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Hyperhomocysteinemia and Pregnancy: About a Case and Literature Review

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Abstract:- Homocysteine (Hct) is a substance produced in the metabolism of methionine that can be found in our daily diet. The mutation of the methylenetetrahydrofolate reductase gene, especially for women with low folate intake. Hyperhomocysteinemia (HHct) can be due to several factors, such as a lack of folic acid, a deficiency in vitamins B6 and B12, hypothyroidism, medications, genetic anomalies, aging, and renal dysfunction. Increased homocysteine levels in peripheral blood can lead to vascular diseases, coronary artery dysfunction, atherosclerotic changes, and embolic diseases. As a result, increased thrombogenicity in pregnant women upstream of the trophoblast plug, leading to clot formation and early or late abortion. Recent studies have reported that hyperhomocysteinemia is associated with many pregnancy complications, including abortive disease, pre-eclampsia, premature delivery, retroplacental hematoma, fetal growth restriction, and gestational diabetes. Therefore, to prevent thrombosis, treatment relies on anticoagulants, sometimes combined with low-dose aspirin, especially for its anticoagulant effect. In this article, we report a case of a patient with a history of abortive disease on hyperhomocysteinemia who had a full-term pregnancy, while reminding the metabolism of homocysteine, its impact on pregnancy, and the interest in prescribing folic acid to avoid complications related to hyperhomocysteinemia.

Keywords:- *Hyperhomocysteinemia, Pregnancy, Abortive Disease, Thrombophilia.*

I. INTRODUCTION

Homocysteine is a sulfur-containing amino acid that is an intermediate step in the cellular metabolism of the essential amino acid methionine. However, most homocysteines are remethylated into methionine. This is through an enzyme-catalyzed synthesis of S-adenosylmethionine, the major methyl donor involved in many biochemical reactions (DNA, protein, neurotransmitter, hormone, synthesis of phospholipids, etc.)(Figure 1). The MTHFR gene mutation is linked to elevated total homocysteine levels, especially for women with a folate deficiency [1]. The MTHFR gene polymorphism is a major cause of hyperhomocysteinemia [2]. Folate, along with vitamins B12 and B6, has a significant impact on Hct function [3]. Many factors are the cause of hyperhomocysteinemia, including genetic abnormalities, folate deficiency, a deficiency in vitamins B6 and B12, hypothyroidism, medications, aging, and renal dysfunction [4]. Increased homocysteine levels in peripheral blood can lead to vascular diseases [5], coronary artery dysfunction, atherosclerotic changes [5], and embolic diseases [6]. The Hct rate is lower during pregnancy compared to normal values [7]. The Hct dose tends to drop in the first trimester; it reaches its lowest value in the second trimester; subsequently, it regularly increases towards the end of pregnancy until it reaches the beginning of pregnancy level [8]. Hyperhomocysteinemia reduces the nitric oxide released by the vascular endothelium, causing the formation of a thrombosis, which in turn affects placental perfusion [9], and can therefore have an impact on pregnancy; it can be responsible for an abortive disease, preeclampsia, preterm delivery threat, retroplacental hematoma, and intrauterine growth restriction [9]. The objective of this review is to address the importance of hyperhomocysteinemia research and its complications in pregnant women by reporting the case of a patient with a history of an abortive disease who carried a pregnancy to term after folate supplementation and anticoagulation.

II. OBSERVATION AND CLINICAL CASE

A 36-year-old patient with blood group A positive, with a history of abortive illness with 7 spontaneous non-aspirated and non-cureted miscarriages in the first trimester and a high vaginal delivery at 7 months for retroplacental hematoma in the context of pre-eclampsia of a newborn who died on day 2 of life due to respiratory distress. During the follow-up of her abortive illness, the patient underwent a comprehensive evaluation that showed hyperhomocysteinemia without other biological anomalies; she consulted in our facility with a ninth pregnancy estimated at 12 weeks of amenorrhea where an ultrasound was performed showing a singleton pregnancy evolving correspond to gestational age without trophoblastic detachment. The patient was seen in prenatal care on a monthly basis and was placed throughout the pregnancy on progestative combined with antiplatelet therapy with low-molecular-weight heparin-based therapy with Lovenox 0.4 per day associated with vitamin supplementation. A prenatal assessment was requested and showed gestational diabetes on 75g OGTT, therefore she was placed on diet alone with good glycemic control. The patient had good blood pressure readings throughout the pregnancy without notable uterine bleeding. A prophylactic cesarean was scheduled at 39 weeks of amenorrhea, the clinical examination on the day of the high vaginal delivery showed a patient in good general condition with normal blood pressure, apyretic, with correct uterine height of 32 cm. The speculum examination showed a

healthy-looking cervix without notable bleeding. The prophylactic high vaginal delivery allowed the head extraction of a male newborn with an Apgar score of 10, birth weight of 3200 grams, received by the pediatrician. The postoperative period was simple for both the mother and the newborn.

III. DISCUSSION

Although the mechanisms of vascular changes associated with hyperhomocysteinemia are not yet fully understood, animal studies have allowed us to provide specific details [10]. In the case of endothelial changes, the effects mainly occur at the level of the vessel wall [11]. The lesions observed consist of vascular fibrosis and dysfunction of the endothelial cells. Vascular endothecia are predisposed to vacuolation and desquamation, exposing the subendothelial tissue and activating thrombus formation. Homocysteine decreases in the first trimester of pregnancy, reaches a minimum in the second trimester, and increases somewhat to reach initial levels during term [12]. Consequently, searching for homocysteine during pregnancy is difficult. On the other hand, it is possible to search for mutations in CBS or MTHFR genes during pregnancy.

Inherited thrombophilia and hyperhomocysteinemia, or a combination of both, may be responsible for recurrent miscarriage, with a genetic susceptibility to venous thrombosis [13]. A third of abortive illnesses are due to hyperhomocysteinemia [13], as is the case in our patient. A deficiency in vitamin D and folates could raise the level of homocysteine by reducing the enzyme involved in its metabolism. The MTHFR genotype can double or triple the morbidity of fetal losses [14]. Maternal genetic mutations cause renal embolic disease or heart disease. However, it may not have the same adverse effects on placental circulation early in pregnancy [9]. Quere reports the case of a patient who had 2 fetal losses at 28 and 26 weeks of amenorrhea and three early miscarriages, the only anomalies in the etiological balance were hyperhomocysteinemia and the MTHFR gene mutation [15]. A prescription of folic acid and vitamin B6 during subsequent pregnancies allowed this patient to have a living child, and this is almost the case of our patient who was able to carry a term pregnancy after having seven fetal losses.

Recent studies have reported that homocysteine levels in women with pre-eclampsia are increased compared to normotensive pregnant patients [16]. However, a significant difference in its levels between patients with PE and non-pregnant women was not found [17], which suggests that hyperhomocysteinemia in PE is due to changes in blood volume rather than a MTHFR gene mutation [17]. Several studies aim to determine if hyperhomocysteinemia can be used to predict the risk of pre-eclampsia [18]. High homocysteine levels were detected in the first or second trimesters of pregnancy, but could not be directly linked to pre-eclampsia. The reason for the high homocysteine level in early pregnancy could be due to the alteration of vascular endothelial cells at the beginning of pregnancy. As this lesion worsens, leading to placental ischemia, ultimately resulting in pre-eclampsia [19]. On the other hand, homocysteine levels during the second trimester do not help predict the risk of pre-eclampsia in women with chronic hypertension during pregnancy [20]. Homocysteine levels in patients with retroplacental hematoma were significantly higher than in patients with normal pregnancies [21]. A comparative retrospective case-control study of patients with retroplacental hematoma compared to other patients who had normal pregnancies without any signs or symptoms of metrorrhagia showed an elevation of homocysteine levels in patients with retroplacental hematoma [22]. However, in other studies, authors revealed that hyperhomocysteinemia was not necessarily associated with a retroplacental hematoma [23]. In our patient, blood pressure was correct throughout the pregnancy without detectable signs of abnormal bleeding.

Among the actions of homocysteine on endothelial cells is vascular obstruction, which can cause premature birth. However, the prevalence of decidual angiopathy is not significantly related to premature birth. A association between neurological malformations and hyperhomocysteinemia has been described in literature. In fact, AFTN is not due to a direct effect of homocysteine, but to a dysfunction of methionine synthase (MS), a key enzyme in remethylation and also involved in the synthesis of the basic protein of myelin. Hyperhomocysteinemia can impact amino acid transfer in the placenta, which could cause intrauterine growth restriction. Some authors reveal that compared to normal pregnancies, homocysteine levels are higher in patients who have had pregnancies with intrauterine growth restriction, which could be due to damage to endothelial cells that can cause alteration of uterine and placental blood flow. In our patient who had a full-term pregnancy, the birth weight was eutrophic, it seems premature to retain a direct impact of hyperhomocysteinemia on fetal growth. Hyperhomocysteinemia is a congenital thrombophilia, just like antithrombin deficiency, protein C or protein S deficiency, resistance to activated protein C (due to mutations in the Leiden gene V) and factor II mutations. Pregnancy itself is a thrombosis risk factor. Therefore, the association between hyperhomocysteinemia and pregnancy represents a high thromboembolic risk situation. The prescription of anticoagulants in addition to vitamin therapy to patients is even advised once congenital thrombotic trends have been identified. In our case, this prophylaxis consisted of treatment with calciparine at the beginning of pregnancy, low molecular weight heparin at the end of pregnancy, then resumption of calciparine at the end of pregnancy, during childbirth and 1 month after childbirth.

IV. CONCLUSION

The activity of homocysteine during normal pregnancies and its impact is a widely debated topic. According to literature, homocysteine levels are not constant during pregnancy. The genetic polymorphisms associated with hyperhomocysteinemia and its metabolism are clearly associated with complications during pregnancy. However, clinical trials aimed at demonstrating this require a lot of resources. High-dose folic acid supplementation during pregnancies can help women suffering from complications due to hyperhomocysteinemia.

Conflicts of interest: The authors declare no conflicts of interest.

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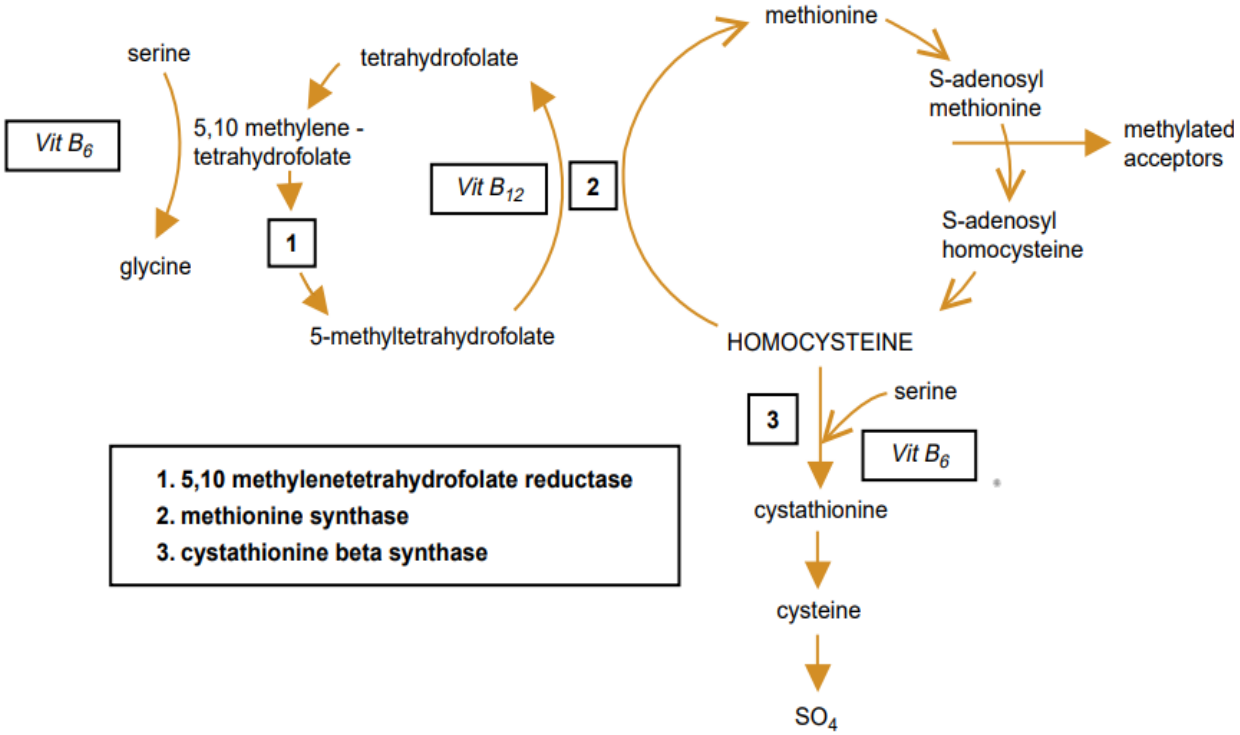

Figure 1. Metabolic pathways of homocysteine.