CASE REPORT

Homocysteinemia: A Rare Cause of Recurrent Pregnancy Loss Coexisting with Deep Vein Thrombosis

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Abstract

Deep vein thrombosis (DVT) and venous thromboembolism are major health problems and are leading causes of maternal morbidity and mortality. Recurrent pregnancy loss either early or late is a serious problem and has both psychological and physical impacts. Thrombophilia is one of the most important causes of DVT as well as recurrent pregnancy loss as it worsens the physiological hypercoagulable case which exists in pregnancy. Homocysteinemia is rare but an important cause of DVT and recurrent pregnancy loss. Serum homocysteine levels in pregnancy have been linked to preeclampsia, recurrent abortions, and low birth weight. Diagnosis of this condition is missed on a routine basis due to extremely less frequency of the evaluation of serum homocysteine levels. Here, we report a case of hyperhomocysteinemia as an underlying cause of bad obstetric history and DVT which are a few of the classic presentations of the entity seen in the single patient. The condition was diagnosed by a multidisciplinary approach.

Keywords: Deep vein thrombosis, Homocysteinemia, Preeclampsia, Recurrent pregnancy loss.

Journal of South Asian Federation of Obstetrics and Gynaecology (2020): 10.5005/jp-journals-10006-1824

Introduction

Deep vein thrombosis (DVT) during pregnancy is associated with high mortality and morbidity.[1] The incidence of venous thrombosis in pregnancy is approximately 1 in 1,000–2,000 pregnancies. Pregnancy being a hypercoagulable state is one of the important factors contributing to venous thrombosis. During pregnancy, a history of hereditary or acquired thrombophilia or a history of previous DVT has been determined to be the most important risk factors. Homocysteinemia remains a risk factor for DVT after well-established risk factors are excluded. Due to the rare association of the condition with DVT, serum homocysteine levels are not included in the routine investigations carried out for the diagnosis of DVT or recurrent pregnancy loss, hence leading to early and specific management of DVT.

Case Description

A 22-year-old patient with a h/o spontaneous abortion in the second month of her pregnancy presented to casualty at 28 weeks of gestational age with c/o acute abdominal pain and bleeding pre vaginal (PV) since 6 hours. The patient was drowsy and afebrile on touch. On general examination, the patient was pale, and bilateral pedal edema was present. On admission, the patient had a weak and thready pulse with pulse rate (PR) 112/minute, blood pressure (BP) was recorded to be 150/100 mm Hg, and albuminuria +2. On abdominal examination, the patient's uterus was tense and tender and was disproportionately larger than the average gestational age. Fetal heart rate was absent following which an emergency obstetric ultrasound was done. Obstetric ultrasound showed a single fetus in a transverse lie with no fetal cardiac activity and hypoechogenic retroplacental clot with intraplacental anechoic areas suggestive of intrauterine fetal demise owing to abruptio-placenta. The patient's hemogram and biochemical laboratory tests had the following values: Hb-7 g%, TLC-13,200/mm^3, platelets-1.23 lakhs/mm^3, S. LDH-1,017/mm^3, S. uric acid 0.66/mm^3. After evaluating the patient's condition, lab investigations and assessing the risk of complications of preeclampsia leading to placental abruption and the fetal demise of duration more than 6 hours, an emergency cesarean section was done. Intraoperatively, a hematoma covering 60% of the placenta was observed. A male baby who did not cry was delivered. The placenta was extracted and sent for histopathological examination (Fig. 1). Two units of whole blood were transfused to the patient postoperatively. The patient was started on tab Labetalol 50 mg bd following which her raised BP was well controlled. Owing to a history of two unexplained pregnancy losses, the patient was evaluated for structural and endocrinal abnormalities, chromosomal anomalies, antiphospholipid antibody panel test which came out to be normal. The lab investigations were not suggestive of any acute or chronic infection in the patient. Her postoperative period in the hospital was uneventful and the patient was discharged on the 5th postoperative day. The patient had c/o pain, swelling, and redness in right lower limb on 9th day of puerperium (Fig. 2) for which she visited medicine out patient department (OPD) and was advised a color Doppler of bilateral lower limbs in view of symptoms

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How to cite this article: Singh N, Acharya N, Acharya S. Homocysteinemia: A Rare Cause of Recurrent Pregnancy Loss Coexisting with Deep Vein Thrombosis. J South Asian Feder Obst Gynae 2020;12(5):328–330.

Source of support: Nil

Conflict of interest: None

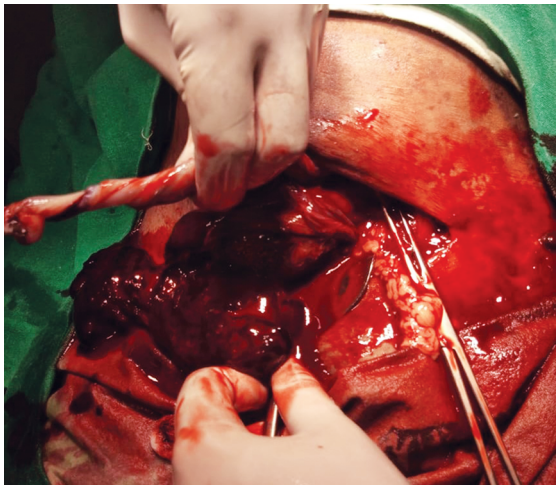

Fig. 1: Gross appearance of placenta intraoperatively during LSCS with massive hematoma at 28 weeks of gestation

suggestive of DVT. Thrombosis of femoral, superficial femoral, popliteal, and posterior tibial veins was noted in color Doppler of the right lower limb. The patient was admitted to medicine intensive care unit (ICU) following which all the risk factors contributing to DVT were assessed and a battery of investigations was done to rule out the specific cause of DVT in this case. The investigations also included serum homocysteine levels which are not a part of the routine investigations and are rarely considered as a causative factor. However, in this case, the patient's lab investigations came out to be normal except for plasma homocysteine level which was elevated (26.58 µmol/L). The patient was started on low molecular weight heparin (enoxaparin) for the management of DVT along with oral vitamin B6 and B12 tablets once and folic acid 500 µg twice daily for the treatment of hyperhomocysteinemia. The patient had a hospital stay of 7 days and was discharged after relief of symptoms. She conceived spontaneously and visited the obstetric OPD for her regular visits. She was advised to continue low molecular weight heparin as a prophylactic measure for DVT and folic acid tablets supplementation once daily to maintain plasma homocysteine levels well within a normal range. A multidisciplinary approach involving physicians and obstetricians helped her in having an antenatal period without any undue complications. The patient presented to casualty at 35 weeks of gestation with c/o appreciation of decreased fetal movements persistently. Ultrasonography (USG) obs findings were normal and color Doppler showed normal color flow and spectral waveform. Keeping in mind a bad obstetric history of the patient an elective cesarean section was performed and the patient delivered a healthy female child of birth weight 2.5 kg. Her intraoperative and postoperative period was uneventful. This case is unique as a simple investigation and treatment of the cause, in this case, could help the patient in having a favorable pregnancy outcome.

Discussion

Pregnancy and the puerperium are well-established risk factors for venous thromboembolism (VTE). The likelihood of women developing DVT is five times more as compared to the non-pregnant state. The risk of DVT is accentuated when pregnancy is associated with some specific comorbidities like inherited or acquired thrombophilias, a previous history of thrombosis, antiphospholipid syndrome, lupus, heart disease, and sickle cell disease.[2]

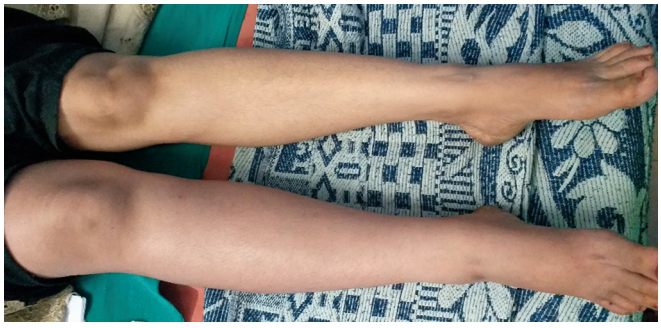

Fig. 2: Unilateral pedal edema in right calf seen in a patient on 9th day of puerperium

Homocysteinemia has been reported as one of the risk factors contributing to recurrent pregnancy loss. Insufficient supplementation of vitamin B12 and folic acid and inherited disorders within the methionine homocysteine metabolic pathway such as MTHFR C677T gene polymorphism can lead to hyperhomocysteinemia.[3]

Homocysteine is a sulfur-containing amino acid that is formed by the demethylation of methionine. Transsulfuration is an important step in homocysteine metabolism where cystathionine beta-synthase (CBS) catalyzes the conversion of homocysteine to cysteine. Cystathionine beta-synthase is a vitamin B6 (pyridoxine)-dependent enzyme where B6 is an essential cofactor.[4]

Increased incidence of preeclampsia has been noted in women who have raised plasma homocysteine levels in early pregnancy compared to women who have normal levels of blood pressure throughout pregnancy. The incidence can be three times more than that of normotensive pregnant women. Endothelial dysfunction which is pathophysiology implied in preeclampsia can be brought about by homocysteine.

Stoïkova et al. conducted a study and concluded that women with severe preeclampsia had significantly higher serum homocysteine levels than those with mild form ($F = 0.025$). The study finds a link between the serum homocysteine as an endothelial dysfunction marker and the development of preeclampsia and a relation between the severity of preeclampsia and the degree of the elevation of the serum homocysteine levels.[5]

Nutritional deficiency[2] (folic acid deficiency) and/or inherited disorder of methionine metabolism have been a causative factor of hypercystinemia which in turn might be a risk factor for recurrent fetal loss. Hence in such patients, a probable association between raised serum homocysteine levels and vitamin B6 and folic acid should be looked into so that a non-teratogenic regimen to restore the normal metabolic is begun and there is a successful maternal and perinatal outcome.[6] Gris et al. reported an association between increased levels of Hcy and a first early pregnancy loss.[7] Del Bianco et al. found 25% of women with a recurrent loss have hyperhomocysteinemia or at least a pathological methionine loading test.[7]

Inadequate vascular supply to the placental vascular bed might lead to placental insufficiency, rupture of the placenta, recurrent pregnancy loss, and preeclampsia. A systematic literature review was carried out by Ray and Laskin to evaluate the risk of placental pathologies in the presence of metabolic disorders. It was observed among four studies that folic acid deficiency, though statistically insignificant was a prominent risk factor for placental

insufficiency and rupture. There was also an association between placental rupture and infarction in the presence of homozygosity of methylenetetrahydrofolate reductase gene and hyperhomocysteinemia with or without methionine loading test. A wide number of observational studies had a common consensus that folate deficiency, hyperhomocysteinemia, and homozygosity for methylenetetrahydrofolate reductase thermolabile variant are probable risk factors for placenta-mediated diseases.[8]

The substantial and vast amount of data obtained from the research has shown a significant association between mild to moderate hyperhomocysteinemia and vascular disease. Hyperhomocysteinemia is a contributing factor for both arterial and venous thromboembolic events. Langman et al. conducted a retrospective case-control study and observed that fasting hyperhomocysteinemia is a remarkable risk factor for venous thromboembolic disease.[9]

The intricate pathway of homocysteine metabolism is regulated by vitamin B6 and folic acid. Vitamin B12 and folic acid are effective contributors to the neural and global development of fetus and embryo. It is not feasible to assess vitamin B12 levels on a routine basis. There is a very poor relationship between levels of intracellular methylfolates[2] (active form of folate) and total plasma and/or folates in the red blood cells. A rise in homocysteine levels beyond the normal range has been seen in the case of pyridoxine and intracellular methylfolate deficiency.[10]

Extensive planning and implementation regarding the management of vitamin B12 deficiency is required but minimal measures have been taken by clinical practitioners and policymakers in India. A reduction of total plasma homocysteine levels has been noted after vitamin B12 supplementation in women in late pregnancy who previously had normal folic acid reserve but had a deficiency of vitamin B12. Hyperhomocysteinemia is typically managed with vitamin B6, B9, and B12 supplementation.[11]

Conclusion

Homocysteinemia should be considered as a possible diagnosis in a pregnant woman presenting with recurrent pregnancy loss and DVT. Early diagnosis and a simple regimen of vitamin supplementation can prevent pregnancy loss especially recurrent pregnancy loss which is physically and emotionally taxing for a couple.

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