Hypercoagulability linked to pregnancy in a group of Colombian patients, observational study of binding clinical and laboratory alterations.

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Abstract

Introduction: The present study sought to study thrombophilias associated with venous thromboembolism during pregnancy. **Methods**: The present study is of a descriptive observational type in which the clinical and laboratory alterations were analyzed in a cohort of Latin American pregnant women with the denominator of thrombotic events during pregnancy. **Results**: The mean age was 24.5+7.6 years, of which 9 patients (10.3%) had a history of thromboembolism , 23 patients (26.4%) had had at least one fetal loss. Elevated Antiphosphatidylserine antibodies were found in 23 patients (26.4%), elevated antibodies against Beta2-Glycoprotein in 20 patients (22.9%), positive lupus anticoagulant in 16 patients (18.3%), elevated Factor VIII in 13 patients (14.94%), Elevated Factor IX in 15 patients (17.2%), Elevated Factor XI in 12 patients (13.7%), Prothrombin Mutation in 7 patients (8.07%). **Conclusions**: The results found here indicate the high prevalence rate of thrombophilic alterations. underdiagnosed in pregnant women.

Keywords: Coagulation, Thrombosis, Gynecology.

Introduction

A genetic abnormality causes thrombophilia (1, 2), which can also be identified postnatally as a disorder (acquired), or it can be identified as a susceptibility to thrombosis. When one or more hemostasis-related elements, such as coagulation factors, plasma proteins, blood flow, vascular surfaces, and cellular components are disrupted, hypercoagulability eventually results. This is how thrombosis develops. In turn, thrombosis develops in the veins or arteries. The first step in treating a patient with thrombosis rationally is to determine whether the hypercoagulable disease is acquired or genetic. The hemostatic system is altered during pregnancy to a hypercoagulable state, which is more dangerous during childbirth. Recurrent pregnancy loss (REP), which affects about 5% of women of reproductive age, is defined as two or more spontaneous abortions (3).

According to recent studies, thrombophilia is one of the factors that contributes to PRE (2, 3). The existence of some mutations that alter a gene that encodes a plasma protein implicated in the anticoagulant mechanism leads to the development of hereditary diseases (4). One of the risk factors for reproductive diseases is hereditary thrombophilia. Thrombophilia is a significant tendency that eventually results in thrombosis (4). This variance is caused by a number of reasons, primarily the synergy of the coagulation factors and their interaction with blood components and other cells. With age, the likelihood of receiving a thrombotic pathology diagnosis rises for a variety of reasons, pregnancy being one among them. The condition known as venous thromboembolism (VTE) is characterized by a variety of characteristics, with inherited or acquired factors providing the most definitive clinical signal. A woman with a known prothrombotic condition should be assessed as such before, during, or after pregnancy (6). Patients who are at risk for developing thrombosis should be examined for thrombophilias.

According to certain research, VTE complicates 1.2 out of every 1,000 births. The diagnosis, prevention, and treatment of pregnancy-associated VTE are particularly challenging due to the necessity to take into account the health of both the mother and the fetus. These challenging issues are addressed by current recommendations (6). Studying families having a known history of VTE served as the starting point for research into hereditary thrombophilia (7). Hereditary thrombophilia was regarded as a rare genetic illness in the 20th century. Over time, specific diagnostics for hereditary thrombophilia emerged (5). Age, immobility, prolonged orthostatism, obesity, diet, smoking, high estrogen levels, use of contraceptives (increases the risk of suffering a VTE up to three times), and last but not least, pregnancy and the postpartum period all increase the likelihood of a thrombotic episode occurring (9).

Although screening for hereditary thrombophilia is frequently not properly reviewed, it should be recognized that pregnant women unquestionably have a significant risk of having VTE, especially if they have a family history of the condition. Pregnancy increases the risk of bleeding and thromboembolic events. The uteroplacental entity is distinct, and its major purpose is to keep the maternal and fetal circulations in touch, which is essential for fetal survival (10). As a result, the circulation must be created and kept in contact. Fetal hemoglobin (HbF) makes up almost 2% of adult humans' total hemoglobin (Hb) (10). It is believed that HbF has a physiological role in facilitating the transfer of oxygen from maternal to fetal circulation. Rehabilitating uteroplacental circulation necessitates multiple integrated systems because bleeding and thrombotic activities can affect the exchange of nutrients and gases, such as oxygen and carbon dioxide, at the boundary between the maternal and fetal circulations (11).

Obstetric emergencies can be caused by coagulopathies during pregnancy, such as deep vein thrombosis (DVT) and recurrent pregnancy loss (REP), however these situations could be prevented if women were closely monitored for warning signals that could indicate the need for testing to detect them. Basic laboratory tests, such as a global coagulation panel with the complete blood count (CBC), prothrombin time (PT), partial thromboplastin time (PTT), and plasma fibrinogen, can be used to predict coagulopathies.Changes in the placenta's size and function have a significant impact on the fetus and its capacity to survive in the intrauterine environment. It is impossible to pinpoint precise risk ranges for major adverse events in the presence of genetic thrombophilic mutations, given the amount of research that either support or disprove the association between hereditary thrombophilia and pregnancy issues (12). Prothrombotic episodes, which are common during pregnancy, become more noticeable as the gestation period goes on. A healthy pregnancy depends on the formation of adequate placental circulation, and inherited thrombophilia may increase the likelihood of pregnancy's unfavorable placental-mediated outcomes (13). Factors VII, VIII, IX, and fibrinogen concentrations rise by 2- to 3-fold and by 20% to 1,000%, respectively, during pregnancy.

Blood coagulation factors XIII, XII, and XI during a typical pregnancy These changes raise the risk of maternal thromboembolism while simultaneously protecting against potentially fatal bleeding during pregnancy and during the third trimester of gestation (14). The incidence of VTE is thought to range between 0.5 and 2.2 per 1,000 patients. The risk of thrombosis is five times higher in pregnant women, and it is greatest between weeks 6 and 12 after delivery (15). Because of the hypercoagulable condition caused by high levels of estrogen and progesterone during pregnancy, clotting factors are upregulated and anticoagulant levels are decreased (15).

It is well established that thrombosis during pregnancy, as well as underlying thrombophilia, can have catastrophic repercussions for both the mother and the fetus (15). This includes thrombotic episodes that take place during gestation and the postpartum period. Increased fibrin turnover is the outcome of biological hypercoagulability, which is a phrase used to explain abnormalities in blood coagulation and fibrinolysis that have a thrombotic look during pregnancy. The most vulnerable marker of secondary fibrinolytic activation, D-dimers (DD), which are present in higher amounts, serves as evidence for this (16). These are then divided into three risk categories based on the thrombophilic profile: high, moderate, and low risk.

High-risk thrombophilia

Antithrombin III deficiency (AT III).

The direct target of AT III, which is thrombin, is one of the key plasma inhibitors of active coagulation factors (17). Given that acquired deficits are more prevalent, it has been demonstrated that AT III deficiency is a risk

factor for venous thrombosis. However, this problem can be resolved by using the proper anticoagulation regimen (17). Defects in AT, which are shown by lowered inhibition of factor Xa, can occur after heterozygous mutations in the AT gene are found (1). Before using heparins or low molecular weight heparins to treat anticoagulation, the AT III level should be measured. It has been proven that its lowering raises thrombosis risk by up to 50%.

Protein C and S deficiencies

A decrease in protein C or S activity characterizes protein C or S deficits, which are rare diseases (18); Mammen first diagnosed protein C insufficiency in 1960. Contrary to protein S, which raises the risk of thrombosis by about 10%, it is known to raise it by as much as 20%. As a result, higher thrombin production and a propensity for thrombosis are caused by genetic protein C and S deficiency (1).

Moderate risk thrombophilia

Resistance to activated protein C and factor V Leiden

Dahlback and Hildebrand (19), who identified a mistake in the anticoagulant response when activating protein C (PCA), initially revealed the presence of resistance to activated protein C in the early 1990s. It has been established that hereditary thrombophilia and PCA resistance are associated (19). Several screening programs included factor V Leiden, a hereditary hemostasis deficiency and low risk factor for thrombosis associated with the potential for having a first and recurrent venous thromboembolism. Additionally, it has been linked to thrombosis, especially in women who also have other risk factors such pregnancy, advanced age, using oral contraceptives, hyperhomocysteinemia, and protein C and protein S deficiency (20).

Prothrombin gene mutation (Factor II)

In 1996, Poort made the first mention of prothrombin, also known as factor II, which is a precursor to thrombin (21). The prothrombin mutation G20210A, which affects up to 6% of the population and ultimately raises the risk of thrombosis, is recognized by the substitution of the guanine nucleotide (G) for the adenine nucleotide (A) at position 20210. Although having a heterozygous position is known to have a minimal risk of developing issues related to VTE, this risk rises during pregnancy (22). However, prothrombin activity gradually rises in response to both oral contraceptive use and pregnancy (22).

Factor VIII

Elevated levels of factors VIII, IX, and in patients with a history of VTE increase the risk of thrombosis (up to 10%).

Low risk thrombophilia

Hyperhomocysteinemia

Homocysteine is an amino acid that is created when methionine is demethylated (23). An amino acid that is frequently seen is homocysteine (23). Hyperhomocysteinemia, or elevated homocysteine levels, can result from a variety of genetic causes as well as a diet deficient in folic acid and B vitamins. Although elevated levels can result in repeated miscarriages, the methylenetetrahydrofolate gene reductase (MTHFR) is not associated with a materially increased risk of thrombosis in the absence of elevated homocysteine levels (23).

Methodology

The current study is a descriptive observational type from a hospital in Colombia, and it analyzed clinical and laboratory changes as well as the classification of a cohort of Latin American pregnant women's profiles with thrombotic events as the common denominator throughout pregnancy and up until postpartum. 120 days .

The clinical records of all pregnant women without a history of saphenectomy surgery, those without an autoimmune or rheumatological disease other than primary antiphospholipid syndrome, and lastly all patients who underwent evaluation by gynecology and hematology and underwent profile studies for thrombophilia that included antiphospholipid syndrome antibodies, coagulation prot, and other markers

It was approved at meeting 027-2015 with the blessing of the institution's ethics committee, where it was conducted. Any pregnant woman who underwent follow-up from the first trimester to 12 weeks after giving birth and who did not experience fetal losses did not meet the inclusion criteria because the primary goal of the study was to evaluate venous or arterial thrombotic events rather than fetal losses. The fact that the paraclinical tests were performed on patients without anticoagulant treatment or other drugs that might have affected the results is notable.

Results

The patient sample was made up of 87 patients with the following characteristics reflected in (Table 1).

Table 1. Epidemiological and baseline conditions of the patient sample.

Variables	Values
Age	24.5 ± 7.6 years
Weeks of gestation upon admission	22.9 ± 14.5 weeks
History of thromboembolism	9 patients (10.3%)
Pharmacological management for previous thromboembolic events	5 patients (5.7%)
Previous fetal deaths on 2 or more occasions	23 patients (26.4%)

Table 2 shows the venous and arterial thrombotic alterations as well as the gestational age in the study patients.

Variables	Values
Gestational age at the time of diagnosis of the thromboembolic event	27.6 ± 8.3 weeks
venous thromboembolism	11 patients (12.6%)
arterial thromboembolism	1 patient (1.4%)

Antiphospholipid syndrome antibodies , coagulation protein C, S, Antithrombin III, mutations against factor V Leiden, mutations in MTHFR, Hyperhomocysteinemia , prothrombin mutation are presented. and finally elevation of factors VIII, IX and XI.

Variables	Values
Elevated Antiphosphatidylserine Antibodies	23 patients (26.4%)
Elevated antibodies against Beta2-Glycoprotein	20 patients (22.9%)
Positive lupus anticoagulant	16 patients (18.3%)
Low Protein C Levels	6 patients (6.9%)
Low Protein S levels	3 patients (3.44%)
Decreased antithrombin III	4 patients (4.59%)
Factor V Leiden mutations	2 patients (2.87%)
Mutations in MTHFR	0 patients (0%)
Hyperhomocysteinemia	1 patients (1.13%)
Prothrombin mutation	7 patients (8.07%)
Elevated factor VIII	13 patients (14.94%)
Elevated factor IX	15 patients (17.2%)
Elevated factor XI	12 patients (13.7%)

Finally, Table 4 shows the alterations reported in those patients who presented venous and arterial thromboembolism.

Venous thromboembolism	Alterations found
Patient 1	Antiphosphatidylserine antibodies elevated, Antibodies against Beta2, Glycoprotein elevated, Lupus anticoagulant positive, Protein C and S levels low, Factor VIII, IX, XI elevated
Patient 2	Antiphosphatidylserine antibodies elevated, Antibodies against Beta2, Glycoprotein elevated, Protein C levels low, Prothrombin mutation , Factor VIII, IX, XI elevated
Patient 3	Antiphosphatidylserine Antibodies , Antibodies against Beta2, High Glycoprotein , Prothrombin Mutation , Factor V Leiden Mutations, High Factor VIII, IX, XI, Low Protein C Levels
Patient 4	Antiphosphatidylserine antibodies elevated, Antibodies against Beta2, Glycoprotein elevated, Prothrombin mutation , Hyperhomocysteinemia , Factor VIII, IX, XI elevated
Patient 5	Antiphosphatidylserine antibodies elevated, Antibodies against Beta2, Glycoprotein elevated, Lupus anticoagulant positive, Protein C and S levels low, Factor VIII, IX, XI elevated
Patient 6	Low Protein C levels , High Factor VIII, IX, XI, Low Antithrombin III
Patient 7	Protein S levels , High Factor VIII, IX, XI, Low Antithrombin III Factor VIII, IX, XI high, Prothrombin mutation
Patient 8	Protein C levels , High Factor VIII, IX, XI,
Patient 9	Factor VIII, IX, XI elevated, Antithrombin III low, Factor VIII, IX, XI elevated
Patient 10	Antiphosphatidylserine antibodies elevated, Lupus anticoagulant , Prothrombin mutation , Factor VIII, IX, XI elevated
Patient 11	Antiphosphatidylserine antibodies elevated, Antibodies against Beta2, Glycoprotein elevated, Prothrombin mutation , Factor V Leiden mutations , Factor VIII, IX, XI elevated
Arterial thromboembolism	**Alterations found**
Patient 1	Antiphosphatidylserine antibodies elevated, Antibodies against Beta2, Glycoprotein elevated, Lupus anticoagulant positive, Prothrombin mutation , Factor VIII, IX, XI elevated, Antithrombin III low

Discussion and conclusions

A known pathogenic factor of severe pregnancy problems is thrombophilia. Modifications of procoagulant factors, which are highly prevalent mutant genes that can raise the risk of developing thrombosis, have been studied (24–25). These modifications include homozygous or heterozygous mutations in the methylenetetrahydrofolate reductase (MTHFR) gene at positions C677T and A1298C, homozygous or heterozygous mutation of the factor V Leiden (FVL) gene at position G1691

The average age at admission was 24.5 + 7.6 years, and the average gestational age in weeks was 22.9 + 14.5. Nine patients (10.3%) had a history of thromboembolism on at least one occasion, according to the study.

Thromboembolic problems were evident in a non-zero percentage of patients, and of them, 23 patients (26.4%) experienced at least one fetal loss. These results are consistent with information from investigations conducted at other latitudes (27). The gestational age was 27.6 + 8.3 weeks at the time the thromboembolic episode was diagnosed. 11 of these patients (12.6%) and 1 (1.4%) of these patients, respectively, experienced venous thromboembolism and arterial thromboembolism. These findings concur with those of prior research (28).

The most common thrombophilic hematological changes were increased antiphosphatidylserine antibodies in 23 patients (26.4%), antibodies against beta2-glycoprotein in 20 patients (22.9%), lupus anticoagulant positivity in 16 patients (18.3%), and increased factor VIII in 13 individuals. Factor XI raised in 12 patients (13.7%), Factor X elevated in 15 patients (14.94%), Factor IX up in 15 patients (17.2%), Prothrombin Mutation in 7 patients (8.07%), and the others in a lower proportion, as noted in the table and has been observed in other research (29).

According to Table 4, which lists the key variables or thrombophilic changes linked to venous and arterial thromboembolic events, 66.6% of the patients, or 8 of the 12%, fulfill Saporro and Sidney's criteria for antiphospholipid syndrome. Factor VIII, IX, in addition to those described in earlier investigations (30).

The healthy development of the placenta is associated with a successful pregnancy result. The findings in this study show that thrombophilic changes are rather common. The history is a deciding factor in underdiagnosis in pregnant women, however thrombophilic profile tests in asymptomatic women are uncommon. Future research from our location is still needed to determine whether pregnancy problems and thrombosis are equivalent.

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