Succesful Management of the Pregnancy Complicated with Thrombophilia, Uterine Unicollis and Previous Pregnancy Loss: A Case Report

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A 28 years old multigravid admitted to our maternal fetal medicine unit because of a second trimester loss of pregnancy due to preterm labor at 28 week. Her obstetrical history was uneventful. Ultrasonographic examination revealed a unicornuate uterus with rudimentary horn. Hyperhomocysteinemia caused by MTHFR heterozygosity and decrease in Protein S levels were found by blood analysis. Low dose aspirine and LWM Heparin were started 6 weeks before conception. Follow-up of the pregnancy in the functional unicornus resulted in a healthy baby delivered by cesarean section at 37 week due to chronic intrauterine hypoxia and uterine anomaly.
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Key Words: Unicornuate uterus, Rudimentary horn, Thrombophilia

Case Report

A 28 years old multigravid primiparous patient admitted to our maternal fetal unit because of second trimester loss in her first pregnancy. Her first pregnancy was followed-up in a primary health center and it was normal until 28 week at when preterm labor started. She vaginally delivered a 1200 gram male fetus which became exitus at 10 hour postnatally. The postmortem study of the baby revealed no abnormality. 1 year later, she admitted to our clinic for prenatal counselling. Her general history was uneventful; she had no history of thromboembolic event, her menstruation periods were normal. And she had no remarkable family history. The vaginal and the cervical examinations were normal. Transvaginal ultrasound examination was done and a right uterine unicollum with a rudimentary horn on the left was observed. Her urinary system was normal by abdominal ultrasound examination. Blood analysis showed a decrease in the level of protein S and hyperhomocysteinemia (fasting plasma homocystein 12 µmol/L) was noted. MTHFR C677T mutation was studied and heterozygosity was observed. Plasma and red blood cell folic acid and vitamin B12 levels were in normal limits. Low molecular weight Heparin; Nadroparine calcium 1 x 0.3ml (Fraxiparine; Sanofi Synthelabo, Istanbul, Turkey), low dose aspirin (1x 80mg) and folic acid and vitamin B6-B12 supplementation 1 x 1 (Becozyme-C Forte; Roche, Istanbul, Turkey) were started. She became pregnant 6 weeks later and the pregnancy was in the functioning uterine unicollum. Drug therapies were continued. At 30 week, due to regular uterine contractions tocolytic theraphy, nifedipine 30 mg/day (Nidilat, Sanofi Synthelabo, Istanbul, Turkey) was begun. At 37 week gestation, cesarean section was done due to chronic intrauterine hypoxia and uterine anomaly and a 2800 gram male fetus was delivered. Postnatal period was normal; the patient and the baby were discharged 3 days after the operation. At 6 week postpartum control physical examination was normal and medication was ceased. 1 year later, she admitted to our clinic because she had been planning an another pregnancy. Drug theraphies were reinstituted in the same schedule and then she became pregnant. She is 35 weeks pregnant at the moment.

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Discussion

Hemorrhage during parturation is a life threatining condition. As an evolutionary process, life makes adaptations in the coagulation system during pregnancy leading to increased coagulation and decreased fibrinolysis. As the changes favor coagulation, the life-saving adaptations may lead to life-threatining thromboembolism.Venous thromboembolism (VTE) is the leading cause of death for pregnant women in Western countries. Pregnant women have 2-15-fold higher risk for venous thromboembolism compared to non-pregnant women. The risk factors for VTE during pregnancy are thrombophilia, personel or family history of VTE, obesity, operative delivery and advanced maternal age.[1] Pregnancy increases the risk of VTE through venous stasis, changes in blood coagulability and damage to vessels.[2]

Acquired and inherited thrombophilias are common problems in the field of obstetrics and other disciplines.Thrombophilia by definition represents acquired and/or genetic conditions that predispose patients to both venous and arterial thromboembolic events.[3] In pregnancy, the tendency for hypercoagulability increases markedly when thrombophilia is also present. Normally if antithrombotic mechanisms such as antithrombin III, protein C and S are in nor-

mal levels and functioning properly, thrombosis is prevented but any abnormality in these anticoagulant mechanisms lead to thrombosis. Complemant system is activated and endothelial damage eventually occurs. Endothelial dysfunction with vasoconstriction leads to plasental ischemia and abnormal placental development and disturbances of haemostasis may lead to inadequate perfusion of the intervillous space, decreased placental perfusion and placental infarcts and inadequate fetomaternal circulation; in turn these result in preeclampsia, intrauterine growth restriction (IUGR), placental abrubtion, stillbirth and probably premature delivery.[4-7] Isolated acquired or inherited thrombophilias may slightly alter the mechanism of coagulation depending on the type but when 2 or more types are together, thrombotic complications are more severe and require treatment.[4,8-9]

Homocystein is a nonessential amino acid formed during metabolism of methionine. Homocystein levels are influenced by both genetic and lifestyle factors.[10-11] Hyperhomocysteinemia may result from defects or deficiencies of the enzymes involved in homocysteine metabolism, or deficiencies of their vitamin cofactor. High homocystein levels are associated with the development of venous and arterial thrombosis.[12] In obstetrics, hyperhomocysteinemia is very important because it has been associated with several pregnancy-related complications including placental infarcts, preeclampsia, placental abruption, intrauterine growth retardation and neural tube defects. High levels of homocystein may also interfere with embriyonic development through defective chorionic villus vascularization.[13] Folate deficiency is the most common acquired cause of hyperhomocysteinemia. The most common inherited cause of hyperhomocysteinemia is methylenetetrahydrofolate reductase (MTHFR) enzyme mutation. MTHFR is an enzyme that reduces 5,10-methylene tetrahydrofolate (THF) to 5-methyl THF and it is a cofactor in the methylation pathway from homocystein to methionine[14-15] (Figure1). Adequate folic acid, vitamin B12 and B6 intake are essential for enzymatic steps. Multiple variants of the MTHFR mutation are known. A common polymorphism at nucleotide 677 of the MTHFR gene, C677 T (ala→val), affects the activity of the enzyme, resulting in a more labile enzyme with decreased activity, which leads to lower folate and elevated homocysteine levels. Heterozygous or homozygous MTHFR C677T polymorphisms can cause mild to severe hyperhomocysteinaemia, which impairs endothelial cell function and promotes thrombosis. An important point in the management of hyperhomocysteinemia is folate supplementation because adequate folate supplementation may prevent phenotypic expression of the mutation.[3] Vitamin B12 and B6 supplementations are also important in the management of MTHFR mutation. A multivitamin regimen including folic acid, vitamine B6 and B12 should be started before pregnancy.[3] In order to keep blood homocystein levels in normal limits, we advice MTHFR mutation carriers to take folic acid daily either with dietary products or with multivitamins.

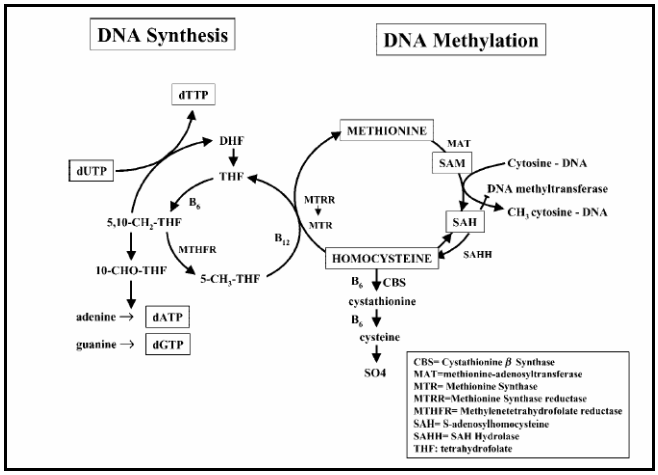

Figure 1. Metabolic pathways in the one-carbon metabolism involved in the DNA synthesis and methylation. Martinez-Frias ML, Perez B, Desviat LR, Castro M, Leal F, Rodriguez L, Mansilla E, Martinez-Fernandez ML, Bermejo E, Rodriguez-Pinilla E, Prieto D, Ugarte M. Maternal polymorphisms 677C-T and 1298A-C of MTHFR, and 66A-G MTRR genes: is there any relationship between polymorphisms of the folate pathway, maternal homocysteine levels, and the risk for having a child with Down syndrome? ECEMC Working Group. Am J Med Genet A. 2006 May 1; 140(9):987-97.

Deficient folic acid metabolism caused by MTHFR mutation may also be associated with multiple sclerosis,[16] Down Syndrome,[17] bipolar disorder and schizophrenia[18] and with some types of cancers i.e hepatocelluler carcinoma[19] and lymphoproliferative diseases.[20]

Protein S is the principal cofactor of activated protein C and the deficiency mimic protein C deficiency with increased fibrin formation. Patients with protein S deficiency have 2 times deep vein thrombosis risk when compared with non-thrombophilic patients. According to a meta-analysis by Reye et al, there is a significant association between protein S deficiency and non recurrent fetal loss occuring after 22 weeks.[21]

In our patient another limiting factor is uterine unicollus. Both decreased space and local defects add up to placental insufficiency and this leads to increased obstetrical complications including early and late miscarriages, preterm labor, preeclampsia and abruptio placenta. Patients with uterine malformations seem to have an impaired pregnancy outcome as early as their first pregnancy.[22] Unicornuate and didelphys uterus have term delivery rates of 45%. Uterine malformations are closely related to an abnormal uterine capacity which may impair fertility capacity.[23] The presence of a malformed uterus in a woman is thought to impair normal reproductive performance by increasing the incidence of early and late abortions, preterm deliveries as well as the rate of obstetrical complications.[24] According to Buttram and Gibbons[25] uterine malformations are classified into 6 major groups. Our patient's uterus unicollus with a non-communi-

cating rudimentary horn comprises the group 2a. This group of patients are usually asymptomatic in non-pregnant conditions. Hematometria in the non-communicating horn may lead to cyclic abdominal pain and it may even lead to rupture of the horn unless diagnosed. Rudimentary horn may be excised before pregnancy or if observed during any operation but in order to prevent adhesions related with excision, we prefer conservative management with careful observation. If pregnancy occurs in the rudimentary horn, it may cause serious hemorrhage and can be fatal.[26] Pregnancy in the normally functioning unicollus is also prone to obstetrical complications. Classically, it has been assumed uterine malformations are associated with late miscarriages and preterm deliveries but Raga et al[23] showed that early miscarriages may also be seen and that shows uterine malformations cannot only create a problem of space, but also that there might be local defects that interrupt normal early embryo development after implantation. We are in a point of view that when a mullerian anomaly is detected in a patient with pregnancy loss, thrombophilia should also be kept in mind; an experienced obstetrician should not solely base the diagnosis on anatomical abnormalities.

Finally, patients admitting with late fetal loss or recurrent early miscarriages should be investigated for anatomic malformations and inherited thrombophilias. According to the type of the malformation, conservative or surgical measures should be taken. Thrombophilic patient should carefully be investigated. Thrombophilia parameters should not be accepted as isolated markers but should be viewed as a part of a systemic autoimmune response. One should not hesitate to start proper medications when thromboembolic events are imminent. Our choice is LMW heparin and low dose aspirin with a multivitamin preparate including folic acid, vitamin B6 and B12. The drugs should be used throughout the pregnancy and should be ceased 24 hours before the labor. We start the drugs 12 hours after the labor and stop all at postnatal 6 weeks. Close follow-up of these patients in the pregnancy period is suitable to prevent threatining complications due to chronic placental insufficiency caused by placental thrombosis cascade.

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