Review Article

The Putative Role of Factor V Leiden and Prothrombin Mutations in Pregnancy Complications

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Abstract

Context: Thrombophilia is an inherited or acquired predisposition in developing thrombosis. The two common thrombophilia polymorphisms are factor V Leiden (FVL) and factor II/ prothrombin G20210A (PT) gene mutations which can contribute to negative pregnancy outcomes such as miscarriage, in-vitro fertilization (IVF) failure, preeclampsia, intrauterine growth restriction (IUGR), placental abruption, stillbirth, and pregnancy-associated venous thromboembolism. This review study sought to describe the effects of FVL and PT mutations on pregnancy complications.

Evidence Acquisition: In this review study, a comprehensive search was performed on Iranian and international databases including MEDLINE, PubMed, Scopus, Web of Sciences, Proquest and Google Scholar for articles published during 1996-2018. Out of 220 reviewed articles, 80 papers were ultimately selected.

Results: According to these 80 selected papers, the possible relations of PT and FVL with recurrent pregnancy loss (RPL) have been widely evaluated. Several studies indicated higher risk of recurrent early miscarriages, implantation failure and fetal loss after IVF among women with FVL and PT mutations.

Conclusion: Observational studies have suggested the benefits of screening patients for thrombophilic polymorphisms in identification of women with higher risk of developing thromboembolic events and other related pregnancy complications. Based on such screening programs, prophylactic therapy can be limited to a selected group of women who truly need it.

Keywords: Thrombophilia**,** Factor V Leiden, Hyperprothrombinemia, Mutation, Pregnancy Complications.

1. Context

Thrombophilia is an inherited or acquired predisposition in developing either venous or arterial thrombosis. Thrombosis is a common cause of death in the U.S. [1].The combined prevalence of different types of thrombophilia in the general population exceeds one in ten. The most commonly reported type of acquired thrombophilia is the antiphospholipid syndrome (APS). The diagnostic criteria for this condition are presence of antiphospholipid antibodies consisting anti-cardiolipin antibodies (aCL) and/or lupus anticoagulant (LA); and/or anti-β-2-glycoprotein I antibodies (aβ2-GPI) for two or more separate occasions, at least 12 weeks apart [2]. Inherited risk factors of thrombophilia include protein C, protein S, and antithrombin (AT III) deficiency,

Factor V Leiden (FVL), and prothrombin G20210A (PT) gene mutations [3, 4]. FVL and PT may cause miscarriage, preeclampsia, intrauterine growth restriction[1], placental abruption, and stillbirth in pregnant women [5, 6]. Thrombophilic disorders are in fact believed to exacerbate the state of hypercoagulability in pregnancy and lead to the formation of microthrombin and placental insufficiency [7].

Thrombophilia is a complex disorder with various risk factors. The most commonly reported form of acquired thrombophilia is the APS. FVL, i.e. the underlying cause of activated protein C resistance and PT are considered as two major genetic risk factors for the condition. Despite their significance, these two factors generally remain underdiagnosed due to the absence of symptoms and low risk of thrombosis in their carriers. Nevertheless, the presence of the mentioned factors may become clinically evident following exposure to other predisposing factors including pregnancy, oral contraceptives, hormone replacement therapy, and vessel wall disorders which encourage stasis and boost the risk of life-threatening thrombotic events [6]. Extensive research over the past 50 years has confirmed significant relationships between thrombophilia (both inherited and acquired) and elevated risk of serious obstetric complications such as miscarriage, stillbirth, severe preeclampsia, placental abruption, IUGR, and other adverse obstetric outcomes. Although the exact involved mechanisms are unknown, inadequate maternal-fetal circulation and decreased placental perfusion caused by abnormal placental vasculature and disturbances in hemostasis might be responsible for the mentioned complications [8].Since higher frequency of FVL, PT, and methylene tetrahydrofolate reductase (MTHFR) C677T mutations has been documented in women with such complications[9]. Based on the results of previous studies, the rates of preterm births have increased over time. Furthermore, thrombophilia may have negative impacts on pregnancy outcomes, especially preterm birth and the consequent neonatal and childhood injuries and deaths, and exert a heavy economic burden on society and families.

Hence, the present study aimed to estimate the prevalence of FVL and PT in women with pregnancy complications such as: preterm birth, recurrent pregnancy loss (RPL), and other pregnancy complications. It will thus provide the chance to determine the pathogenesis of this condition.

2. Evidence Acquisition

In this review study, a comprehensive search was performed on several international databases including PubMed, EMBASE, ISI Web of Science, Scopus, and Google Scholar along with Iranian databases such IranMedex, Magiran, and Scientific Information Database. Boolean operators (OR, AND) were applied to produce combinations of appropriate keywords (i.e. factor V Leiden, prothrombin G20210A, factor II, mutation, pregnancy complications). Using advanced search options of each search engine, articles were retrieved if they were published during 1996-2018 and had one of the first four keywords in either their title or their abstract. The only inclusion criterion was dealing explicitly with FVL and PT in women with pregnancy complications. Hence papers in English and Persian languages were surveyed if they reported effect of FVL and PT mutations on pregnancy complications and studies without quantitative outcome data were excluded. The reference list of the retrieved papers was inspected and searched over other search engines. The algorithm of the including studies in our review is shown in Figure 1 (Figure 1).

[1] IUGR

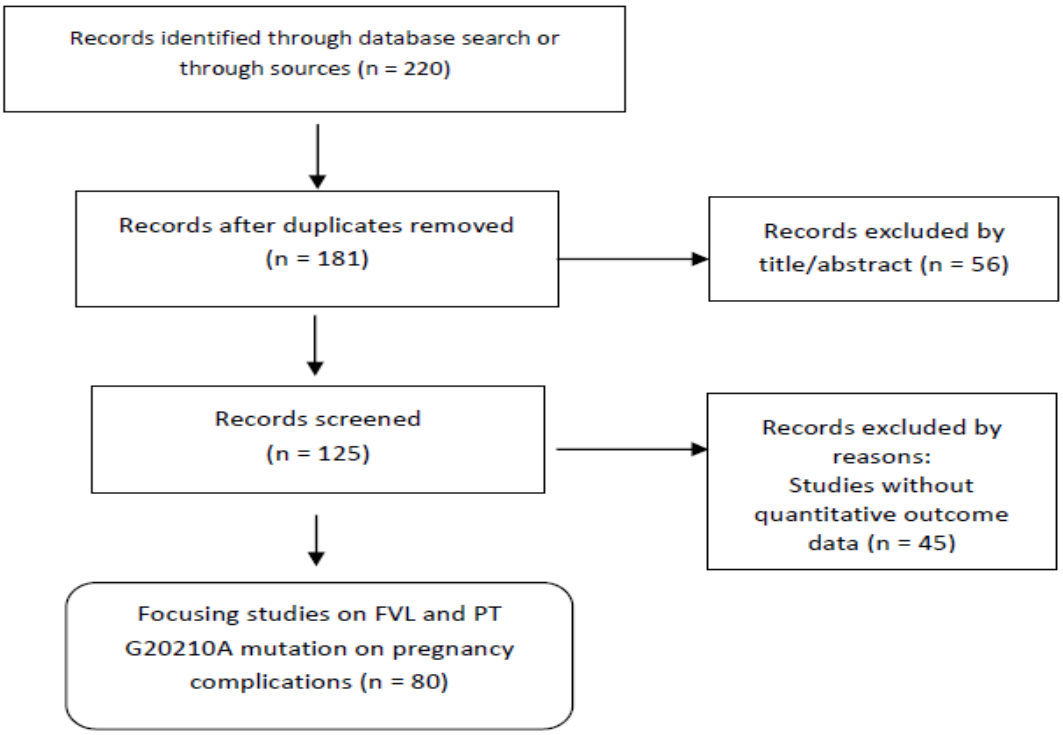

Figure 1. The algorithm of including studies in the review

3. Results

While the initial search yielded 220 articles, the number was reduced to 80 after eliminating duplicate or irrelevant papers (based on the number of citations). The role of Factor V Leiden and Prothrombin mutations in pregnancy complications are described in this section:

1. Factor V Leiden (FVL)

FVL is an inherited autosomal dominant trait [10]. It involves a guanine to adenine substitution at nucleotide position 1691 in the factor V gene. The result would be a defective factor V molecule, called FVL, which is intrinsically resistant to cleavage by activated protein C (APC) [6]. Therefore, the disorder is characterized by a poor functional resistance of coagulation factor V to APC. FVL is the most frequent hereditary cause of venous thrombosis and is in fact 10 times more frequent than any other anticoagulant protein deficiency. The condition accounts for about 20%-25% of all thrombotic events and 40%-45% of cases of hereditary thrombophilia [11]. Zygosity can also have significant effects on the risk of venous thrombosis, i.e. heterozygosity and homozygosity, as FVL increases the risk of the condition by three to ten- and eighty to one-hundred-folds, respectively. FVL is believed to have emerged about 21000-34000 years ago when Caucasians separated from Asians [12]. The prevalence of FVL in thrombophilic patients has been reported as about 3.3% in Iran and 2.5% in Saudi Arabia. However, the exact prevalence of the mutation in the general population is still not clear [13]. In a systematic review of 14 studies, it was observed that the effect of FVL mutation on spontaneous abortions and IVF failures was confirmed by all of the studies, while there was no observed relationship between FVL mutation with IUGR, preeclampsia, placental abruption or small for gestational age newborns (SGA)[14].

2. Prothrombin G20210A

Prothrombin (factor II) is the precursor of thrombin. PT involves a guanine to

adenine transition at position 20210 of the prothrombin gene. It is an autosomal dominant trait and the second most prevalent genetic cause of thrombophilia [15]. It increases plasma levels of prothrombin and the risk of venous or arterial thrombosis, thromboembolic disease and severe subsequent IUGR, preeclampsia, placental abruption, and preterm labor[16].

The frequency of PT varies in different societies. It is more prevalent in the Middle East, but is rare in other Asian countries such as Japan[17]. The prevalence of PT was reported as 0.02% and 1%-4% in black and white patients, respectively. Moreover, the prevalence of FVL and PT among healthy Iranians was estimated at 2.9% and 1.6%, respectively[18]. Gawish introduced PT and FVL as crucial risk factors for neonatal stroke in Saudi newborns and recommended their monitoring as a part of routine tests for Saudi fetuses and pregnant women[6].The risk of thrombosis among heterozygous carriers have a five to ten-fold increased risk of FVL and homozygotes have a fifty to one-hundred-fold increased risk. The risk of thrombosis is also three to ten times higher in individuals heterozygous for PT [19]. Inherited risk factors, e.g. genetic defects such as PT G20210A and external factors such as oral contraceptives, pregnancy, surgical procedures, prolonged immobilization, aging, HRT, malignancies, obesity, prolonged catheterization, and inflammatory conditions seem to elevate the risk of thrombosis. These factors are often necessary for symptomatic carriers of FVL [20, 21]. While numerous studies have tried to shed light on the association between different polymorphisms and pregnancy complications including miscarriage, preeclampsia, and IUGR, limited research has focused on thrombophilia [22]. Kocher et al. established a relation between PT and preterm delivery among white women [10]. Uvuzetal., however, refuted a significant association between preterm delivery and thrombophilic gene polymorphisms [22].

3. Pregnancy Complications

3.1 Recurrent Pregnancy Loss (RPL)

RPL is a prevalent disturbing health issue. While it is classically defined as the loss of three or more consecutive pregnancies before the fetus has reached viability (affecting 1-2% of women), the term has been recently redefined to include two or more losses (thus present in over 5% of reproductive women). Although the cause of up to 50% of these cases remain unexplained [23-25], thrombophilia has been suggested as a probable cause of RPL[3]. Several studies have shown higher risk of recurrent early miscarriages, second-trimester abortion, or other complications in women with inherited thrombophilia. Thrombophilia is in fact responsible for up to 40% of RPL cases and the second cause of the condition (after chromosomal abnormalities), particularly in the first four months of pregnancy. During the past two decades, research has confirmed a significant relationship between RPL and antiphospholipid syndrome (APS) which is an acquired thrombophilic state[25]. According to recent studies, certain types of inherited thrombophilia, such as FVL and PT are more common in women with unexplained RPL[26]. Among all thrombophilic mutations, the relations of PT and FVL with the incidence of RPL have been more widely studied [27].

In 2000, a Greek study recruited 80 women with RPL and 100 healthy controls to identify any possible associations between RPL and FVL, PT, and MTHFR C677T mutations. FVL and PT was found in about 25% of women with a history of fetal loss (regardless of the presence of additional pathologies) and concluded that these two mutations (but not MTHFR C677Thomozygosity) could be risk factors for RPL. Furthermore, the prevalence of the mentioned mutations was high in women with second trimester pregnancy loss (40%) and primary fetal loss (33%). Both FVL and PT served as dramatic predisposing factors when primary RPL was involved

[11].Mohamed et al. reported significantly higher prevalence of spontaneous miscarriages in women with FVL, PT, and MTHFR gene mutations compared to the normal population [28].

While FVL is rare in Asians and Africans, it is more common in European populations (5%-9% of healthy individuals) [12, 29]. A meta-analysis suggested that race significantly affects the association between FVL and RPL [30]. Another nested case-control study on Caucasian women from a delimited Mediterranean area indicated FVL and PT to have significant relations with the risk of spontaneous abortion occurring from the 10th week of the first intended pregnancy on. However, no clear conclusions could be reached about non-Caucasian women in whom the frequency of thrombophilic mutations was substantially low [31]. In contrast, some researchers did not accept FVL as a risk factor for RPL. For instance, according to an Iranian case-control study, FVL and PT were not frequently found in women with RPL [32]. Another retrospective case-control study found no significant differences in the allele frequencies and genotype distribution for FVL and PT gene polymorphisms between patients with RPL and controls. It also refuted any significant relationships between the mentioned factors and infertility (except an increased frequency of association between the two gene polymorphism AA G1691A/GAG20210A and GA G1691A/GG G20210A compared to the control group) [33]. Meanwhile, early abortion cases were more frequent among women with heterozygous PT G20210A than in those with heterozygous FVL (28% vs. 16%). Although similar findings were reported in cases with either late or combined late and early miscarriage, the difference was not statistically significant. The same study showed a very high risk of pregnancy loss among patients carrying both genotypes, i.e. the mutant allele of FVL and prothrombin. The researchers hence concluded that RPL among Saudi women was strongly associated with thrombophilic mutations related to both FVL and PT[6].

Goodman et al. reported significantly higher frequency of FVL and PT gene mutations among American women with a history of RPL[34]. In contrast, another study on a similar population of American women did not detect any differences in the frequency of definite FVL or PT gene mutations. Nevertheless, significantly higher prevalence of homozygous mutations and total gene mutations was observed in patients with RPL than in controls [35]. Some studies have rejected any significant associations between the two frequent thrombophilic mutations (FVL and PT) and RPL. These studies, however, have documented higher APCR (but not significantly) in subjects with RPL than in healthy women. Meanwhile, the higher prevalence of vascular complications in women with FVL seems reasonable since APC sensitivity ratios may be reduced during a normal pregnancy even in women with normal factor V genotype[27]. Previous meta-analyses introduced FVL and PT as the only thrombophilic mutations involved in RPL[36, 37]. Di Micco et al. suggested inherited thrombophilia, especially the PT variant, as a risk factor for RPL[38]. However, the absence of any relationships between RPL and the mentioned prothrombotic states has been discussed in some other studies[39, 40].

As discussed earlier, the frequency of thrombophilic mutations varies in different ethnic groups and societies. Therefore, researchers from different parts of the world have tried to shed light on the relationships between inherited thrombophilia and RPL in different populations. A case control study in Colombia, i.e. a tri-ethnic population comprising about 70% Caucasians, 15% Amerindians, and 15% Africans[41, 42] found no associations between RPL and hereditary thrombophilia by either single nucleotide polymorphism

(SNP) genotypes, such as FVL, PT, and MTHFR C677T, or functional phenotypes, e.g. APCR and protein C and AT III deficiency. Considering the negligible frequency of thrombophilia associated SNPs in not only the controls, but also the patients, the researchers concluded that testing for hereditary thrombophilia was unnecessary in the initial evaluation of patients with RPL [43]. Similarly, FVL and PT were rarely detected in Malay women with RPL [44].On the other hand, Brazilian FVL carriers had a 4.9 times higher risk of RPL than their non-carrier counterparts. Likewise, the risk of RPL was five times higher in Uruguayan women heterozygous for FVL than in non-carriers[45]. Two prospective cohort studies have also reported the absence of any associations between hereditary thrombophilia and RPL [43]. Kazerooni et al. detected elevated levels of thrombophilic parameters in patients with a combination of polycystic ovary syndrome (PCOS) and RPL. They also found FVL mutations to be more frequent in these individuals than in PCOS patients without RPL. They hence highlighted associations between increased RPL rates and hyperhomocysteinemia, APCR, and FVL in patients with PCOS [46].A case-control study in Portugal negated any relations between either FVL or PT and RPL during the first 10 weeks of gestation. It thus concluded that testing for these mutations in the initial screening of women with RPL and negative personal thromboembolic history was not cost-effective [25]. Similarly, in a controlled study, Dilley et al. found the frequency of FVL and PT to be similar in 60 women with RPL and 92 controls without a history of miscarriage [47]. Two prospective multicenter studies on over 4,000 pregnant women during their first trimester did not show an increased miscarriage rate in FVL and PT carriers [48]. A European prospective research on women with a history of miscarriage reported no significant differences in pregnancy outcomes between carriers and non-carriers of FVL and PT[49].

Controlled studies on European Caucasian women with a history of unexplained RPL could not establish a relationship between RPL in the first trimester and either FVL or PT [50, 51]. Meanwhile, previous meta-analyses have suggested FVL-related losses to be more common after the 14th week than in the first trimester [36, 52]. In a study on Caucasian women with unexplained RPL, Ivanov et al. found FVL to have a similar prevalence in subjects with embryonic losses and controls (9.6% vs. 7.0%). In contrast, FVL was more prevalent (18.6%) in women who experienced pregnancy losses during the10th-14th weeks of gestation[53].

Considering the controversial results of previous studies, clinicians prefer to incorporate FVL and PT tests in RPL investigation protocols[52, 54]. However, while evidence about the relations between these two mutations and RPL stem from case-control studies [55, 56], such studies might have been biased by various factors [48]. Nonetheless, most studies have reported similar findings about the association between these two mutations and RPL. Moreover, the associations between the mentioned polymorphisms and RPL seem to be weaker in cases of first trimester loss compared to second trimester RPL [30]. Apparently, the exact effect of hereditary thrombophilia on RPL is still a controversial issue. Recent research has in fact led to greater uncertainty about the existence of an association between the mentioned conditions[57, 58]. One small study reported the frequency of PT in subjects with RPL and controls as 9% and 2%, respectively[11]. Another case-control study consisting of 102 patients with two or more consecutive abortions and 128 women without miscarriage calculated the rates among women with RPL and controls as 6.7% vs. 0.8% respectively [59]. Due to lack of adequate evidence, recent guidelines on the assessment and management of

women with RPL, published by the Royal College of Obstetricians and Gynecologist and the American College of Obstetricians and Gynecologists do not assert the need for routine thrombophilia screening and anticoagulant therapy [60].

3.2 Placental-Mediated Pregnancy Complications

Pregnancy loss, preeclampsia, placental abruption, and birth of small for gestational age (SGA) infants are stressful and catastrophic events for not only women and their families, but also the whole society [61].While a successful pregnancy requires adequate placental circulation, thrombophilia is believed to increase the risk of placental insufficiency through micro- and/or macro-vascular placental thrombosis and negative impacts on trophoblastic growth and differentiation. There have also been debates over the possible role of FVL and PT in implantation failure and fetal loss after in vitro fertilization (IVF) [62].

3.3 IVF Failure

The critical role of FVL in embryonic implantation and cell adhesion, smooth muscle cell proliferation, and vasculogenesis during fetal development has been confirmed. Roqué et al. identified the benefits of FVL in facilitating embryonic implantation [63, 64]. In fact, the existence of FVL in either the mother or the infant has been associated with higher implantation rates in pregnancies resulting from intracytoplasmic sperm injection (ICSI)[65]. About one-third of women undergoing IVF will achieve a successful pregnancy[66].

However, the success of embryo transfer after IVF depends on several factors including inherited or acquired thrombophilia. Thrombophilia is known to disturb the angiogenesis and vasculogenesis (required for a successful pregnancy) and thus contribute to early pregnancy loss and implantation failure [67]. Thrombosis or infarcts in the placental sections may imply a hemostatic abnormality caused by thrombophilia [68]. Significantly higher rates of pregnancy loss have been found in heterozygous and/or homozygous carriers of FVL, PT, and MTHFR gene mutations compared to their control counterparts. Al Husseini et al. confirmed an association between the presence of FVL and higher rates of fetal loss following IVF [69]. Similarly Azem et al. suggested higher frequency of thrombophilia in subjects with recurrent IVF-embryo transfer failure than in those without such an experience [70]. Qublan et al. reported FVL to be more common in women with recurrent IVF failure than in subjects with successful IVF experience and healthy women [67]. Moreover, microthrombosis at the implantation site may alter the invasion of syncytiotrophoblast to mother's vessels and lead to implantation failure or fetal loss. In fact, the existence of at least one thrombophilic factor has been proved in female patients with recurrent IVF-embryo transfer failures[70].On the other hand, following the detection of greater ICSI success in FVL carriers, Göpel et al. concluded that the thrombotic tendency in mothers with FVL mutation promoted successful fetal implantation [65]. However, significantly higher frequency of PT has been discovered in women with IVF pregnancy loss than in their control counterparts [11]. Rey et al. suggested PT mutation to double or triple the risk of RPL after IVF [37]. Colman et al. compared healthy fertile women with those experiencing recurrent implantation failure and highlighted the presence of at least three gene mutations in the latter group [35]. In a study performed for the purpose of examining the relationship between undiagnosed thrombophilic factors and IVF failure, Qublan et al. compared 90 women with more than two consecutive failed IVF attempts (group A) and two control groups (group B and C). The first control group (group B) comprised of 90 women whose

first IVF embryo transfer led to successful pregnancy. The second control group (group C) consisted of 100 women with spontaneous conception, at least one unsuccessful pregnancy, and no history of miscarriage. The researchers found higher frequency of FVL in group A (14.4%) than in groups B(1%) and C (2%) [67]. While Grandone et al. published similar findings [71], other researchers have generally failed to establish such an association[70], though it seems that the results of past studies support negative roles of these two gene mutations in IVF outcomes. In conclusion, more experimental studies are recommended to confirm the ineffectiveness of these two polymorphisms on IVF outcomes.

3.4 Preeclampsia

Preeclampsia is a multisystem vascular disorder affecting 5%-8% of pregnant women in the second half of gestation, which is one of the major causes of maternal and perinatal morbidity and mortality [72, 73]. A cumulative meta-analysis of prospective cohort studies estimated the prevalence of PT gene mutation among over 9000 women at 2.9%. However, no significant relation could be established between this mutation and preeclampsia[61]. Meanwhile, the European Prospective Cohort on Thrombophilia (EPCOT) suggested significantly higher frequency of stillbirth, preeclampsia, and placental abruption among FVL carriers [74]. Moreover, significant relations have been documented between severe preeclampsia and FVL mutation, hyperhomocysteinemia, AT III and proteins S and C deficiencies [8].

3.5 Preterm Birth

Preterm birth, defined as childbirth before 37 weeks of gestation, is associated with high levels of long-term health consequences [72, 75], mortality, and morbidity in neonates and infants [76]. A single-center case-control study on women with preterm infants (born before 36 weeks of gestation) rejected any significant relations between three common thrombophilic polymorphisms (FVL, PT, and MTHFR) and preterm birth of unknown cause, history of abortion, and venous thrombosis. In addition, the preterm and term infants were not significantly different in the frequency of the mentioned gene mutations [77]. Nevertheless, in a cohort of 205 low birth weight (LBW) infants, Göpel et al. reported prematurity to be significantly associated with both FVL and PT. They, however, failed to confirm the observed association in another population (n =102) of preterm infants of multiple pregnancies [78]. Silver et al. conducted a prospective cohort of over 4,000 low-risk women. They did not notice any significant relationships between PT and either gestational age at delivery or obstetric complications such as pregnancy loss, preeclampsia, placental abruption, and SGA neonates [48].

3.6 Intrauterine Growth Restriction (IUGR)

There is little evidence to suggest a relationship between IUGR and thrombophilia [8]. A retrospective study on the prothrombotic risk factors of IUGR in Germany revealed that inherited risk factors, particularly FVL, boosted the risk of LBW. The effect was more noticeable in children with either homozygous or combined prothrombotic defects [79]. In a very large study, Infante-Rivard et al. refuted the idea that inherited thrombophilia served as a clinically significant cause of IUGR [80].

3.7 Thromboprophylaxis in Pregnancy

Prophylaxis with low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH), with or without aspirin, has been suggested to prevent poor pregnancy outcome in women with gestational vascular complications and history of

pregnancy-related complications [51]. However, as prophylactic therapy may not be required in all pregnant women, identification of high-risk patients through screening for thrombophilic polymorphisms can limit the treatment to a specific group [81]. A recent prospective observational study found that the odds of preeclampsia, intrauterine fetal death (IUFD), placental abruption, or venous thromboembolism were not higher in heterozygous carriers of FVL mutation. Nevertheless, these results may not be generalizable since almost 50% of the studied patients had been treated with heparin. Based on previous research, women with RPL, placental abruption, preeclampsia, infertility, implantation failures, IVF-embryo transfer failures, thromboembolic disease at a young age and without a particular cause, a family history of venous thromboembolism (a first-degree relative before the age of 50 years), or thrombosis in an unusual site should be investigated for thrombophilia. FVL evaluations are particularly important in these patients because the mentioned gene mutation confers a higher risk of not only venous thromboembolism, but also obstetric complications [39, 53, 82]. In a Cochrane review, Empson et al. evaluated 13 trials performed on a total number of 849 women. They confirmed that a combination of aspirin and UFH could decrease pregnancy loss by 54% [83]. Kupferminc et al. conducted a case-control study in 2011 and found the risk of stillbirth, placental abruption, and preeclampsia to be higher in women with thrombophilia. They concluded that LMWH treatment of women with previous severe pregnancy complications and thrombophilias significantly reduces the rate of recurrence. Hence they suggested heparin as an effective measure to both prevent and treat the mentioned conditions [7]. Prophylactic administration of LMWH was also reported to successfully decrease the risk of obstetric complications in female carriers of FVL or PT who had a history of pregnancy complications [84]. While LMWH is as effective as UFH, it is safer and associated with lower risk of developing heparin-induced thrombocytopenia. Moreover, cases of osteoporosis and fracture formation have been reported in pregnant women who were exposed to UFH for long periods of time [85]. In women with antiphospholipid syndrome, guidelines recommend prescribing aspirin and heparin to women with recurrent miscarriage. Aspirin or LMWH to improve pregnancy outcome in women with unexplained recurrent miscarriage has no benefit and should not be prescribed. Whether anticoagulant therapy prevents recurrent miscarriages in women with inherited thrombophilia or in women with severe pregnancy complications remains controversial because of conflicting results from clinical trials [86].

4. Discussion

Based on the present review, evidence indicated higher risk of recurrent early miscarriages, implantation failure and fetal loss after IVF among women with FVL and PT mutations. So screening patients for thrombophilic polymorphisms in identification of high risk women for developing thromboembolic events and other related pregnancy complications is beneficial. It would determine the target group for prophylactic therapy

Since the outbreak of all types of thrombophilic states including inherited (such as PT and FVL) and acquired (such as APS) in women with pregnancy complications is not so infrequent, every specialist should consider these conditions and investigate them in their patients with recurrent fetal loss or severe complication of the pregnancy. The most commonly reported type of acquired thrombophilia is the antiphospholipid syndrome (APS). Of women with recurrent pregnancy loss, 10%–20% have detectable aPL. A meta-analysis done by Abou-Nassar concluded that antiphospholipid antibodies appear to

be most consistently associated with late fetal loss, with LA being the strongest and most consistent antibody associated with placenta mediated pregnancy complications (87). PT and FVL are the most extensively studied thrombophilic mutations in association with RPL. Several studies have shown that women with inherited thrombophilia, such as FVL and PT mutations carry a higher chance for recurrent early miscarriages and second trimester abortion. Heterozygosity for FVL or PT gene mutation increases the risk of venous thromboembolism during pregnancy, implantation failure, and fetal loss after IVF. However, one study suggested higher ICSI success in mothers with FVL and suggested the thrombotic tendency in FVL carriers to have some advantages in fetal implantation. While associations have been established between severe preeclampsia and FVL, hyperhomocysteinemia, and AT III and proteins S and C deficiencies, no such relations have been identified in case of PT. Moreover, there is still controversy over the effects of these two polymorphisms on preterm delivery. In fact, while some studies suggested similar gestational age at delivery among carriers and non-carriers of these mutations, a retrospective analysis demonstrated that inherited thrombophilia, mainly FVL, increased the risk of giving birth to LBW infants. In conclusion, according to previous research, screening patients for thrombophilic polymorphisms might be helpful in identifying patients with increased risk for thromboembolic events and other related adverse pregnancy outcomes.

Furthermore, such screening would determine the target group for prophylactic therapy. Nevertheless, based on Royal College of Obstetricians and Gynecologists and the American College of Obstetricians and Gynecologists guidelines, there is still a lack of evidence in favor of routine thrombophilia screening and anticoagulant-based interventions during pregnancy. Therefore, this study recommends that the screening for thrombophilias be encouraged. The study also suggests that LMWH treatment is more effective in reducing adverse pregnancy outcome in thrombophilias.

The most major limitation of this study was that the authors did not systematically review all available studies. Therefore, it is recommended for other researchers to do a systematic review on these two factors in future. Regardless of the limitations of the current study, the authors believe that the results emphasize the relevance of the topic of thrombophilias in pregnancy complications and point out the need for further research.

5. Conclusion

According to our review, the possible relations of Factor V Leiden and Prothrombin G20210A Mutations with recurrent pregnancy loss have been widely evaluated. Several studies indicated higher risk of recurrent early miscarriages, implantation failure and fetal loss after IVF among women with FVL and PT mutations. Accordingly, studies have suggested the benefits of screening patients for thrombophilic polymorphisms in identification of women at higher risk of developing thromboembolic events and other related pregnancy complications. Furthermore, such screening would determine the target group for prophylactic therapy, who truly need it.

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Conflict of Interest

The authors declare no conflict of interest.

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