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Frequency of Thrombophilic Factors in Patients with Recurrent Pregnancy Loss

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Abstract: Background: A category of hereditary diseases known as Thrombophilia induces irregular blood clotting. Pre-eclampsia, late miscarriages, premature delivery, fetal growth restriction, and deep venous thrombosis are all associated with Thrombophilia. A higher incidence of recurrent pregnancy loss (RPL) or recurrent early pregnancy loss (REPL) in the initial 6–10 weeks of conception may be seen in homozygous individuals for particular thrombophilic variables. A healthy uteroplacental circulation is necessary for a favorable pregnancy outcome. It has been hypothesized that maternal Thrombophilia could raise the probability of preeclampsia and intrauterine growth retardation (IUGR). ACE D/D (angiotensin-converting enzyme deletion/deletion) genotype and PAI 4G/4G (plasminogen activator inhibitor-1 4G/4G) genotype have been associated with an increased risk for these conditions and high blood pressure (hypertension).

Aim of this study is to determinate the frequency of the different thrombophilic mutations in patients with recurrent pregnancy loss.

Methods: A prospective cohort study included 309 pregnant patients with gestational age from 6 to 12 gestational weeks. The patients have a history of recurrent pregnancy loss in the past. Inherited Thrombophilia test was performed on each research participants as part of preconception counseling.

Results: Plasminogen activator inhibitor 1(PAI – I) 4G/4G was the most prevalent form of thrombophilic mutation identified (82,83%), followed by MTHFR mutation (85.43%), mutations in the prothrombin gene (12,61%) and factor V Leiden (12.29%). Additionally, (12.62%) of pregnant women had IUGR babies, (29,44%) of patients had preeclampsia as a diagnosis and gestational diabetes (24,27%).

In conclusion - The genetic landscape significantly impacts the trajectory of pregnancy-related complications. This study sheds light on the pivotal roles played by genetic mutations, elucidating potential avenues for refined clinical management and targeted interventions. The early detection of these genetic variations paves the way for enhanced personalized care strategies, ultimately benefitting the well-being of both maternal and fetal domains.

Keywords: *Thrombophilia, hereditary, pregnancy, genetic disorders, fetal growth*.

1. Introduction

Thrombophilia is an inherited (hereditary) propensity for thrombosis that can also be identified in later life (acquired). Thrombosis occurs when haemostasis, the process by which blood clots are formed and broken down, is disrupted in any way. Variables in blood clotting, plasma proteins, blood movement, vascular walls, and cell components all contribute to an abnormally high propensity for blood clotting. This causes thrombosis to form in the affected blood vessel. The first step in treating a patient with thrombosis rationally is determining if the patient's hypercoagulable disease is inherited or acquired. The haemostatic system is altered throughout pregnancy, becoming hypercoagulable, a condition that is unavoidable near the time of delivery. About 5% of reproductive-age women have RPL, defined as two or more unexpected losses. Recent research has linked thrombophilia as a cause of RPL. Some mutations in a gene that codes for a plasmatic protein involved in the anticoagulant mechanism lead to the development of an inherited condition [1]. Hereditary thrombophilia is a genetic susceptibility to developing thrombi due to an inadequacy in anticoagulant factors such antithrombin (AT), protein C (PC), or protein S (PS). People under the age of 40 with this syndrome are at increased risk for getting potentially fatal thrombosis. Vein thromboembolism (VTE) is a

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potentially fatal blood clot that can occur in both children and adults, and it can sometimes occur at a young age. There are a variety of problems that can develop in infants and newborns as a result of this condition. Although thrombosis can occur in any blood vessel, the most common types of VTE are deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE). Therefore, it can be challenging to diagnose and treat thrombophilia in pregnant women because thrombosis can occur at any time throughout pregnancy or after giving birth. While inherited AT deficiency is very uncommon, it is associated with an increased risk of thrombosis, and there is currently no agreement on how this condition ought to be managed throughout pregnancy and delivery. Pregnant women with thrombophilia and their infants are not yet supported by any consensus-based guidelines for care. PS deficiency is common among thrombophilia patients, and thrombosis can occur during pregnancy; however, this illness is rarely detected before pregnancy, and managing thrombosis during pregnancy presents a number of unique obstacles [2]. The term advanced maternal age (AMA), refers to pregnancies that occur in women who are 35 or 40 years of age or older while they are pregnant or giving birth. The presence of AMA is linked to negative perinatal outcomes such as fetal death as well as negative maternal outcomes such as the need for emergency surgical births. It is recommended in the guidelines of several nations that women be induced with an AMA in order to reduce the risk of undesirable outcomes associated with pregnancy. Pregnancies that progress into late or postterm stages are more common among women with AMA. Although the risk of fetal death is modest in absolute terms, postterm pregnancy is linked to poor perinatal and mother outcomes. This holds true irrespective of the maternal age [3]. Thrombophilia is the name given to a set of diseases in which blood clots more frequently than normal. Anomalies can be congenital or acquired, or both. Secondary risk factors for the disease include oral contraceptive use, heparin-induced thrombocytopenia, antiphospholipid antibody syndrome, neoplasia, obesity, smoking, and surgical procedures. Thrombophilia can be caused by a lack of antithrombin III, protein C or S, or a loss of histidine-rich glycoprotein, or by a mutation in factor V. This group also contains prothrombin-related Thrombophilia. Deep vein thrombosis and venous thromboembolism are more likely to occur in people with Thrombophilia. However, there is considerable variation in the clinical presentation of hereditary Thrombophilia; The splanchnic veins, cortical veins, and retinal veins are all possible locations for thrombosis. Some people never develop thrombosis, others may not show symptoms until adulthood, and others endure recurrent thromboembolism in their 20s [4]. Reproductive failure (RF) is defined as the inability of a female to conceive or complete a pregnancy. Multiple symptoms, including infertility, UI, Reproductive Implantation Failure (RIF), miscarriage, and RPL, define human RF. Various scholarly organizations have proposed multiple definitions of RPL. The prevalence of RPL varies depending on the purpose and ranges from 1% to 5% of all couples. Only 1% or less of pregnant women will suffer more than three consecutive losses, and 2% of women will miscarry twice in a row [5]. Figure 1 depicts the framework of Thrombophilia and Outcomes in Pregnancy.

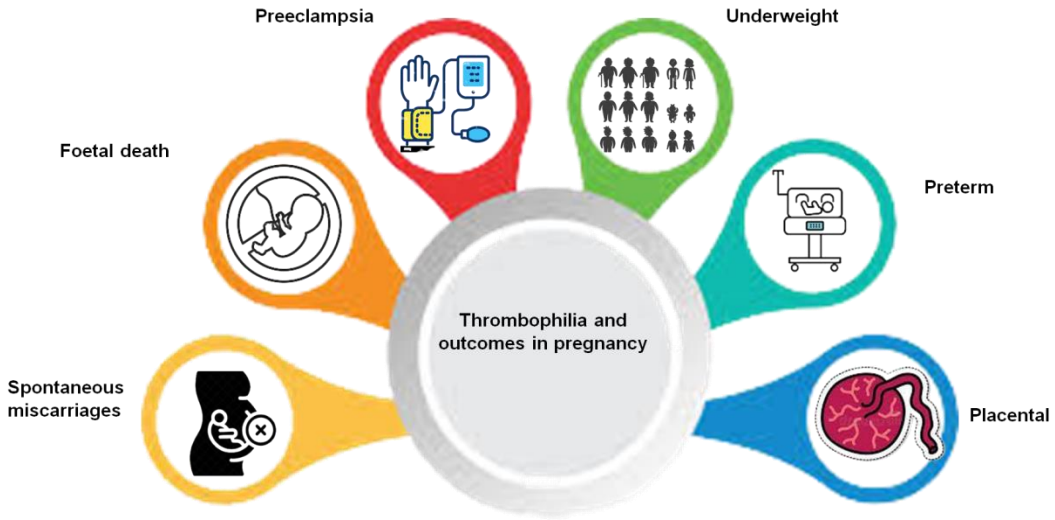

Figure 1: Framework of Thrombophilia and outcomes in pregnancy

A dynamic equilibrium between fibrinolysis and thrombosis is required throughout pregnancy. This balance must be preserved throughout pregnancy for beneficial coagulation in the third trimester. To allow for trophoblastic invasion and alteration of the spiral arteries during placentation and implantation, the proper balance of proteolysis must be maintained. Antifibrinolytic drugs. For the purpose of regulating the fibrinolytic pathway, plasminogen activator inhibitor-1 (PAI-1) limits tPA's action. Tissue plasminogen activator (tPA) is an enzyme that converts plasminogen into plasmin and then cleaves fibrin into breakdown products. When PAI-1 blocks tPA, a prothrombotic environment results. PAI-1 is secreted during pregnancy by trophoblasts, activated platelets, endothelial cells, and the placental vasculature. Among the several mechanisms by which pregnancy promotes a general rise in thrombotic risk factors is progesterone's induction of an increase in decidual PAI-1 expression and placental PAI-2 release. During a woman's pregnancy, these two things happen simultaneously. Elevated levels of PAI-1 indicate endothelial dysfunction, but high levels of PAI-2 are typically employed as a proxy for placental function. PAI-1 is a protein that endothelial cells secrete. In healthy pregnant women, third-trimester PAI-1 levels rise by 4-5 and quickly return to normal following delivery [6]. Recent research has linked RPL to the genetic disorder hereditary Thrombophilia, which increases the risk of

thromboembolic illness. Contradictory results have been discovered in the study looking at the relationship between Factor V Leiden gene heterozygosity and fetal demise after ten weeks, particularly if it is the first time after 20 weeks. This shows that the relationship is minor and mostly restricted to high-risk groups. Due to alterations in the numerous coagulation factors brought on by pregnancy, many hereditary diseases have a higher propensity for thrombogenesis during pregnancy [7]. Due to a wide variety of social and cultural factors, there has been a significant movement in maternal age at childbirth during the past few decades. The mean age at delivery in Italy increased from 25.2 years in 1981 to 31.7 years in 2015. Worldwide, there is a tendency toward delaying childbearing, which coincides with a reduction in pregnancies at younger ages, making these more and more uncommon in emerging nations. Negative pregnancy outcomes are thought to be possible at either end of the reproductive age spectrum. Preterm birth, low birth weight, a low Apgar score, and postnatal mortality are all more likely in teenagers who give birth. It is still up for debate whether this association is caused by biological immaturity, socioeconomic difficulties, behavioral problems, or a lack of access to high-quality prenatal care. On the other hand, postponing parenthood increases the risk of obstetric and maternal problems. After the first article on the "elderly primigravida" was published in 1950, other researchers have looked into how age affects the outcome of births. The majority of research indicates a connection between advanced mother age and cesarean delivery, preterm birth, low birth weight, and perinatal death [8]. Unfortunately, even when a healthy pregnancy is achieved, the mother and child may still lose their lives. Human reproduction is notoriously difficult. RPL can occur when the normal balance of maternal and fetal immune systems is upset, which is necessary for a healthy pregnancy and the delivery of a healthy baby. By enabling the selection of euploid embryos, technology and scientific advancement in assisted reproductive technology (ART) have created new instruments to understand better the elements that affect the reproductive result. Nevertheless, more than 30% of euploid embryos do not implant for reasons that are not fully understood [9]. We focused on hereditary Thrombophilia and unfavorable pregnancy outcomes due to these conditions.

Following are the remaining sections of this study: The related works are presented in section 2, the methodology is explained in section 3, the study's results are analyzed in section 4, there is discussion in section 5, and the conclusion is presented in section 6.

2. Related Work

In this companion piece, the writers examine a range of technical reports and scholarly articles by various authors. Other authors address the issues with distributed and integrated systems. The study [10] compared the rates of miscarriage and late obstetrical complications between women who had a history of RPL and had O-APS or hereditary Women with thrombophilia or a history of recurrent miscarriage or stillbirth were followed at the pregnancy at risk and recurrent pregnancy loss clinics. Due in large part to defective thrombosis, RPL-RIF is both common and difficult to treat. It set out to determine the risk factors linked with numerous thrombophilia-related genes and variations found in the RPL-RIF in the Indian population, given the prevalence of this condition [11]. The research [12] aimed to evaluate the reproductive outcomes of women seeking help for recurrent miscarriages at a specialized clinic. Patients that visit a specialized recurrent miscarriage clinic for evaluation and treatment have a high live birth rate among subsequent pregnancies. Pregnancy after a repeated miscarriage does not appear to enhance the chance of complications with the next pregnancy. The research [13] determined the prevalence of three thrombophilic variants in Egyptian couples with RPL: “Factor V Leiden (FVL), Prothrombin G20210A (PT), and Methylenetetrahydrofolate reductase (MTHFR) A1298C”. To offer therapy solutions, the study [15] built a prediction model of placenta-mediated pregnancy problems (PMPC) by analyzing the effects of Thrombophilia, antithrombotic medications, and materno-fetal characteristics. It has been speculated that thrombophilia genes may have a role in repeated miscarriages. It examined the role of “MTHFR C677T, A1298C, F2G20210A, and F5L G1691A” polymorphisms in recurrent miscarriage in Iranian women [16]. In pregnant women with Thrombophilia, fetal growth limitation is a common complication. Predicting unfavorable obstetrical outcomes using cutting-edge AI algorithms is an exciting new frontier. This study [17] focused on predicting "small for gestational age" (SGA) newborns in a group of pregnant patients with Thrombophilia, which assessed the predictive efficacy of a "Feed-Forward Back Propagation Network (FFBPN)." Although screening for Thrombophilia is not explicitly indicated in guidelines, many doctors do it routinely in their RM patients out of concern for a higher prevalence. Pregnancy-related Thrombophilia is a worldwide phenomenon, and as its prevalence rises, so does the importance of finding effective prophylactic measures to mitigate its effects. To obtain data on the anthropometric and socioeconomic characteristics, as well as the genetic and risk factor profiles, of expectant women in western Romania [18]. The prevalence of inherited and acquired Thrombophilia was investigated in this study [19], which analyzed data from a massive RM patient group. Hereditary thrombophilia, a condition of blood coagulation caused by genetics, accounts for almost 60% of idiopathic thromboembolic events. Many pregnancy issues, including preeclampsia, recurrent miscarriage, intrauterine growth restriction, premature placental separation, and premature birth, may be linked to the association of hereditary thrombophilia with pregnancy [20]. The study [21] goal was to identify IHT in the first trimester of pregnancy in women who had no other vascularization-based grounds for thrombophilia screening. There was also an evaluation of the effectiveness of LMWH therapy on placental vascularization and PO. Finally, a system for dividing thrombophilias was devised that takes into account the hazards they represent during pregnancy. In the 53 years after the first description of an inherited prothrombotic syndrome (antithrombin deficiency), much has been learned about the genetic and environmental factors that increase the risk of “venous thromboembolism (VTE)” in carriers [22].

3. Methodology

Thrombophilia, is the term used to describe a propensity or inclination to form blood clots. Either inheritance or acquisition is options. Genetic changes that influence the clotting process in the body are the root cause of inherited Thrombophilia.

3.1 Patient’s data

In Bulgaria's city of Burgas, between January 2021 and December 2023, prospective 36-month cohort research was carried out there. Women in the study were between 6 and 38 weeks along in their

pregnancies. Hereditary thrombophilia testing, including protein C, protein S, antithrombin III, and homocysteine levels, were performed on all research subjects. Gene variants were identified in factor XIII, factor V Leiden, MTHFR, and prothrombin G20210A. The University Multi-profile Hospital for Active Treatment – Burgas, ethical committee authorized the study, and all participants gave their informed consent.

3.2 Adverse pregnancy outcomes

A collection of genetic disorders collectively called inherited Thrombophilia raises the chance of forming unnatural blood clots. Pregnancy complications are more common in women with these illnesses. Thrombophilia can be caused by several genetic disorders that compromise the body's natural capacity to regulate blood clotting. Common hereditary thrombophilias include, but are not limited to, the "Factor V Leiden mutation, the prothrombin gene mutation (G20210A), and deficiencies in naturally occurring anticoagulant proteins such protein C, protein S, and antithrombin". Numerous variables can raise the risk of blood clot formation during pregnancy. Among them are hormonal adjustments, an increase in blood coagulation factors, and a decrease in blood flow brought on by the expanding uterus. These elements may increase the likelihood of blood clots forming in women with hereditary Thrombophilia, which could have negative pregnancy consequences. The following are some possible negative effects of hereditary Thrombophilia during pregnancy:

- **Recurrent miscarriage:** In particular, during the first trimester of pregnancy, women with thrombophilic disorders may be more susceptible to recurrent miscarriages.
- **Intrauterine growth restriction (IUGR):** This term describes a situation in which the baby's womb growth is abnormal. A baby's growth and development may be hampered by inherited Thrombophilia, resulting in decreased blood supply to the placenta.
- **Preeclampsia:** This pregnancy problem is characterized by organ damage, proteinuria (the presence of protein in the urine), and elevated blood pressure. Because Thrombophilia affects blood vessel function and raises the risk of blood clots, it can hasten preeclampsia onset.
- **Placental abruption:** Placental abruption, in which the placenta separates from the uterine wall too early in pregnancy, is a serious complication that increases the risk of premature delivery for those with genetic Thrombophilia. The baby's oxygen and nutritional supply may be compromised by placental abruption, resulting in bleeding.
- **VTE:** Vein thrombosis and pulmonary embolism are just two of the blood clots that can form in a pregnant woman with inherited thrombophilia. The mother and kid are equally at risk from these diseases and illnesses.

It's critical that women who are known to have hereditary Thrombophilia have the right prenatal care and therapy. Prenatal care that focuses on close monitoring, preventative anticoagulant medicines, and other precautions to reduce the risk of unfavorable outcomes may be necessary. Women with genetic Thrombophilia may or may not experience complications during pregnancy. The risk varies based on the thrombophilic condition, additional risk factors, and personal characteristics like lifestyle and medical history. Pregnant women with hereditary Thrombophilia need to speak with their healthcare specialists for individualized advice and care.

3.3 Pregnancy loss

3.3.1 First trimester miscarriage

Maternal age is a strong independent risk factor for miscarriage in the first trimester, according to recent studies of population registries in Denmark and Norway. Despite controlling for other factors like parity, history of miscarriage, and spontaneous/induced abortion rates, AMA remains a major independent risk factor. In the first trimester, the risk of miscarriage was lowest for women in their twenties (8-10%), and it increased dramatically for those over the age of 30. Rates of miscarriage during the first trimester vary widely by age group, from 17–25% for women aged 35–40, 33–51% for those aged 40–45, and 57–75% for those aged 45+. Given that they are based on women who disclose a miscarriage to a healthcare provider and do not include those who handle early pregnancy losses completely at home, these statistics most likely indicate a systematic undercounting of first-trimester losses.

3.3.2 Second trimester miscarriage

Women of advanced maternal age (AMA) have a higher risk of miscarriage in both the first and second trimesters compared to younger women. First and second trimester loss rates for women over 40 are 1.5 and 1.7 percent, respectively, while the overall loss rate is between 0.4 and 0.9 percent.

3.3.3 Stillbirth

The relationship between stillbirth and AMA is more difficult to assess than the findings around earlier pregnancy loss. Women over the age of 40 were found to have a higher risk than those between the ages of 35 and 39, according to major population-based registries suggesting an association between maternal age and risk.

3.4 Statistical analysis

SPSS version 21 was utilized for data collection and analysis due to its superior statistical capabilities. The data classification scheme conducted coding, data analysis, and statistical tests. In addition, a cluster analysis and Cramer's V (Cramér's phi) test were executed. There are only two possible values for Cramér's V, 1 (showing perfect correlation) or 0 (representing no relationship between the variables). Table 1 explains how to interpret Cramer V values based on published research. Finding groupings of subjects with shared characteristics is the goal of cluster analysis, where the similarity between subjects is taken to mean some aggregate measure of all of their shared features.

Table 1: A description of Cramer V values

Value	Interpretation
<0.10	Poor association
0.10-0.30	Weak to moderate association
1	Perfect association
0.50	Strong association
0	No association
0.30	Moderate association
0.30-0.50	Moderate to strong association

4. Results

Since thrombophilic mutations are only detectable through laboratory analyses and the normalcy interval observed is sensitive to the reagents employed in those analyses, Cluster analysis was used to uncover protein S and C actual significance. This led us to apply cluster analysis to classify thrombophilic mutations as lacking, average, or excessive. The average patient in the study was 31.75±4.75 years old and had a body mass index of 26.44 ±3.81.

A blood protein called protein S is essential for controlling blood coagulation. It is a cofactor for protein C, preventing the body from forming blood clots. Protein S deficiency is a disorder marked by low levels or decreased protein S function, and it can raise the risk of thrombosis or irregular blood clotting. Protein S ranged in value from 20.1% to 111.8%, with a mean of 49 %. There were 68 individuals with protein S shortage, 241 with normal protein S levels, as shown by the cluster analysis in Figure 2.

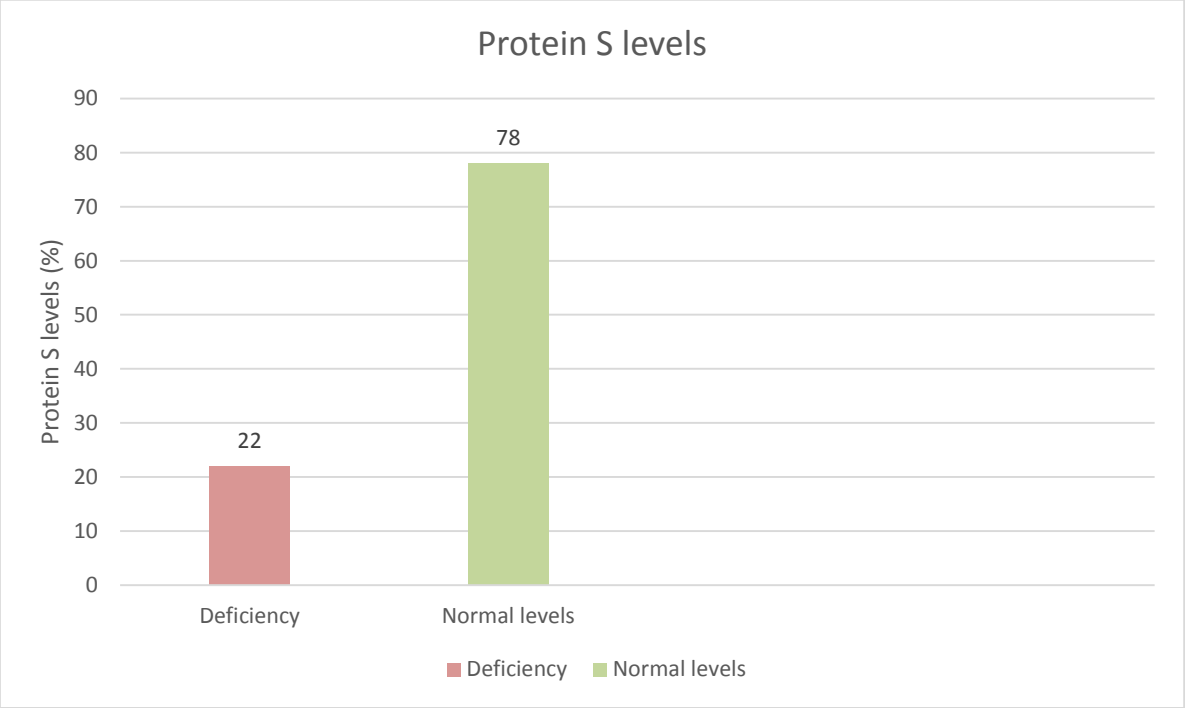

Figure 2: Protein S level

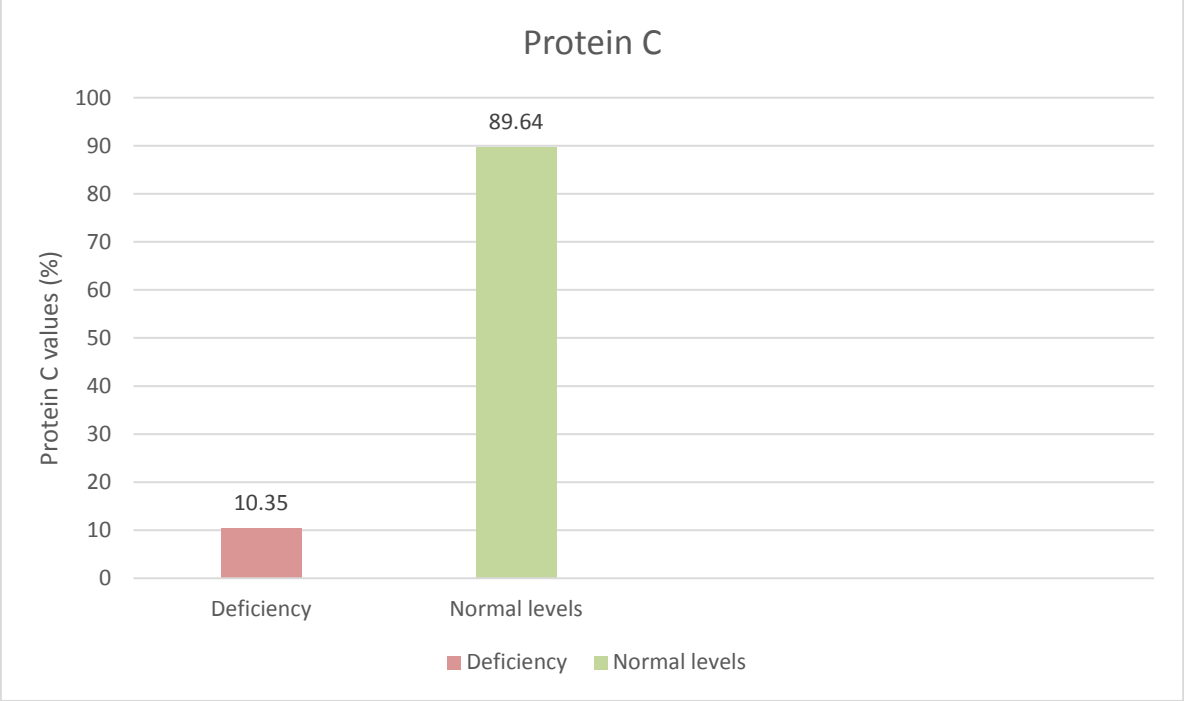

Figure 3: Protein C level

Figure 3 depicts the protein C level. Protein C helps control blood coagulation. It inhibits blood clotting factors as an anticoagulant. Low protein C levels or function increase the risk of irregular blood coagulation. Protein C assays measure blood protein C levels. The test measures blood protein C levels and function. Protein C levels are reported as percentages of a reference range. Protein C deficiency is hereditary or acquired. Mutations create type I or type II inherited deficits. Protein C synthesis is decreased in type I deficiencies and malfunctioning in type II deficiencies. Protein C ranged from a mean of 114.37% to a maximum of 1078.0 (standard deviation of 7.5). Cluster analysis revealed that 32 individuals had protein C deficiency, 277 had normal protein C levels.

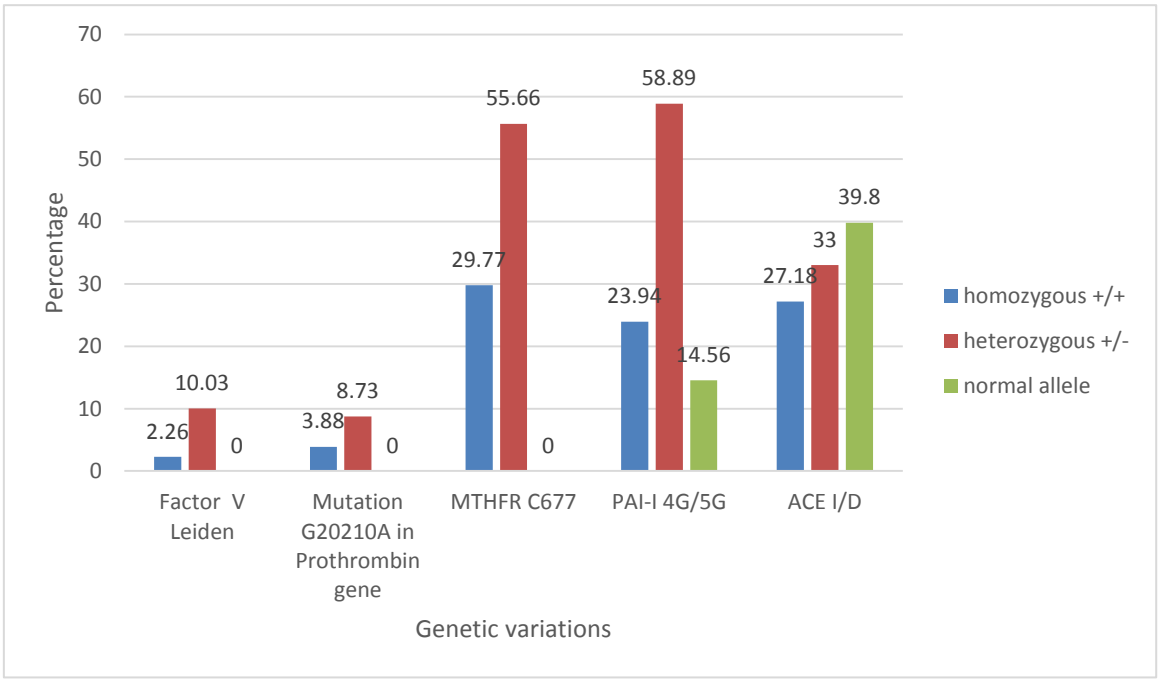

Figure 4: Thrombophilic mutation spectrum

Figure 4 depicts the Thrombophilic mutations. The most common mutation in the surveyed group of patients is heterozygous carriage of PAI-I 4G/4G - 58.89%, followed by heterozygous carriage of MTHFR 55.66% and ACE D/D 27.18%, Leiden factor V mutation 12.29%, and prothrombin gene mutation 12.61%.

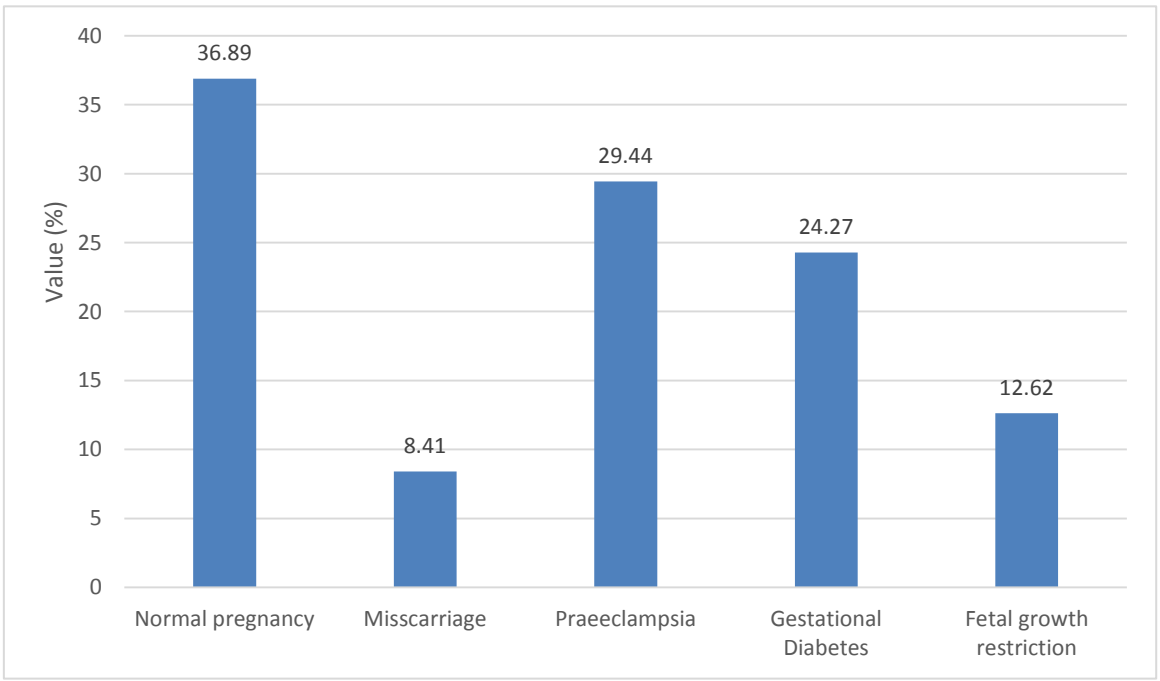

Figure 5: Obstetric pathology prevalence

Figure 5 depicts the obstetric pathology. Obstetric pathology is an evaluation of conditions that affect pregnancy and childbirth. Certain obstetric pathologies are more or less common depending on the situation under consideration. Obstetric pathology shows that 29,44% of pregnant women experienced preeclampsia, 12,62% of their babies were born with intrauterine growth restriction and 24,27% develop gestational diabetes and 36,89% of the patient had a normal pregnancy.

The Chi-square test was used to evaluate the direction of the observed association and was limited to data having a P value of 0.05 or less in the study. A prothrombin mutation and intrauterine growth limitation were significantly correlated, according to the findings (Cramer's V=0.33, P0.001). In comparison to pregnant women without this thrombophilic mutation, patients with a mutation in their prothrombin gene and antithrombin deficiency had an elevated risk of delivering a child with intrauterine growth restriction by 11.69-fold and 60.37-fold, respectively in Table 2. With a significance level of less than 0.001, the Cramer's V coefficient, which gauges the strength of a link between two variables, was determined to be 0.59. This data strongly suggests that antithrombin deficiency correlates with intrauterine growth restriction.

Table 2: Relationship between limits to intrauterine growth and a diagnosis of prothrombin mutation and antithrombin deficiency

Factors	Prothrombin mutation			Antithrombin deficiency		
	95% confidence level			95% confidence level		
Items	Value	Minimum	Maximum	Value	Minimum	Maximum
The ratio of odds for IUGR (yes/no)	11.695	5.177	26.418	60.374	23.562	154.697
Total patients	309			309		

5. Discussion

The plasma proteins C and protein S rely on vitamin K and play an important role in the body's innate anticoagulant mechanism. Women are deficient in proteins C and S and at risk for thrombosis during pregnancy, have been described on multiple occasions [23]. However, not all of these women develop thrombotic problems. Results from this study [24] showed that most protein C and S levels were within the typical range. On the other hand, a diagnosis of protein C deficit was made in 14.8% of patients, and a diagnosis of protein S insufficiency was completed in 7% of patients. Both intrauterine growth restriction (IUGR) and preeclampsia are major contributors to the morbidity and mortality experienced by fetuses and newborns [25]. IUFD, preeclampsia, and placental abruption have all been associated in certain studies to inherited thrombophilia; however the connection between IUGR and thrombophilia is still up for debate [26]. There is a spectrum of illnesses, including preeclampsia and other hypertensive disorders of pregnancy that is linked to a marked increase in the risk of morbidity and mortality for both women and their unborn children. It is estimated that between 3 and 10 percent of all pregnancies are affected by this condition in the general population [27].

In this particular investigation, a diagnosis of preeclampsia was made for 16% of the participants. Preeclampsia affected 16 percent of patients, and 7 percent of births were related to fetal intrauterine growth restriction. Preeclampsia, fetal mortality, and intrauterine growth restriction are just a few of the negative pregnancy outcomes linked to maternal thrombotic diseases in recent research. We don't consider Thrombophilia an infection because the onset of a medical condition is not at the time of its diagnosis but rather when the first symptoms of that condition become apparent to the patient. A confluence of different risk factors still brings on the pathological disease known as Thrombophilia. Thrombophilia is the name given to a group of illnesses characterized by a persistently hypercoagulable condition and an increased propensity for thrombosis. Thrombophilia is known to be associated with major pregnancy problems such as preeclampsia and intrauterine developmental retardation. Unfortunately, no treatment can cure Thrombophilia; the only treatment option is preventative treatment with anticoagulants. As a result, doctors consider women who have been told they have genetic Thrombophilia to have high-risk pregnancies.

6. Conclusion

In the presented study, we focus on the significance of carrying various thrombophilia factors for adverse pregnancy outcomes. We found a reduced level of protein S in all patients with hereditary thrombophilia. The results showed a predominance of the MTHFR C677T mutation followed by carriage of PAI-I 4G/4G and ACE D/D, which correlates with a high frequency of developing preeclampsia, gestational diabetes, and intrauterine growth retardation during pregnancy. We believe it is appropriate to investigate the discussed thrombophilia factors in all patients planning pregnancy who have a history of recurrent miscarriages. Such a widespread preconception screening would help prevent and diagnose a significant portion of obstetric pathology early. This current study once again demonstrates the role of genetic mutations as underlying factors in diseases that have not had a clear etiology until this point. Early diagnosis and individualized treatment approach enable better therapeutic outcomes for healthy pregnant women and their uncomplicated pregnancies.

Declaration of competing interest

The authors declare that they have no conflict of interests.

Authorships

Zlatko Kirovakov contributed with the literature review and wrote the article. Nadezhda Hinkova, Emiliana Konova, and Stefani Markova provided critical revision and final approval of the finalized manuscript. All authors have read and approved the final manuscript.

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