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Case Report

ATTRITION OF A DESIRED PREGNANCY, IN A 37-YEAR-OLD WOMAN WITH TROMBOPHILIA WITH 2 PREVIOUS MISCARRIAGES

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ABSTRACT

Thrombophilias are inherited or acquired conditions that predispose individuals to thromboembolism. Thrombophilic disorders increase obstetric complications, such as early pregnancy loss, fetal growth retardation, placental abruption, and preeclampsia. Recurrent pregnancy loss affects 1% to 3% of women of reproductive age, and a large proportion of these losses remain unexplained. Genetic thrombophilia is the cause of approximately 49% -- 65% of the complications during pregnancy(1).

This article presents a clinical case study of a patient who has experienced two previous unsuccessful pregnancies, who is proven to be a heterozygote via mutant allele of MTHFR (Ala222Val) and PAI-1 (4G/5G), with heightened levels of NK cells with increased cell activity, and evidence of inhibiting embryotoxin in a blood test performed via DNA isolation, and DNA analysis via real time PCR.

Key words: pregnancy, gestation, PAI-1, mutant allele MTHFR, thrombophilia, NK cells

INTRODUCTION

Thrombophilia is a congenital or developed condition, which leads to factors that encourage the development of thromboembolism. Thrombotic illnesses lead to the formation of blood clots, which could block blood vessels and risk the health and life of the mother and fetus. During the course of a normal pregnancy, many of the physiological processes normally occurring in the body of the gestating individual change, including their coagulation status. In the presence of hereditary thrombophilia, even if the individual is not aware of it, during the pregnancy the thrombogene potential for a hereditary condition is considerably elevated. Congenital thrombophilia is determined by several genes, whereby frequently no clinical evidence is observed up until the advent of pregnancy. Genetic thrombophilia is the cause of approximately 49% -- 65% of the complications during pregnancy (1).

This article presents a clinical case study of a patient who has experienced two previous unsuccessful pregnancies, who is proven to be a heterozygote via mutant allele of MTHFR (Ala222Val) and PAI-1 (4G/5G), with heightened levels of NK cells with increased cell activity, and evidence of inhibiting embryotoxin in a blood test performed via DNA isolation, and DNA analysis via real time PCR.

PRESENTATION

Congenital and developed thrombophilias are conditions that are among the most frequently encountered factors causing thromboembolism. Other factors leading to its development are: the high BMI index, multiple pregnancy, infections, preeclampsia, immobility and the advanced age of the mother. They may lead to spontaneous abortion, death of the fetus, intrauterine retardation of the fetus, placental calcification/abruption and increases in the arterial blood pressure of the mother that may cause preeclampsia, eclampsia and HELLP syndrome. During the course of a normal pregnancy, the coagulatory changes observed in the patient include an increase of factors Vc, VIIc, Xc and von Wilebrand, as well as a decrease in the functional and free protein S. An insignificant change is observed in the levels of protein C or antithrombin III for the duration of the pregnancy. However, the Plasminogen

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Activator Inhibitor (PAI) levels increase, which leads to weakened fibrinolytic activity.

Such coagulatory changes may occur by themselves on in combination, and may lead to the occurrence of a multifactor condition that disrupts the course of normal pregnancy. One of the most frequently occurring cases is connected with antithrombin, protein S, and protein C deficiency.

CASE STUDY

This article presents a rare clinical case study of a patient who has experienced two previous spontaneous abortions, is a heterozygote via mutant allele of MTHFR (Ala222Val), and heterozygote under PAI-1 (4G/5G), with heightened levels of NK cells with increased cell activity, showing an inhibiting embryotoxin and increased TLA. Applied therapy utilizing a Low Molecular Weight Heparin, immunoglobulin, and Intralipid led to a successful gestation and birth.

The patient is a female aged 37, experiencing a regular 28-day menstrual cycle with 5-6 day menses period, with two prior spontaneous abortions concluding in the evacuation of the uterus contents via curettage.

The gynaecological examination determined the presence of external sex organs showing no prior birth, normal deep vagina, Portio Vaginalis Colli Uteri (PVCU) – conical. Uterus of normal size and shape, soft elastic and mobile. Adnexa Uteri – no palpatory variation detected on either side.

Transvaginal echography showed a uterus of normal size and shape. Adnexa Uteri – no pathological variations were detected via ultrasound on either side.

The patient was appointed a genetic panel test for thrombophilia **(Table 1),** immuno-phenotyping test, NK cell and thrombocytic-leukocytic aggregates test, and embryotoxic test. The results showed heterozygote condition under mutant allele MTHFR (Ala222Val), heterozygote condition under PAI-1 (4G/5G), elevated NK cells (13.7 per 2-13 norm) with increased cellular activity (11.1% per 10% norm), evidence of inhibiting embryotoxin (+) and elevated Thrombocyte-Leukocyte aggregates (2.6 per 1.6% norm).

Table 1. *Genetic panel test for thrombophilia*

Test	Result	Comment
Factor II (Prothrombin) (F2, G20210A)	G/G	Homozygote under normal allele
Factor V Leiden (F5, G1691A, Arg506Gln, R506Q)	G/G	Homozygote under normal allele
MTHFR (C677T, Ala222Val)	C/T	Heterozygote
MTHFR (A1298C, Glu429Ala)	A/A	Homozygote under normal allele
PAI-1 (SERPINE1) (4G/5G)	5G/4G	Heterozygote
Factor XII (F13A1, G103T, Val34Leu)	G/G	Homozygote under normal allele

Laboratory test results also showed the presence of Anticardiolipin IgG/IgA/IgM 2.8 (N<10.0), Анти – b2GPI - IgG/IgA/IgM 2.4 (N<10.0), Antiprothrombin Screen 1.0 (N<20 U/ml) и Anti-annexin V IgG 0.9 (N<5).

Appointed Therapy: Folic acid – meta form 1 tablet every 2 days, Methil-B12 (1000 gamma) every 2 days; Vitamin D (1000) 1 tabl/day, Intravenous Immunoglobulin in the following frequency: 5 g Immunoglobulin 2-4 days prior to ovulation, and 5 ml Intralipid 20% 2-4 days post positive pregnancy test. Aspirin protect 1 tablet every 2 days, pre- and during pregnancy for several weeks. Post positive pregnancy test: Fraxiparine or Clexane 0.4 every 2 days, dynamic testing of anticoagulant therapy (every third week: thrombocyte count, D-dimer and ArTT). If D-dimer is elevated, start Nataspin-H.

The patient attended a consultation on the first day of her menstrual cycle. A gynaecological examination was performed, and a plan was drafted for conception. On day 12 from the start of the menstrual cycle, after gynaecological examination and measurement of the dominant follicle in the ovary, the first infusion of 5 g of Immunoglobulin was performed in the medical center. The patient handled the medication well, no side effects were observed. The next infusion was carried out 3 days after the result of a blood pregnancy test – bCHG-1200mIU/ml., 5 ml

Intralipid 20%. Anti-coagulation therapy was appointed with a Low Molecular Weight Heparin – Fraxiparin 0.4 ml every 2 days. Levels of D-dimer, ArTT and thrombocytes were within normal limits. The patient was examined again in week 8 of gestation, presenting a regularly developing pregnancy in the uterus. An ultrasound examination determined an embryo with a heartbeat. During monthly follow-up examinations, the fetal development matched the gestation age with normal results of biochemical serum screening and follow-up fetal morphology in week 21. In week 38, the patient gave birth via C-section to a baby weighing 3320 g and 51 cm tall. The anticoagulation therapy was continued during the surgery and discontinued thereafter.

DISCUSSION

In the process of a normal gestation period, the change in hemostatus of the individual, leading to a hypercoagulable state, has been proven for decades and explained form a physiological and pathophysiological position. Pregnancy leads to changes in the coagulation and fibrinolytic system and considerably increases the risk of developing thromboembolism(2). A pregnancy developing normally leads to an increase of most coagulation factors: Factor VII, VIII, X, XII and fibrinogen, while the group of coagulation inhibitors – protein C and protein S – usually decrease. Of major importance is the Plasminogen Activator Inhibitor (PAI) test, which shows a tendency of elevation during pregnancy. Coagulation and fibrinolytic processes are physiologically dictated by hormonal changes in the body of the individual. They are as a whole an inherent defense mechanism that activates in cases of placental bleeding, during the birthing process and in the postnatal period.

Many studies have proven the role of thrombolytic defects in individuals who experience early-term pregnancy loss, death of the fetus, intrauterine retardation of the fetus, placental abruption, placental calcification and conditions of preeclampsia, eclampsia, and HELLP syndrome(3). There are proven clinical cases observing conditions of Disseminated intravascular coagulation (DIC) syndrome and fetal bradycardia of the fetus(4, 5).

The case presented in this article shows that, in an existing combination of heterozygote condition under mutant allele MTHFR (Ala222Val), heterozygote condition under PAI-1 (4G/5G), elevated NK cells (13.7 per 2-13 norm) with increased cellular activity (11.1% per 10% norm), evidence of inhibiting embryotoxin (+) and elevated Thrombocyte-Leukocyte aggregates (2.6 per 1.6% norm), a pregnancy can be developed and carried to term through influencing it in targeted moments during its progress.

The role of Plasminogen Activator Inhibitor (PAI) during a pregnancy is considerable and influences processes of trophoblastic invasion during the implanting and development of the zygote and the remodeling of the spiral uterine arteries in the endometrium. The mutation in the PAI-1 gene leads to a deficit of oxygen, nutrition, and the production of some of the immune memory cells (B-cells, TNFa). These processes may lead to an early pregnancy loss, preeclampsia, and intrauterine retardation of the embryo (6).

Conversely, the mutation of the Methylenetetrahydrofolate reductase (MTHFR) or conditions of hyperhomocysteinemia may lead to premature ovarian deficiency, disruptions in the implantation of the zygote, and habitual abortions. 5,10-methyltetrahydrofolate reductase is a leading enzyme in the metabolism of folic acid. It transforms the 5,10-methyltetrahydrofolate to 5-methyltetrahydrofolate, which is of major importance for the synthesis of nucleotides, methylating of homocysteine and DNA, construction of neurotransmitters and phospholipids. More and more studies show that heterozygote mothers and fathers under the MTHFR C677T gene are connected to cases of poor-quality of oocytes, aneuploidy embryos, and low-vitality of embryos (7).

In the early stages of pregnancy, the decidual NK cells (dNK) are the most frequently encountered type of NK cells in the uterus. The increase of the uterine NK (uNK) cells during the secretion phase of the menstrual cycle and during early stages of pregnancy is well known and plays a considerable role in the development of the pregnancy. The decidual NK cells assist the migration of the trophoblast towards the endometrium via promoting angiogenesis through the expression of ligands for key NK receptor activators. This leads to the release of VEGF (Vascular Endothelial Growth Factor) and SDF-1 (stromal cell derived factor-1), which are extremely important for the angiogenesis process. This role of NK cells

during pregnancy leads to the emergence of conditions such as preeclampsia, habitual abortions and spontaneous early-term abortions (8).

The serum of women experiencing habitual abortions and other pathologies during the pregnancy shows embryotoxin. It unites a group of antigens and cytokines that lead to pathology during the pregnancy. High percentage of embryotoxicity is discovered in women experiencing endometriosis and unexplained infertility factor. Thus far, it is known that hormonal therapy and immunotherapy lower the levels of embryotoxic factors in the blood of the mother, which assists in the development and carrying to term of the pregnancy(9).

CONCLUSION

In conclusion, we can surmise that congenital and developed thrombophilias are a risk factor for pregnancy. The correct and timely diagnosis presents an opportunity for a follow-up therapeutic scheme to assist in the development and carrying to term of a desired pregnancy.

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