

Homocysteinemia: Cause of a Rare Case Coexisting DVT and Recurrent Foetal Loss in Pregnancy

Nidhi Singh¹, Neema Acharya², Sourya Acharya³, Jaya Kore⁴

¹Junior Resident, Department of Obstetrics and Gynaecology, ²Professor and Head of Department, Department of Obstetrics and Gynaecology, ³Professor of Department of Medicine, ⁴Assistant Professor of Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences Sawangi Meghe, Wardha

Abstract

Deep vein thrombosis and venous thromboembolism is a major health problem and one of the leading causes of maternal morbidity and mortality. Recurrent pregnancy loss either early or late is a serious problem and has both psychological and physical impact. Thrombophilia are 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 deep vein thrombosis 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 routine basis due to extremely less frequency of the evaluation of serum homocysteine levels on a routine basis. Here we report a case of hyperhomocysteinemia as underlying cause of bad obstetric history and DVT which are few of the classic presentations of the entity seen in the single patient. The condition was diagnosed by multidisciplinary approach.

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

Introduction

Deep vein thrombosis during pregnancy is associated with high mortality and morbidity.⁽¹⁾ The incidence of venous thrombosis in pregnancy is approximately 1 in 1000-2000 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 most important risk factors. Homocysteinemia remains a risk factor for DVT after well-established risk factors are excluded. Due to rare association of the condition with deep vein thrombosis, serum homocysteine levels

are not included in the routine investigations carried out for diagnosis of deep vein thrombosis or recurrent pregnancy loss, hence leading to early and specific management of DVT.

Case Report: A 22-year-old patient with a history of spontaneous abortion in the second month of her pregnancy presented to casualty at 28 weeks of gestational age with a chief complaint of acute abdominal pain and bleeding per vagina since 6 hours. The patient was drowsy and afebrile on touch. On general examination, the patient was pale and bilateral pedal oedema was present. On admission, the patient had a weak and thready pulse with PR 112/min, 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 transverse lie with no fetal cardiac activity and hypoechogenic retroplacental clot with intraplacental anechoic areas suggestive of intrauterine fetal demise owing to abruptio placentae. Patient's haemogram and biochemical laboratory tests

Corresponding Author:

Dr. Neema Acharya

Professor and Head of Department of Department of Obstetrics and Gynaecology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences Sawangi Meghe, Wardha

had the following values: hb-7 gm%, TLC-13200/cumm, platelets-1.23 lakhs/cumm,S. LDH-1017/cumm,S uric acid 0.66/cumm. After evaluating the patient's condition,lab investigations and assessing the risk of complications of preclampsia leading to placental abruption and foetal demise of duration more than 6 hrs, an emergency caesarean section was done intraoperatively a hematoma covering 60% of the placenta was observed. a male baby who did not cry was delivered placenta was extracted and sent for histopathological examination [image 1]. 2 units of whole blood were transfused to the patient postoperatively. Patient was started on tab Labetolol 50 mg bd following which her raised BP was well controlled. Owing to history of two unexplained pregnancy losses, 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 5th postoperative day patient had c/o pain,swelling and redness in right lower limb on 9th day of puerperium [image 2]for which she visited medicine OPD and was advised a colour doppler of bilateral lower limbs in view of symptoms suggestive of DVT .thrombosis of femoral, superficial femoral, popliteal, posterior tibial veins was noted in colour doppler of right lower limb. The patient was admitted in medicine 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 patient's lab investigations came out to be normal except plasma homocysteine level which was elevated[26.58 micromole/l]. 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 mcg twice daily for the treatment of hyperhomocysteinemia. 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 in order 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. Patient presented to casualty at 35 weeks of gestation with c/o appreciation of decreased foetal movements persistently. USG OBS findings were normal and colour doppler showed normal colour flow and spectral waveform. keeping in mind a bad obstetric history of patient an elective caesarean 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 favourable pregnancy outcome.



Figure 1: Gross appearance of placenta extracted post LSCS at 35 weeks of pregnancy



Image 2: Unilateral pedal edema in rightcalf seen in patient on 9th day of puerperium

Discussion

Pregnancy and the puerperium are well-established risk factors for venous thromboembolism (VTE). The likelihood of women developing DVT is 5 times more as compared to nonpregnant 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⁾

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 sulphur-containing amino acid which is formed by demethylation of methionine. Transsulphuration is important step in homocysteine metabolism where cystathionine beta-synthase catalyses the conversion of homocysteine to cysteine. CBS is vitamin B6 (pyridoxine) dependant 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 in

normotensive pregnant women. Endothelial dysfunction which is pathophysiology implied in preeclampsia can be brought about by homocysteine.

V Stoïkova *et al* conducted a study and concluded that the women with a severe preeclampsia had a 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 and/or inherited disorder of methionine metabolism have been a causative factor of hypercystinemia which in turn might be a risk factor for recurrent foetal 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 nonteratogenic regimen to restore the normal metabolic is begun and there a successful maternal and perinatal outcome.⁽⁶⁾ Gris *et al* reported an association between increased levels of Hcy and a first early pregnancy loss. Del Bianco *et al* found 25% of women with recurrent loss to have hyperhomocysteinemia or at least a pathological methionine loading test⁽⁷⁾

Inadequate vascular supply to placental vascular bed might lead to Placental insufficiency, rupture of placenta, recurrent pregnancy loss and pre-eclampsia. A systematic literature review was carried out by JG *et al* 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⁾

Substantial and vast amount of data obtained from the research has shown significant association between mild to moderate hyperhomocysteinemia and vascular disease. Hyperhomocysteinemia is contributing factor

for both arterial and venous thromboembolic events. Langman *et al* conducted a retrospective case control study and observed that fasting hyperhomocystinemia 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 and effective contributors to neural and global development of foetus and embryo. It is not feasible to assess vitamin B12 levels on a routine basis There is very poor relation between levels of intracellular methylfolates (2)active form of folate]and total plasma and/or folates in the red blood cells. Rise in homocysteine levels beyond the normal range has been seen in 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 policy makers 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 deficiency of vitamin B12. Hyperhomocystinemia is typically managed with vitamin B6, B9 and B12 supplementation.⁽¹¹⁾

Conclusion

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

Ethical Clearance: Taken from institutional ethics committee.

Source of Funding: Self.

Conflict of Interest: Nil.

References

1. Deep venous thrombosis in pregnancy: incidence, pathogenesis and endovascular management (2) Internet]. (2)cited 2020 Apr 18]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5778511/>
2. Devis P, Knuttinen MG. Deep venous thrombosis in pregnancy: incidence, pathogenesis and endovascular management. *Cardiovasc Diagn Ther.* 2017 Dec;7(Suppl 3):S309–19.
3. Kupfermanc MJ. Thrombophilia and pregnancy. *Reprod Biol Endocrinol RBE.* 2003;1:111.
4. Sztenc S. (2) Hyperhomocystinemia and pregnancy complications]. *Ginekol Pol.* 2004 Apr;75(4):317–25.
5. Stořkova V, Ivanov S, Mazneřkova V, Tsoncheva A. (2) Serum homocysteine levels in pregnant women with preeclampsia]. *Akush Ginekol (Sofia).* 2005;44(6):16–9.
6. Del Bianco A, Maruotti G, Fulgieri AM, Celeste T, Lombardi L, Amato NA, et al. (2) Recurrent spontaneous miscarriages and hyperhomocystinemia]. *Minerva Ginecol.* 2004 Oct;56(5):379–83.
7. Gris J-C, Perneger TV, Quéré I, Mercier E, Fabbro-Peray P, Lavigne-Lissalde G, et al. Antiphospholipid/antiprotein antibodies, hemostasis-related autoantibodies and plasma homocysteine as risk factors for a first early pregnancy loss: a matched case-control study. *Blood.* 2003 Nov 15;102(10):3504-13.
8. Ray JG, Laskin CA. Folic acid and homocyst(e)ine metabolic defects and the risk of placental abruption, pre-eclampsia and spontaneous pregnancy loss: A systematic review. *Placenta.* 1999 Sep;20(7):519–29.
9. Hyperhomocyst (e) inemia and the Increased Risk of Venous Thromboembolism: More Evidence From a Case-Control Study | Venous Thromboembolism | JAMA Internal Medicine | JAMA Network (2)Internet]. (2)cited 2020 May 28]. Available from: <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/415732>
10. Quéré I, Mercier E, Bellet H, Janbon C, Marès P, Gris J-C. Vitamin supplementation and pregnancy outcome in women with recurrent early pregnancy loss and hyperhomocystinemia. *Fertil Steril.* 2001 Apr 1;75(4):823-5.
11. Katre P, Bhat D, Lubree H, Otiv S, Joshi S, Joglekar C, et al. Vitamin B12 and folic acid supplementation and plasma total homocysteine concentrations in pregnant Indian women with low B12 and high folate status. *Asia Pac J Clin Nutr.* 2010;19(3):335–43.