Gestational Thrombophilia: Main Approaches to Diagnosis and Treatment

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Abstract

The woman's body undergoes several physiological changes during the gestational period. Risk factors and comorbidities can cause pathophysiological changes in this period, especially in the maternal vascular system, triggering thrombophilia. This clotting disorder increases the thrombus formation risk, especially in the uteroplacental circulation. The study aimed to conduct a thorough review of the main approaches to diagnosis and treatment in reducing patient morbidity and mortality. This is an integrative review with qualitative data searched in Pubmed, BVS and Cochrane Library. A total of 629 studies were found, 596 were excluded outside the inclusion criteria, and 33 were selected. According to the careful search, thrombophilias can be hereditary or acquired, the former when there is a predisposition to venous occlusion and the latter from other clinical conditions. Pregnancy is a pro-thrombotic event and increases the chances of thrombus occurrence, triggering a series of pregnancy complications, such as intrauterine death, early or late miscarriage, and premature birth. However, if diagnosed early, there is a favorable prognosis for the woman and the fetus. To reduce these impacts of gestational thrombophilia, it is imperative to train primary health care and private clinics professionals to promote and treat health and basic diagnostic tests on pregnant women. Thus, performing early intervention avoiding the development of maternal-fetal complications.

Keywords: Thrombophilia; Pregnancy; Venous Thromboembolism; Diagnosis.

1. Introduction

Gestational thrombophilia (GT) is one of the leading causes of morbidity and mortality, and it can happen during pregnancy or postpartum. For a better disease comprehension, it is necessary to understand its classification, either hereditary or acquired, which predisposes the patient to thromboembolism. Thus, hereditary alterations are due to protein C, S and antithrombin deficiency, Factor V Leiden (FVL) mutation, and prothrombin gene mutation. The acquired ones are due to an antiphospholipid syndrome, which triggers a pro-thrombotic state, leading to venous and arterial thrombosis[1,2].

Considering the classification above aspects, it is essential to point out that hereditary thrombophilia (HT) is diagnosed by the presence of a hereditary abnormality that can trigger vascular obstruction but requires interaction with another component, hereditary or acquired, to cause the thrombotic episode. In clinical analysis, the hereditary ones are expressed with venous thromboembolism (VTE). However, there are related characteristics, such as high incidence in young people with frequent recurrence, family history of thrombotic events, migratory or diffuse thrombosis or in an unusual location, and thrombotic episode disproportionately severe to the triggering stimulus[1]. It should also be added that HT is dominant autosomal and often a consequence of changes linked to physiological coagulation inhibitors and are differentiated by the deficiency of a physiological coagulation inhibitor protein (antithrombin, protein C, and protein S); Q506 mutation of the FVL gene (FV G1691A) responsible for the phenomenon of resistance to activated protein C; and G20210A mutation of the prothrombin gene that favors prothrombin synthesis[2].

Regarding acquired thrombophilia (AT), factors arising from clinical situations that lead to venous thrombosis can be highlighted, such as age, oral contraceptives, hormone replacement therapy, heparin use, pregnancy and puerperium, limb immobilization, local trauma, neoplasms, antiphospholipid antibodies, significant surgeries, infections and nephrotic syndrome[3]. In 60% of cases, this type of thrombophilia is more aggressive than the hereditary type due to the antiphospholipid syndrome. During the gestational period, the human body undergoes physiological changes that affect coagulation and the fibrinolytic system. In case of system disequilibrium, a state of hypercoagulability develops, and pregnant women are at high risk of VTE[4]. The incidence rate of VTE in pregnant women ranges from 0.6 to 1.7 cases per thousand pregnancies[5]. In addition, 50 to 60% of these thromboses occur during the puerperium[6].

In this context, the risk of VTE in pregnant women is four times higher than in nonpregnant women of childbearing age. However, there is still no scientific emphasis on integrating thrombophilia research in prenatal care[7]. Importantly, prenatal care, pregnancy, the puerperium, and the predisposition to the development of thromboembolism should be considered an inherent risk to women.

It is worth noting the high occurrence of thrombophilia in patients with gestational complications, such as intrauterine death, early or late miscarriage, and premature delivery. Thus, screening for thrombophilia is necessary for pregnant women with one or more clinical problems and a history of thromboembolism due to an apparent risk factor. For this reason, surveillance and investigation of symptoms are essential for prompt treatment initiation[8].

Facing this reality, the present paper addresses the GT theme, covering from the conceptual foundations to the fundamental attention to diagnosis and treatment, threading a vital theme for cognitive learning for medical students and medical residents in gynecology and obstetrics. Therefore, the present

study aimed to demonstrate the main approaches to early diagnosis and treatment in reducing the morbidity and mortality of patients, highlighting the pathology characteristics.

2. Methodology

This is an integrative review methodology that was chosen for a scientific investigation of qualitative data on gestational thrombophilia, along with diagnosis and early therapeutic intervention in reducing morbidity and mortality, which focused on the following steps: theme selection; literature search; selection, reading, and literature analysis; review writing and references. MeSH adopted the search strategy through the descriptors: Thrombophilia, Pregnancy, Venous Thromboembolism, and Diagnosis. This research was conducted from February to September 2021.

The electronic databases PubMed, Cochrane Library, the VHL, and university textbooks were searched for the qualitative data analysis. In addition, a combination of the keywords using the Boolean operator "AND" was employed.

As inclusion criteria, articles were selected in full, studies were written in English, Portuguese, and Spanish, titles or abstracts containing the theme "diagnosis and treatment of gestational thrombophilia" were considered. Then, 624 studies were compared and subjected to eligibility analysis, and in the end, 33 were selected. After selecting the studies, the bibliographic references of each study were analyzed and classified for the search according to the proposed theme.

3. Literature Review & Discussion

The literature findings compendium synthesizes the integrative review's qualitative data on the disease's aspects and diagnoses, the pathology's mechanism and complications, and the gestational thrombophilia treatment. Thus, 367 studies were identified in Pubmed, 14 in the Cochrane Library, 246 in the VHL, and two from the University Library. After removing duplicate articles and irrelevant studies by reading the title and abstracts, 596 studies were excluded, selecting 33 studies that met the inclusion criteria.

3.1. Disease Diagnosis

Conditions such as smoking, obesity, stasis, hypercoagulability, recent surgery, trauma or hospitalizations, and family history, such as someone in the family with deep vein thrombosis, are risk factors more prevalent in patients with the disease[9]. Another aspect that must be considered is the unawareness of the risks in performing surgeries, specifically in c-section deliveries. Moreover, the GT appearance becomes more relevant when associated with factors, such as hereditary, family history of thromboembolic events, obesity, over 35 years old, heart diseases, and c-section delivery. It is noteworthy that therapeutic intervention by anticoagulant drugs can trigger adverse reactions such as thrombocytopenia[10].

Thus, the approach in these cases should be individualized, prioritizing the type of thrombophilic defect found, past family history, and additional risk factors that specify the clinical decision regarding the implementation or not of anticoagulant therapy. Noteworthy that the investigation of thrombophilias is

paramount to analyze the impact on adverse obstetric outcomes and choose the best evidence-based intervention[11].

Also, the lack of a better diagnostic and therapeutic approach in pregnancy in patients with HT is added. Some guidelines do not support the search for serum markers for this pathology unless there is a previous personal / family history of thromboembolism. However, HT investigation in women with a history of obstetric complications is helpful in clinical management in gynecology and obstetrics services[8].

As for laboratory investigation, it should be conducted in all suspected situations of this disease, using the functional quantification of coagulation inhibitors [antithrombin (AT), protein C (PC), protein S (PS)], the plasma homocysteine quantification, mutations research (FVL and FIIG20210A) and the presence of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin IgM and IgG)[12]. Thus, it is essential to select patients for thrombophilia screening in a detailed anamnesis on the type and context of thromboembolic events in the family history evaluation since hereditary thrombophilias are autosomal dominant transmission[13].

Ultimately, the diagnosis of AT, PC, and PS deficiency is determined by the plasma concentrations of each protein by functional and immunological methods. Activated PC resistance can be diagnosed by the modified activated partial thromboplastin time (APTT) method or by identifying the FVL mutation by molecular analysis techniques, such as the FII G20210A mutation. Hyperhomocysteinemia is diagnosed by determining homocysteine plasma concentrations, usually using mass spectrophotometry or high-performance liquid chromatography (HPLC) techniques[14].

3.2. Pathology Mechanism and Complications

Thrombosis is considered a multicausal pathology, and in recent years, more profound knowledge about its etiology has been obtained, as well as several factors that contribute to its incidence. Moreover, inheritance combined with genetic factors related to thrombophilia increases the risk of thrombotic episode occurrence[15].

In the early 19th century, Virchow described the mechanisms of thrombosis and reported a state of "altered blood composition", now called the hypercoagulable state. Thrombophilia is classified as a multigenic disorder due to alterations in hemostasis that lead to an increased predisposition (genetic or acquired) of coagulation or fibrinolysis to the occurrence of thromboembolism. During pregnancy, the placenta acts as an endocrine organ that produces large amounts of hormones. These hormones are essential for a woman's bodily changes and fetal development[16].

Therefore, the increased hypercoagulability state in pregnant women is due to thrombophilias, causing thrombosis in the placental vascularization bed, inducing obstetric complications. Concomitantly, compression of the inferior vena cava by the weight of the fetus in utero contributes to the venous blood stagnation, besides favoring thrombotic phenomena, which can result in frequent fetal death episodes, repeated abortions, and premature birth caused by excessive placental thrombosis and uteroplacental vascular insufficiency[17].

Analyzing the qualitative data from the previous studies, it was verified that during the gestational period, three stages were considered that, for different reasons or combination factors, make the woman more predisposed to thrombophilia, namely: the pregnancy period itself, childbirth, and the puerperium.

Another significant aspect is the Antiphospholipid Syndrome. The syndrome acknowledgment puts into question the therapeutic strategy in pregnant women. Once in this disease, it is necessary to prevent thrombosis and mainly fetal death[18]. Recently, meta-analyses have shown an association between antiphospholipid antibodies and placental dysfunction, including the development of preeclampsia. However, no recommendations for screening for these antibodies are available in clinical practice because current clinical cases show that pregnant women with a previous history of placental insufficiency, characterized by the development of severe preeclampsia, benefit from the use of prophylactic antithrombotic therapy with acetylsalicylic acid (ASA) and sodium enoxaparin[19].

Preeclampsia, placental abruption, intrauterine growth restriction (IUGR), and intrauterine fetal death (IUFD) allow maternal and fetal morbidity and mortality. Their etiologies are unknown, but they may all be associated with abnormal placental vasculature and hemostasis disorders, leading to inadequate maternal-fetal circulation[20-26]. Given these findings, the study by Many *et al*.[27] stands out, the research compared placental pathology among 68 women with and without thrombophilia who had severe preeclampsia, severe placental abruption, or stillbirth. The result reveals 32 thrombophilic women (group 1) and 36 nonthrombophilic women (group 2). The authors report that gestational age at delivery, birth weight, and placental weight were significantly lower in group 1. In the study, it was observed that the group of thrombophilic women had a higher number of infarcts in the placental villi ($P<0.01$), more multiple infarcts ($P<0.05$), and a higher incidence of placentas with fibrinoid necrosis of the decidual vessels ($P<0.05$). Thus, placentas with severe complications and women with thrombophilia have increased rates of placental vascular injury. Thus, this pathology is of particular concern in this condition, contributing to fetal or postpartum death.

As far as placental histology and thrombophilia status is concerned, the research of Mousa and Alfirevic[28] should be included. Seventy-nine women were studied with the same problems as mentioned earlier. 30 of 43 women with thrombophilia had abnormal placental histology. 28 of 36 women with negative thrombophilia had abnormal placentas. The placental histology reports were examined to identify the frequency of thrombotic lesions in the placenta, including fetal trunk vessel thrombosis, fetal thrombotic vasculopathy, placental infarction, perivisceral fibrin deposits intervillous thrombosis, and placental floor infarction. However, no specific histological pattern could be identified when the positive and negative thrombophilia groups were compared. The authors suggest a weak correlation between thrombophilia status and pathological changes in the placenta in women with severe pregnancy complications. Similarly, various microscopic abnormalities have been reported in early-onset preeclampsia and renal glomerular filtration (RGF) in women with and without thrombophilia. However, a high rate of placental abnormalities was found[29].

Arias *et al*.[30] evaluated 13 women with thrombotic placental lesions. All pregnant women had complications such as preeclampsia, preterm delivery, IUGR, or stillbirth. In 10 of 13 women, hereditary thrombophilias were found; 7 were heterozygous for the FVL mutation, and 3 had protein S deficiency. Fetal trunk vessel thrombosis, infarcts, hypoplasia, spiral artery thrombosis, and perivisceral fibrin deposits were observed in the study.

3.3. Thrombophilia Treatment

VTE treatment is done with HSA, unfractionated heparin (UFH), and low molecular weight heparin (LMWH) in gestation. The first recommendation will be used in the impossibility of using LMWH. This process by heparins acts immediately when connected to antithrombin III and cofactor II, while APTT and LMWH control the UFH by the anti-Xa factor[31]. It is important to note that UFH and LMWH do not harm the fetus as they do not pass through the placental barrier; however, some maternal complications may occur, such as prolonged UFH use, causing osteoporosis, and thrombocytopenia, bleeding, and allergy. Despite studies showing low rates of expected adverse effects, LMWH experience in obstetrics remains limited[31].

The prophylaxis protocol for pregnant women with thrombophilia is to use it in the second phase of the menstrual cycle whenever there is a possibility of pregnancy conception and to continue until pregnancy confirmation. In the absence of prophylaxis, if conception occurs, it should be started as early as possible. Based on this, for the use of prophylactic anticoagulation, therapeutic anticoagulation should be used in pregnant women who present thromboembolic episodes up to thirty days before the last menstrual period or at any time during the gestational period[32].

Hence, it is crucial to have a weekly blood platelet count in the first three months of anticoagulation in pregnant women taking heparin once it aims to detect possible thrombocytopenia[33].

4. Conclusion

Thrombophilia has become increasingly common in pregnant women. Epidemiological factors, like heredity, previous involvement history, and comorbidities (hypertension, diabetes mellitus, obesity) are risk factors for disease progression.

Concerning therapy, whether replacement or hormonal contraceptive, both in women without risk and in those at risk and with a history of thrombophilia, the anamnesis should be careful, the proper route of administration and the correct choice of hormones for the treatment. Thus, prophylactic and therapeutic guidelines are recommended during prenatal care, pregnancy, and the puerperium.

In order to improve the research and primary and secondary thrombosis prevention in women with personal and family history, it is suggested the implementation of health programs for the prevention of thrombophilia, as well as the professional training for specific treatments and diagnostic tests during prenatal, pregnancy, and postpartum periods, ensuring the initial detection and early intervention, besides promoting health and lower morbidity and mortality in women, therefore avoiding the development of maternal-fetal complications.

Conflict of Interest

The authors declare no conflict of interest.

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