protein C resistance, deficiencies in proteins C and S, mutations in prothrombin, and mutations in antithrombin III.

Maternal Age	Rate of PL (%)	Paternal Age	Rate of RPL (%)
< 20	12.2	< 20	12
20-24	14.3	20-24	11.8
25-29	13.7	25-29	15.7
30-34	15.5	30-34	13.1
35-39	18.7	35-39	15.8
40-44	25.5	40-44	19.5

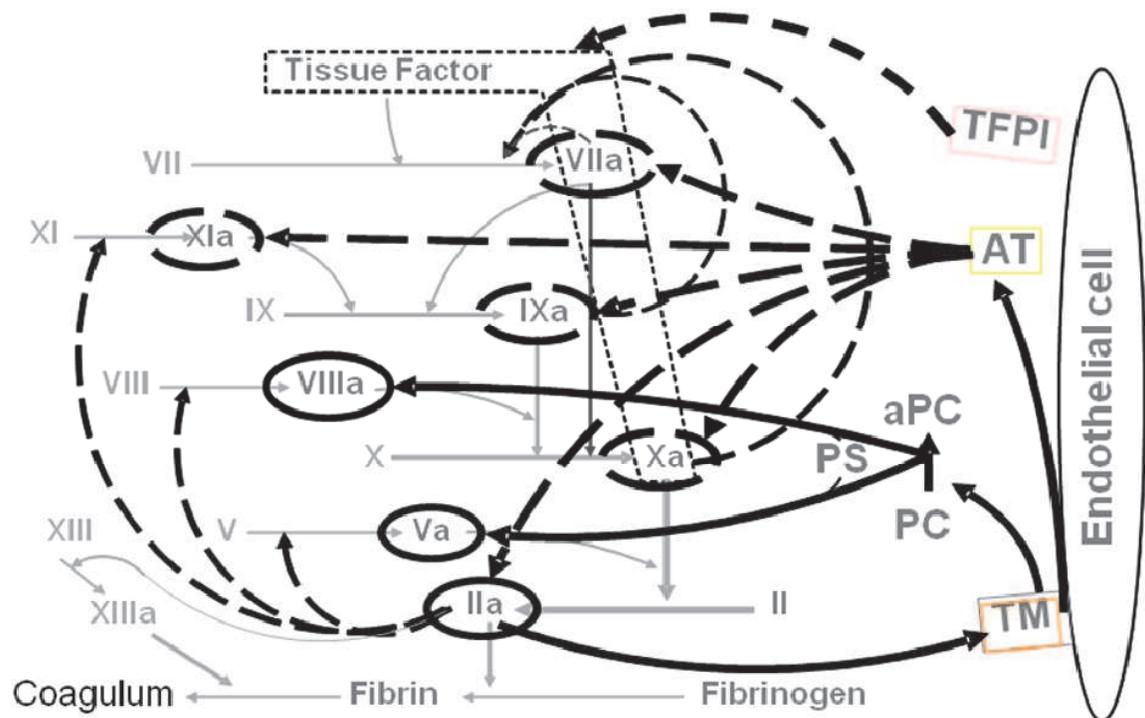
Table 1. The relationship between the spontaneous pregnancy loss and the maternal and paternal age.

Etiology	Proposed Incidence (%)
Genetic Factors	3.5-5
Chromosomal, Single gene defects, Multifactorial	
Anatomic Factors	12-16
Congenital -Incomplete mullerian fusion or septum resorption -Diethylstilbestrol exposure -Uterine artery anomalies -Cervical incompetence Acquired -Cervical incompetence -Synechia -Leiomyomas -Adenomyomas	
Endocrine Factors	17-20
Luteal phase insufficiency, Polycystic ovarian syndrome, Diabetes mellitus, Thyroid disorders, Prolactin disorders	
Infectious Factors	0.5-5
Bacteria, Viruses, Parasites, Zoonotic, Fungal	
Immunologic and Thrombotic Factors	20-50
Cellular mechanisms, Humoral mechanisms, Antiphospholipid Antibody Syndrome, Inherited Thrombophilias such as activated protein C resistance associated with mutations in factor V Leiden, deficiencies in protein C and S, mutations in the gene encoding methylene tetrahydrofolate reductase, mutations in the promoter region of the prothrombin, hyperhomocysteinemia,	

Table 2. Proposed Etiologies for Recurrent Spontaneous Abortion.

2.1 Antiphospholipid antibody syndrome

Pregnancy-specific antigens can elicit humoral responses, and patients with RPL can display altered humoral responses to endometrial and trophoblast antigens (8, 9). Nevertheless, most literature surrounding humoral immune responses and RPL focus on organ-nonspecific autoantibodies associated with APAS. Historically, these IgG and IgM antibodies were thought to be directed against negatively charged phospholipids. Those phospholipids most often implicated in RPL are cardiolipin and phosphatidylserine. Most recently, however, it has been shown that antiphospholipid antibodies often are directed against a protein cofactor, called β_2 glycoprotein 1, that assists antibody association with the phospholipid (10). The association of these antiphospholipid antibodies with thrombotic complications has been termed the antiphospholipid syndrome, and although many of these



aPC: activated protein C

AT: Antithrombin

PC: Protein C

PS: Protein S

TAFI: Trombin activated fibrinolyse inhibitor

TM: Thrombomodulin

Table 3. Coagulation pathway and factors

complications are systemic, some are pregnancy specific—spontaneous abortion, stillbirth, intrauterine growth retardation, and preeclampsia (11).

Diagnosis of this syndrome requires at least one of each clinical and laboratory criterion (12). These are listed below.

Clinical

- One or more confirmed episode of vascular thrombosis of any type
 - Venous
 - Arterial
 - Small vessel
- Pregnancy complications
 - Three or more consecutive spontaneous pregnancy losses at less than 10 weeks of gestation
 - One or more fetal deaths at greater than 10 weeks of gestation
 - One or more preterm births at less than 34 weeks of gestation secondary to severe preeclampsia or placental insufficiency

Laboratory

(Testing must be positive on two or more occasions, 6 weeks or more apart.)

- Positive plasma levels of anticardiolipin antibodies of the IgG or IgM isotype at medium to high levels

- Positive plasma levels of lupus anticoagulant

The presence of antiphospholipid antibodies (anticardiolipin or lupus anticoagulant) during pregnancy is a major risk factor for an adverse pregnancy outcome (13). In large series of couples with recurrent abortion, the incidence of the APAS was between 3% and 5% (14). The presence of anticardiolipin antibodies among patients with known systemic lupus erythematosus portends less favorable pregnancy outcome (15).

A number of mechanisms whereby antiphospholipid antibodies might mediate pregnancy loss have been proposed. Antibodies against phospholipids have been proposed to cause fetal loss because these antibodies inhibit release of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation. In contrast, platelets produce thromboxane A₂ which is a vasoconstrictor that also promotes platelet aggregation. These autoantibodies have also been shown to inhibit protein C activation, which results in coagulation and fibrin C formation. Clinically, these events might lead to hypercoagulability and recurrent thrombosis within the placenta. Women with both a history of early fetal loss and high levels of these antibodies may have a 70 percent miscarriage recurrence (16). In a prospective study of 860 women screened for anticardiolipin antibody in the first trimester reported that 7 percent tested positive (17). Miscarriage developed in 25 percent of the antibody-positive group, compared with only 10 percent of the negative group. In another study, there was no association between early pregnancy loss and the presence of either anticardiolipin antibody or lupus anticoagulant (18).

2.2 Inherited thrombophilias

Thrombophilic disorders have generated considerable interest in the field of RPL. Thrombophilia is an important predisposition to thrombosis due to a procoagulant state. Several blood clotting disorders are grouped under the term of thrombophilia. In table 4, thrombophilic mutations were described. Amongst these, are activated protein C resistance (APCR), protein S deficiency, protein C deficiency, prothrombin mutation, antithrombin III deficiency and hyperhomocysteinaemia (methylenetetrahydrofolate reductase mutation, C677 T MTHFR). Clinical studies suggest that the underlying pathophysiological mechanism is mediated via hypercoagulation, leading to uteroplacental insufficiency with resultant pregnancy loss. The basis for the association between adverse fetal outcomes and heritable thrombophilias has focused on the mechanisms of impaired placental development and function secondary to venous or arterial thrombosis at the maternal-fetal interface. Activation of protein S synergizes with activated protein C, thereby inhibiting the actions of clotting factors V and VIII. Thus, proteins S and C have an anticoagulant effect. Decreased action of these proteins has been postulated to increase the risk for pregnancy loss. Mutation in the gene encoding factor V results in a protein that is resistant to the effects of activated protein C (aPC). The most common of a variety of mutations is at position 506 with a glutamine substitution for arginine, this FV:R506Q mutation is called the factor V Leiden mutation (19, 20, 21). The mutation results in a protein resistant to the effects of aPC. The net result is increased the cleavage of prothrombin to thrombin, which causes excessive coagulability. Inherited decreased or absent antithrombin III activity will lead to increased thrombin formation and clotting. Prothrombin gene mutation is signalled by a defect in clotting factor II at position G20210A. The relative risk for thrombosis in patients with this mutation is two-fold in heterozygotes. Individuals with hyperhomocysteinaemia exhibit a deficiency of folate due to the presence of the methylene tetrahydrofolate reductase mutation (MTHFR C677 T). The thrombotic risk is increased two-

fold in homozygosity; and in the heterozygous state for Antithrombin III deficiency, the risk is 20- to 50-fold. APCR has emerged as the commonest genetic cause of thrombo-embolism. APCR is caused by a point mutation (Factor V Leiden, FVL) in 95% of cases. The risk of thrombosis is increased 5- to 10-fold in heterozygous carriers of FVL, and 100-fold in homozygosity (22, 23) Consistent with general thrombotic risk, carriage of combinations of two or more inherited thrombophilic defects has particularly strong association with adverse pregnancy outcomes (24, 25, 26). Considerable attention has been directed recently toward a possible relationship between thrombophilias and certain pregnancy complications other than venous thrombosis (27). Table 5 summarizes the findings of 79 studies systematically reviewed by Robertson and associates (28).

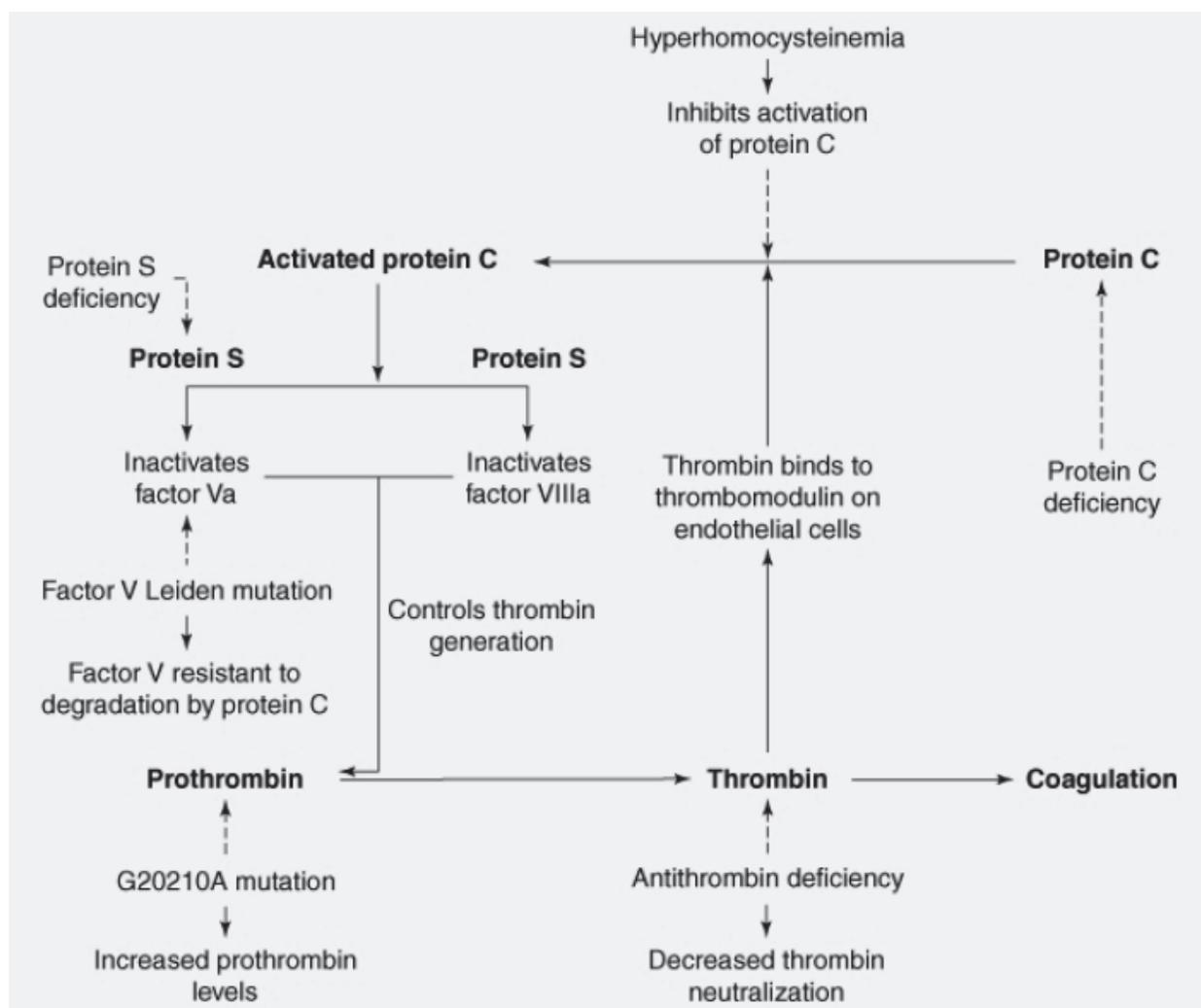


Table 4. Effects of inherited thrombophilia on the coagulation pathway.

Thrombophilia	Early Pregnancy Loss	Stillbirth	Preeclampsia	Placental Abruption	Fetal-Growth Restriction
FVL – homozygous	2.7 (1.3-5.6)	2.0 (0.4-9.7)	1.9 (0.4-7.9)	8.4 (0.4-171.2)	4.6 (0.2-115.7)
FVL – heterozygous	1.7 (1.1-2.6)	2.1 (1.1-3.9)	2.2 (1.5-3.3)	4.7 (1.1-19.6)	2.7 (0.6-12.1)
Prothrombin – heterozygous	2.5 (1.2-5.0)	2.7 (1.3-5.5)	2.5 (1.5-4.2)	7.7 (3.0-19.8)	2.9 (0.6-13.7)
MTHFR – homozygous	1.4 (0.8-2.6)	1.3 (0.9-1.1)	1.4 (1.1-1.8)	1.5 (0.4-5.4)	1.2 (0.8-1.8)
Hyperhomocysteinemia	6.3 (1.4-28.4)	1.0 (0.2-5.6)	3.5 (1.2-10.1)	2.4 (0.4-15.9)	N/A
Antithrombin deficiency	0.9 (0.2-4.5)	7.6 (0.3-196.4)	3.9 (0.2-97.2)	1.1 (0.1-18.1)	N/A
Protein C deficiency	2.3 (0.2-26.4)	3.1 (0.2-38.5)	5.2(0.3-102.2)	5.9 (0.2-151.6)	N/A
Protein S deficiency	3.6 (0.4-35.7)	20.1 (3.7-109.2)	2.8 (0.8-10.6)	2.1 (0.5-9.3)	N/A
Acquired activated protein C resistance	4.0 (1.7-9.8)	0.9 (0.2-3.9)	1.8 (0.7-4.6)	1.3 (0.4-4.4)	N/A
Anticardiolipin antibody	3.4 (1.3-8.7)	3.3 (1.6-6.7)	2.7 (1.7-4.5)	1.4 (0.4-4.8)	6.9 (2.7-17.7)
Lupus anticoagulant	3.0 (1.0-8.6)	2.4 (0.8-7.0)	1.5 (0.8-2.8)	N/A	N/A

Data presented as odds ratios (95-percent confidence intervals). Bolded numbers are statistically significant.

FVL = factor V Leiden, MTHFR = methylenetetrahydrofolate reductase, N/A = data not available.

Table 5. Obstetrical Complications Associated with Some Inherited and Acquired Thrombophilias

2.3 Treatment

The treatment of couples with recurrent miscarriage has traditionally been based on anecdotal evidence, personal bias, and the results of small uncontrolled studies. There are some treatment regimens for APAS that increase live birth rates. The American College of Obstetricians and Gynecologists (12) recommends low-dose aspirin—81 mg orally per day, along with unfractionated heparin—5000 units subcutaneously, twice daily. This therapy, begun when pregnancy is diagnosed, is continued until delivery. Although this treatment

may improve overall pregnancy success, these women remain at high risk for preterm labor, prematurely ruptured membranes, fetal-growth restriction, preeclampsia, and placental abruption (4). The Cochrane review of immune therapy for RPL also addressed IVIg therapy and reported that its use did not alter pregnancy outcomes in patients with otherwise unexplained RPL (29). Although both vaginal and intramuscular progesterone therapy are associated with few minor side effects, their efficacy in the treatment of either unexplained RPL or RPL associated with TH cell dysregulation has never been investigated appropriately. The efficacy and side effects of prednisone plus low-dose aspirin was examined in a recent, large, randomized, placebo-controlled trial treating patients with autoantibodies and RPLs. Pregnancy outcomes for treated and control patients were similar; however, the incidence of maternal diabetes and hypertension and the risk of premature delivery were all increased among those treated with prednisone and aspirin(30). Treatment for thrombophilias remains controversial, but may include heparin and aspirin. Recently, Cochrane Database review concluded that women with recurrent miscarriage and thrombophilia do not benefit from aspirin or heparin therapy (31). Vitamins B6, B12, and folate are important in homocysteine metabolism and hyperhomocysteinemia is linked to RPL. Women with RPL and isolated fasting hyperhomocysteinemia should be offered supplemental folic acid (0.4–1.0 mg/day), vitamin B6 (6 mg/day), and possibly vitamin B12 (0.025 mg/day) (32).

3. References

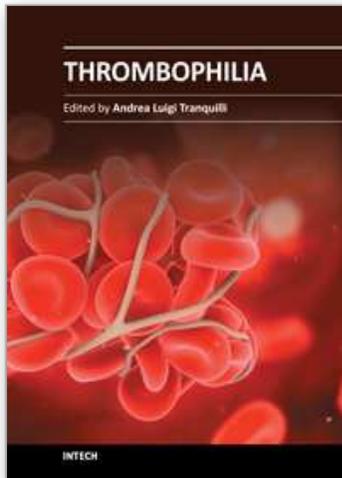
- [1] Stirrat GM. Recurrent miscarriage. *Lancet* 1990; 336: 673-675.
- [2] Hogge, WA. et al. The clinical use of karyotyping spontaneous abortions. *Am. J. Obstet. Gynecol.* 2003; 189, 397-400.
- [3] Regan, L. et al. Influence of past reproductive performance on risk of spontaneous abortion. *BMJ* 1989; 299, 541-545.
- [4] Poland B, et al. Reproductive counseling in patients who have had a spontaneous abortion. *Am J Obstet Gynecol* 1977; 127: 685.
- [5] Knudsen UB, et al. Prognosis of a new pregnancy following previous spontaneous abortions. *Eur J Obstet Gynecol Reprod Biol.* 1991; 39: 31-36.
- [6] Rai, R. and Regan, L. Recurrent miscarriage. *Lancet* 2006; 368, 601-611.
- [7] Reznikoff-Etievan MF, et al. Factor V Leiden and G20210A prothrombin mutations are risk factors for very early recurrent miscarriage. *BJOG*, 2001; 108(12):1251-1254.
- [8] Hill JA, et al. T helper 1-type immunity to trophoblast antigens in women with recurrent spontaneous abortion. *JAMA* 1995;273:1933-1936.
- [9] Eblen AC, et al. Alterations in humoral immune responses associated with recurrent pregnancy loss. *Fertil Steril* 2000;73:305-313.
- [10] McNeil HP, et al. Anti-phospholipid antibodies are directed against a complex antigen that includes a lipid-binding inhibitor of coagulation: beta 2-glycoprotein I (apolipoprotein H). *Proc Natl Acad Sci U S A* 1990;87:4120-4124.
- [11] Harris EN. Syndrome of the black swan. *Br J Rheumatol* 1986;26:324-326.
- [12] American College of Obstetricians and Gynecologists: Antiphospholipid syndrome. Practice Bulletin No. 68, November, 2005.

- [13] Out HJ, et al. A prospective, controlled multicenter study of the obstetric risks of pregnant women with antiphospholipid antibodies. *Br J Obstet Gynaecol* 1992;167:26-32.
- [14] Hill JA. Sporadic and recurrent spontaneous abortion. *Curr Probl Obstet Gynecol Fertil* 1994;17:114-162.
- [15] Kutteh WH, Lyda EC, Abraham SM, Wacholtz MC. Association of anticardiolipin antibodies and pregnancy loss in women with systemic lupus erythematosus. *Fertil Steril* 1993;60:449-455.
- [16] Dudley DJ, et al. Antiphospholipid syndrome: A model for autoimmune pregnancy loss. *Infert Reprod Med Clin North Am* 1991; 2:149.
- [17] Yasuda M, et al: Prospective studies of the association between anticardiolipin antibody and outcome of pregnancy. *Obstet Gynecol* 1995; 86: 555.
- [18] Simpson JL, et al: Lack of association between antiphospholipid antibodies and first-trimester spontaneous abortion: prospective study of pregnancies detected within 21 days of conception. *Fertil Steril* 1998; 69:814.
- [19] Cotter AM, et al. Elevated plasma homocysteine in early pregnancy: A risk factor for the development of severe preeclampsia. *Am J Obstet Gynecol*, 2001; 185:781-5.
- [20] Aubard Y, et al. Hyperhomocysteinemia and pregnancy review of our present understanding and therapeutic implications. *Eur J Obstet Gynecol*, 2000; 93: 157-65.
- [21] Jeanine F. et al. Prenatal Screening for Thrombophilias: Indications and Controversies *Clin Lab Med* 2010; 30: 747-760.
- [22] Kovalevsky G, et al. Evaluation of the association between hereditary thrombophilias and recurrent pregnancy loss: a meta-analysis. *Arch Intern Med* 2004; 164: 558 - 63.
- [23] Rey E, et al. Thrombophilic disorders and fetal loss: a meta-analysis. *Lancet* 2003; 361: 901 - 08.
- [24] Lockwood CJ. Inherited thrombophilias in pregnant patients: detection and treatment paradigm. *Obstet Gynecol* 2002;99:333-341.
- [25] Lockwood CJ. Inherited thrombophilias in pregnant patients. *Prenat Neonat Med* 2001;6:3-14.
- [26] Preston FE, et al. Increased fetal loss in women with heritable thrombophilia. *Lancet* 1996;348:913-916.
- [27] De Santis M, et al: Inherited and acquired thrombophilia: Pregnancy outcome and treatment. *Reprod Toxicol* 2006; 22: 227.
- [28] Robertson L, et al: Thrombophilia in pregnancy: A systematic review. *Br J Haematol* 2005; 132:171.
- [29] Scott JR. Immunotherapy for recurrent miscarriage. *Cochrane Database Syst Rev* 2003; (1):CD000112.
- [30] Laskin CA, et al. Prednisone and aspirin in women with autoantibodies unexplained recurrent fetal loss. *N Engl J Med* 1997;337:148-153.
- [31] Kaandorp S, et al: Aspiring or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome. *Cochrane Database Syst Rev* (1):CD004734, 2009.

- [32] de la Calle M, et al. Homocysteine, folic acid and B group vitamins in obstetrics and gynaecology. *Eur J Obstet Gynecol Reprod Biol* 2003;107:125–134.

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Thrombophilia(s) is a condition of increased tendency to form blood clots. This condition may be inherited or acquired, and this is why the term is often used in plural. People who have thrombophilia are at greater risk of having thromboembolic complications, such as deep venous thrombosis, pulmonary embolism or cardiovascular complications, like stroke or myocardial infarction, nevertheless those complications are rare and it is possible that those individuals will never encounter clotting problems in their whole life. The enhanced blood coagulability is exacerbated under conditions of prolonged immobility, surgical interventions and most of all during pregnancy and puerperium, and the use of estrogen contraception. This is the reason why many obstetricians-gynecologists became involved in this field aside the hematologists: women are more frequently at risk. The availability of new lab tests for hereditary thrombophilia(s) has opened a new era with reflections on epidemiology, primary healthcare, prevention and prophylaxis, so that thrombophilia is one of the hottest topics in contemporary medicine.

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