

## Hyperhomocysteinemia and Pregnancy: About a Case and Literature Review

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### Abstract

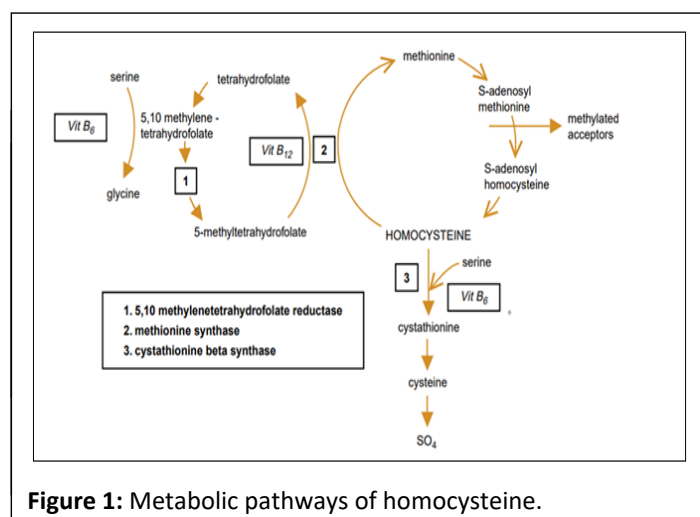
Homocysteine (Hct) is a substance produced in the metabolism of methionine that can be found in our daily diet. Mutation of the methylenetetrahydrofolate reductase gene, especially for women with low folate intake. Hyperhomocysteinemia (HHct) can be caused by several factors, such as lack of folic acid, vitamin B<sub>6</sub> and B<sub>12</sub> deficiency, hypothyroidism, medications, genetic abnormalities, aging and kidney dysfunction. Increased homocysteine in peripheral blood can lead to vascular disease, coronary artery dysfunction, atherosclerotic changes and embolic disease. Hence, increased thrombogenic activity in pregnant women upstream of the trophoblast plug resulting in clot formation and either early or late abortion. Recent studies have reported that hyperhomocysteinemia is associated with numerous pregnancy complications, including abortion disease, preeclampsia, preterm birth, hematoma placentae, fetal growth restriction and gestational diabetes. Thus, to avoid thrombosis, treatment is based on anticoagulants, sometimes combined with low-dose aspirin, especially for its anticoagulant effect. In this article, we report the case of a patient with a history of abortive disease on hyperhomocysteinemia who carried a pregnancy to term, while recalling the metabolism of homocysteine, its impact on pregnancy and the interest of prescribing the folic acid to avoid complications related to hyperhomocysteinemia.

**Keywords:** Hyperhomocysteinemia; Pregnancy; Abortion disease; Thrombophilia

### Introduction

Homocysteine is a sulfur amino acid which is an intermediate step in the cellular metabolism of the essential amino acid methionine. However, most homocysteines are remethylated to methionine. It is by an enzymatic route of synthesis of S-Adenosylmethionine, a major methyl donor involved in numerous biochemical reactions (DNA, protein, neurotransmitter, hormone, synthesis of phospholipids, etc.) (Figure 1). Mutation of the MTHFR gene is linked to elevated expressions of total homocysteine, especially in women with

folic acid deficiency [1]. Polymorphism of the MTHFR gene is a major cause of hyperhomocysteinemia [2]. Folic acid along with vitamins B<sub>12</sub> and B<sub>6</sub> have a strong impact on the functionality of Hct [3]. Many factors cause hyperhomocysteinemia, including genetic abnormalities, folic acid deficiency, vitamin B<sub>6</sub> and B<sub>12</sub> deficiency, hypothyroidism, medications, aging and kidney dysfunction [4]. Increased peripheral blood homocysteine can lead to vascular disease [5], coronary artery dysfunction, atherosclerotic changes [5] and embolic disease [6]. The Hct level is lower during pregnancy compared to its normal values [7]. The Hct dosage tends to drop in the first trimester; it reaches its lowest value during the second trimester; thereafter, it increases steadily at the end of pregnancy until it reaches the level at the beginning of pregnancy [8]. Hyperhomocysteinemia reduces the nitric oxide released by the vascular endothelium, which will cause the formation of thrombosis, which in turn will affect placental perfusion, consequently it can have an impact on pregnancy; and may be responsible for an abortive disease, preeclampsia, threat of premature delivery, retroplacental hematoma, intrauterine growth restriction [9]. The aim of this review is to address the importance of the search for hyperhomocysteinemia and its complications in pregnant women by reporting the case of a patient with a history of abortive disease that carried a pregnancy to term after folic acid supplementation and put on anticoagulant.



## Observation and Clinical Case

36-year-old female patient, group a positive, with a history of abortive disease with 7 spontaneous unassisted and uncorrected losses in the first trimester and a delivery by high route at 7 months for retroplacental hematoma in a context of preeclampsia of a newborn died on day 2 of life for respiratory distress. During the follow-up of her abortive disease, the patient benefited from a complete assessment having objectified a hyperhomocysteinemia without other biological anomaly; she consulted in our training with a ninth pregnancy estimated at 12 weeks of amenorrhea where an ultrasound was performed showing an evolving monofetal pregnancy corresponding to the gestational age without trophoblastic detachment. The patient was seen in prenatal consultation on a monthly basis and was placed throughout the pregnancy on a progestogen associated with an antiplatelet agent with heparin therapy based on lovenox 0.4 per day associated with vitamin supplementation. A prenatal check-up was requested having objectified gestational diabetes on OGTT at 75 g, hence his diet alone with correct glycemic cycles. Knowing that the patient kept correct tendon figures throughout the pregnancy without significant uterine bleeding a prophylactic cesarean section was scheduled at 39 weeks of amenorrhea. The clinical examination on the day of the upper route objectified a patient in good condition general normotensive afebrile correct uterine height at 32 cm speculum examination showed a healthy-looking cervix with no noticeable bleeding. The high prophylactic way allowed the cephalic extraction of a newborn male with an apgar score of 10 births weight 3200 grams received by the pediatrician. The suites are simple for the mother and the newborn.

## Results and Discussion

Although the mechanisms of the 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 occur mainly at the level of the vessel wall [11]. The lesions observed consist of vascular fibrosis and endothelial cell dysfunction. Vascular endothelia are prone to vacuolation and desquamation, exposing 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 baseline levels during term [12]. Therefore, finding homocysteine during pregnancy is difficult. On the other hand, it is possible to look for mutations in the CBS or MTHFR genes during pregnancy.

Hereditary thrombophilias and hyperhomocysteinemia, or a combination of the two, may be responsible for recurrent loss, with a genetic susceptibility to venous thrombosis [13]. A third of abortive diseases are due to hyperhomocysteinemia, as is the case in our patient. A deficiency in vitamin D and folate 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 loss [14]. Maternal genetic mutations cause embolic kidney disease or heart disease. However, it may not have the same adverse effects on placental circulation in early

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 abnormalities of the etiological assessment were hyperhomocysteinemia and the mutation of the MTHFR gene [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 with our patient who was able to carry a pregnancy to term after having had seven fetal loss.

Recent studies have reported that homocysteine expression levels in women with preeclampsia 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, implying hyperhomocysteinemia in PE is the change in blood volume rather than at a mutation of the MTHFR gene [17]. Several studies aim to determine whether hyperhomocysteinemia can be used to predict the risk of preeclampsia [18]. Elevated homocysteine levels have been detected during the first or second trimester of pregnancy without being directly implicated in preeclampsia. The reason for the high level of homocysteine in early pregnancy could be due to the alteration of vascular endothelial cells in early pregnancy. As this lesion worsens thus causing placental ischemia, eventually leading to preeclampsia [19]. On the other hand, the level of expression of homocysteine during the second trimester does not help to predict the risk of preeclampsia in pregnant women with chronic hypertension [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 retro-placental hematoma compared to other patients who had normal pregnancies without signs or symptoms of metrorrhagia showed an increase in homocysteine levels in patients with retroplacental hematoma [22]. However, in other studies, the authors revealed that hyperhomocysteinemia was not necessarily associated with retroplacental hematoma [23]. In our patient, the intentional figures were correct throughout the pregnancy with no signs of detectable abnormal bleeding.

Among the actions of homocysteine on endothelial cells is vascular obstruction, which can be the cause of premature labor. However, the prevalence of decidual angiopathy is not significantly related to preterm delivery [24]. An association between neurological malformations and hyperhomocysteinemia has been described in the literature [25]. 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 the myelin.

Hyperhomocysteinemia can impact the transfer of amino acids into the placenta, which could cause intrauterine growth restriction [26]. Some authors reveal that compared to normal pregnancies, homocysteine levels are higher in patients who have had pregnancies with intrauterine growth restriction [27], this could be due to damage to endothelial cells which can cause impaired uterine and placental blood circulation. In our patient who carried a pregnancy to term, 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, protein C, or protein S deficiency, resistance to activated protein C (due to Leiden mutations of the V gene) and factor II mutations [28]. Pregnancy itself is a risk factor for thrombosis. 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 tendencies have been identified. This prophylaxis consisted in our case of treatment with calciparin at the start of pregnancy, low molecular weight heparin at the end of pregnancy, then resumption of calciparin at the end of pregnancy, during delivery and 1 month after delivery.

## Conclusion

Homocysteine activity during normal pregnancies and its impact is a widely debated topic. According to the literature, homocysteine levels are not constant during pregnancy. Genetic polymorphisms associated with hyperhomocysteinemia and their metabolisms are clearly associated with complications during pregnancy. However, clinical trials aiming to show this require a lot of resources. High-dose folic acid supplementation during pregnancy may help women with complications from hyperhomocysteinemia.

## Conflicts of Interest

The authors declare that they have no conflict of interest.

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