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REVIEW

Acquired Hemophilia during Pregnancy and Postpartum

Hemofilia Adquirida durante el embarazo y postparto

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ABSTRACT

Hemophilia is a genetic disorder that affects blood clotting. Acquired hemophilia A is a bleeding disorder mediated by an autoimmune process, in which antibodies against coagulation factor VIII develop, presenting during pregnancy and postpartum as a cause of obstetric hemorrhage. A literature review was conducted to characterize acquired hemophilia during pregnancy and postpartum. Journals and websites such as SciELO were used, for a total of 21 references, with 76,1 % updated. The disease is characterized by severe bleeding and large ecchymoses on the trunk and extremities. Hormonal changes during pregnancy significantly alter the balance of hemostasis, with the existence of hypercoagulability secondary to an inflammatory state. The clinical picture of acquired hemophilia associated with pregnancy has some characteristics that need to be studied, as well as during the postpartum period.

Keywords: Acquired Hemophilia; Pregnancy; Postpartum; Coagulation Factor VIII.

RESUMEN

La hemofilia es una enfermedad genética que afecta a la coagulación sanguínea. La hemofilia A adquirida es un trastorno hemorrágico mediado por un proceso autoinmune, en el que se desarrollan anticuerpos contra el factor VIII de la coagulación, con presentación durante el embarazo y el postparto como causa de hemorragia obstétrica. Se realizó una revisión bibliográfica con el objetivo de caracterizar la hemofilia adquirida durante el embarazo y postparto. Se utilizaron revistas, páginas web de sitios como SciELO, para un total de 21 referencias, con 76,1 % de actualización. La enfermedad se caracteriza por hemorragias graves y grandes equimosis en el tronco y las extremidades. Los cambios hormonales del embarazo alteran de forma considerable el equilibrio de la hemostasia con existencia de hipercoagulabilidad secundaria a un estado inflamatorio. El cuadro clínico de la hemofilia adquirida asociada al embarazo tiene algunas características que es necesario estudiar, al igual que durante el postparto.

Palabras clave: Hemofilia Adquirida; Embarazo; Postparto; Factor de Coagulación VIII.

INTRODUCTION

In 1803, John C. Otto discovered the genetics of hemophilia A. He found that mothers with no bleeding problems could pass hemophilia on to their sons, and their daughters could pass it on to their grandsons and great-grandsons. He traced the family history he studied to a woman named Smith.

In 1928, Dr. Hopff described the disease for the first time using the word hemophilia. In 1944, Dr. Alfred Pavlovsky succeeded in differentiating between the two types of hemophilia, A and B.[1]

Classic hemophilia is an inherited bleeding disorder caused by a deficiency or decrease in the concentration of either factor VIII or factor IX. This is usually associated with bleeding problems from an early age, and joint bleeding is a typical feature. Like color blindness, the inheritance of hemophilia is linked to sex, so males are predominantly affected by the severe form of hemophilia, which is transmitted by female carriers, who generally do not have significant bleeding problems.[2]

Acquired hemophilia A (AHA) is a bleeding disorder mediated by an autoimmune process in which antibodies develop against coagulation factor VIII, presenting as sudden and severe bleeding in patients with no previous history of coagulopathy. This impairs hemostatic function and presents with bleeding manifestations, which can potentially be life-threatening. Although it is more prevalent in elderly male patients, it can also occur in young women during pregnancy and postpartum or in women with autoimmune diseases. [3]

According to the Dictionary of the Royal Spanish Academy, pregnancy is the period between the egg's fertilization by the sperm and the moment of delivery.[4]

Pregnancy, the nine months during which the fetus develops in the woman's uterus, is a period of great happiness for most women. However, during pregnancy, both the woman and her unborn child face various health risks. For this reason, qualified healthcare professionals must monitor pregnancy.[5]

The postpartum period, also known as the puerperium, can be defined as the period from the end of childbirth to six weeks after delivery when the female body returns to normal.[6]

According to global statistics, acquired hemophilia is fatal for one in five patients who suffer from it. It has a global incidence of 1,5 cases per million per year. The average age of onset is 74 years for men and women and 34 years for women in the postpartum period. Between 2 % and 15 % of cases are associated with pregnancy.[7] According to the 2017 Annual Global Survey, Brazil was the country in the Americas with the highest number of patients, with 10,395. In that year, Cuba reported 400 cases.[8]

At the time of diagnosis, more than 90 % of bleeding episodes are severe and require hospitalization.[9] For this reason, acquired hemophilia must be recognized early and diagnosed quickly to allow treatment of the bleeding, avoiding potentially dangerous invasive procedures while seeking to eradicate the inhibitor.[10]

1983 the National Maternal and Child Care Programme (PAMI) was implemented. This is a centralized program platform run by the Ministry of Public Health to plan, organize, implement, and monitor regulations related to reproductive health throughout the country, childhood, and adolescence, in line with the analysis of the health situation at the local level and with an emphasis on ensuring equitable access to health care. This program continues to work systematically on actions that align with this mandate.[10]

As a priority strategy of the PAMI, the Programme for the Reduction of Maternal Morbidity and Mortality was updated in 2012. Although maternal mortality has declined since 1990 and remains stable at around 40 per 100 000 live births, it is still a cause for concern for the Cuban health authorities. The most common causes are severe hemorrhages (postpartum or due to ectopic pregnancies), infections, spontaneous abortions, and gestational hypertension (pre-eclampsia).[10]

Acquired hemophilia is a cause of obstetric hemorrhage where a delay in diagnosis constitutes a risk of fatal bleeding, but if identified early, the prognosis can be encouraging. It was, therefore, essential to carry out this research, as all knowledge on the subject helps ensure comprehensive maternal care from the training stage onwards and optimize outcomes.

Objective: To characterize acquired hemophilia during pregnancy and postpartum.

DEVELOPMENT

Coagulation factors are a group of proteins responsible for activating the coagulation process, which acts in a cascade, i.e., one activates the next; if one is deficient, coagulation does not occur or is significantly delayed. As a result, the blood is inconsistent and does not form a good clot to stop the bleeding. In severe hemophiliacs, even minor injuries can lead to profuse and even fatal blood loss.[11]

Haemophilia A is a genetic bleeding disorder caused by a missing or defective clotting protein called factor VIII. It is also called classic hemophilia or factor VIII deficiency. In rare cases, it is not inherited but is caused by an abnormal immune reaction within your body.[12] Unlike congenital hemophilia, which only affects men, acquired hemophilia can occur in both men and women. Causes include autoimmune disorders, malignant diseases, certain medications, or pregnancy. In most cases, it affects middle-aged or older people or young women who have just given birth or are in the last stage of pregnancy.[13]

According to Ochoa Marieta C.[2], people with hemophilia are mainly male, but García-Chávez J.[14] states that the groups with the highest incidence are women of childbearing age.

It is characterized by severe bleeding, especially after trauma and expected delivery or cesarean section, and large bruises on the trunk and extremities.[14]

The rate of association with pregnancy is 2 to 21 %.[15] It occurs most frequently after the first delivery, in the

EACH2 registry (Pregnancy-associated acquired hemophilia A: results from the European Acquired Haemophilia registry), in which 42 women were evaluated, acquired hemophilia was associated with the first pregnancy in 31 (74 %), with the second in 7 (17 %) and with the third and fourth pregnancies in two women each (5 %).[16]

Pathophysiology of acquired hemophilia

Factor VIII is a protein with a molecular weight of 265 kDa, and its sequence is composed of amino acids grouped into domains A1-A2-B (heavy chains)-A3-C1-C2 (light chains). Domains A2 and A3 have binding sites for factor IXa, while domain C2 binds to von Willebrand factor and binds factor VIII to the phospholipid membrane.[15]

The autoantibodies formed in acquired hemophilia are of the IgG class, mostly IgG1 and IgG4 subclasses, which are directed against domains A2, A3, and C2 of the factor VIII molecule, interfering with its binding to factor IXa, subsequently causing the deregulation of factor VIII binding to von Willebrand factor, leaving factor VIII vulnerable to enzymatic degradation, which results in the inhibition of the activity of that factor, affecting secondary hemostasis carried out by the binding of factor VIII to von Willebrand factor.[12,15]

CD4+ T cells play an essential role in the humoral response to factor VIII, which depends on a complex interaction between CD4+ T cell subsets, Th1 (stimulates B cells to produce IgG1 and IgG2 antibodies) and Th2 (stimulates B cells to produce IgG4 antibodies). The predominance of Th2 anti-factor VIII antibodies correlates with a more intense response and higher inhibitor titers, while the predominance of Th1 correlates with a greater response to immunosuppressive therapy.[15]

The combination of environmental and genetic factors leads to immune tolerance failure and causes the development of antibodies against factor VIII; specific class II HLA and cytotoxic T lymphocyte antigen (CTLA-4) polymorphisms have been observed with high frequency.[15]

Acquired coagulation defects may be associated with thrombocytopenia or hemostasis defects. The leading causes are pregnancy-related disorders (pre-eclampsia, HELLP syndrome, premature detachment of a typically inserted placenta, sepsis, and surgical site hemorrhages).[15]

Causes of obstetric hemorrhage include uterine atony, retained placental tissue, instrumental delivery, placenta accreta, and laceration of the birth canal. Less common causes include coagulation disorders, such as von Willebrand disease and congenital or acquired hemophilia A; the latter should be suspected if there is a normal platelet count, normal prothrombin time with prolonged activated partial thromboplastin time that is not corrected with plasma.

Hormonal changes during pregnancy significantly alter the balance of hemostasis, especially secondary hypercoagulability due to an inflammatory state. Hypercoagulability is associated with increased procoagulant coagulation factors, decreased fibrinolytic activity, and reduced coagulation inhibitors.[17]

The main changes in coagulation include decreased venous tone, reduced blood flow, mechanical obstruction of the pregnant uterus, venous stasis in the lower limbs due to compression of the inferior vena cava and pelvic venous plexus, and increased prostacyclins, estrogens, and nitric oxide.[9,15]

Biochemical changes include increased fibrinogen and coagulation factors VII, VIII, IX, X, and Von Willebrand (activity of these factors increases by 1,000 %). Specific molecular complexes that form during this process, such as increased soluble fibrin complexes, thrombin-antithrombin complexes, and increased prothrombin fragments, are considered markers of coagulation activation. During pregnancy, alterations have been found in coagulation inhibitor molecules, such as proteins C and S, which are vitamin K-dependent fibrin degraders synthesized in the liver. Protein C is activated by thrombomodulin, which causes a conformational change in thrombin, which activates protein C, which binds to its cofactor protein S and inactivates factors Va and VIIIa, promoting the inhibition of plasminogen activator and finally fibrinolysis. Prekallikrein increases to twice the level found in non-pregnant women and decreases at the onset of labor with an increase in kallikrein.[9,15]

There are also changes in platelets during pregnancy, such as increased platelet aggregation, increased prostacyclins (PG12) synthesized in the vascular wall of maternal and fetal vessels, causing platelet anti-aggregation and vasodilation, a reduction in the response of adenylate cyclase from the third month of gestation, which causes a decrease in cyclic AMP and promotes platelet activation, which in turn is due to an increase in thrombomodulin and thromboxane A2, idiopathic thrombocytopenia due to haemodilution and consumption. Among the changes in the fibrinolytic mechanism, we find an increase in plasminogen activator inhibitors 1 and 2, a decrease in tissue plasminogen activator, and an increase in D-dimer. All of this contributes to a state of hypercoagulability.

The clinical picture of pregnancy-associated acquired hemophilia has some characteristics that should be highlighted. The symptoms can be highly heterogeneous, both in their presentation and identity. One study reported that hemorrhages were always moderate or severe and that half of the episodes had no clearly defined trigger and were therefore described as spontaneous. It has been reported that up to 75 % of women with pregnancy-associated acquired hemophilia are primigravida. Bleeding is almost always subcutaneous, mucosal, or retroperitoneal; haemarthrosis is rare. A relatively better prognosis characterizes acquired hemophilia associated with pregnancy, as spontaneous remissions may occur, and the mortality rate is lower than in other

forms (up to 6 %). Even maternal autoantibodies (auto-Ac) may disappear without treatment.

With adequate prenatal monitoring, it is possible to diagnose acquired hemophilia using activated partial thromboplastin time (aPTT) as part of preoperative testing or if mild bleeding occurs by assessing whether aPTT is prolonged in isolation. There are cases of in-utero transfer of the inhibitor to the product, although bleeding in the child is unusual. When the product clears the maternal auto-Ac, the clinical picture disappears if it has appeared; there is no possibility of this problem returning. The most effective way to monitor the child is with APTT, which shortens until normalization in a maximum of six weeks.

During the immediate postpartum period, platelet concentrations increase, PAI 1 decreases, and antithrombin III and protein C and S increase, normalizing by the fifth week postpartum. In the late postpartum period, coagulation and fibrinolysis factors begin to normalize.[15]

Massive blood loss after delivery is recognized as the most common life-threatening condition in women. Several risk factors predispose women to postpartum hemorrhage, including hematological diseases such as hemophilia, von Willebrand disease, and platelet function defects. Deficiencies of coagulation factors VIII, IX, and XI are also rarely found, as are coagulation disorders such as dysfibrinogenemia, hypofibrinogenemia, and deficiency of prothrombin and factors V, VII, X, and XII.[19]

The research team believes that invasive diagnostic procedures or treatments (including venipunctures or catheterization) should be minimized, as they can worsen bleeding.

Although delayed diagnosis can be fatal, postpartum HAA responds well to procoagulant and immunosuppressive treatment and has a better prognosis than other causes of hemophilia A. For this reason, in the presence of symptoms such as uncontrollable metrorrhagia without an obstetric cause and signs such as abnormal coagulation tests, we should suspect this disease and perform diagnostic tests to confirm the diagnosis so that symptomatic and etiological treatment can be started without delay.

Postpartum-acquired hemophilia occurs most frequently in primiparous women, beginning with hemorrhagic complications in the postpartum period, which can develop up to 12 months after delivery. Hemorrhagic manifestations range from mild bleeding from skin wounds to large subcutaneous and muscular hematomas and even episodes of life-threatening systemic hemorrhage. However, most are oligosymptomatic, presenting postpartum metrorrhagia as the only symptom. In these cases, it is essential to have a high index of suspicion of postpartum-acquired hemophilia since the non-specific symptoms can lead to a delay in diagnosis and pose a significant risk to the patient.

The treatment of acquired hemophilia during pregnancy and postpartum aims to reduce bleeding and increase factor VIII concentrations, decrease factor VIII inhibitor concentrations, and autoantibody VIII production. First-line antihaemorrhagic treatment involves administering recombinant factor VIIa concentrate (90-120 g/kg every three hours) and prothrombin complex concentrate. Plasmapheresis and extracorporeal immunoadsorption may be indicated as alternatives. Prothrombin complex concentrates combine coagulation factors X and VII that regulate the intrinsic coagulation pathway. First-line treatment is based on the administration of bypass or regulatory agents, the prototype being the factor VIII inhibitor regulatory agent (FEIBA) 75 U/kg every 8 to 12 hours, and recombinant activated factor VIII, which stimulates the coagulation cascade. Side effects such as heart attack, thrombosis, or disseminated intravascular coagulation have been reported.[15]

The research team believes treatment should be based on correcting the hemostasis disorder and eliminating the inhibitor, for which steroids and other immunosuppressive drugs (cyclophosphamide, azathioprine, cyclosporine) are used.

If first-line treatments are unavailable, porcine factor VIII is administered, but its disadvantage is adverse reactions, such as allergies and anaphylaxis.[21]

Another alternative is plasmapheresis, or administration of high doses of human factor VIII, which concentrates on cases of poor response to the above drugs. Treatment aimed at reducing factor VIII inhibitor concentrations involves immunosuppressive drugs such as corticosteroids, cyclophosphamide, azathioprine, and intravenous immunoglobulin G. The administration of vincristine, cyclosporine, and mofetilmicofenolato has produced good results. Treatment with prednisone and cyclophosphamide is the first line of treatment. In resistant patients, rituximab (anti-CD20), a B-cell antigen, can be administered, producing selective elimination of these cells through cellular cytotoxicity and apoptosis. However, no significant difference has been found when comparing prednisone with cyclophosphamide or rituximab. When first-line treatments fail, rituximab has shown promising results, becoming a first-line drug.[15,20,21]

Cafasso J.[12] states that Treatment involves replacing the missing clotting factor through transfusions. Factor VIII can be obtained from blood donations but is now usually created artificially in a laboratory. This is called recombinant factor VIII; however, García-Chávez J.[14] states that the first line of treatment should be the administration of recombinant porcine factor VIII.

The research team believes that despite being a rare disorder, all pregnant women and women who have recently given birth should be closely monitored to avoid complications.

CONCLUSIONS

Haemophilia A is a genetic bleeding disorder caused by a missing or defective clotting protein called factor VIII. It is characterized by severe bleeding, especially after trauma and normal or cesarean delivery, and large bruises on the trunk and limbs. The clinical picture of acquired hemophilia associated with pregnancy has some characteristics that need to be studied, as in the postpartum period.

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