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Homocysteine in Hypertensive Disorders: Time to Focus on the Neglected Risk Factor

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Hypertensive disorders of pregnancy are multisystem disorders consisting of pre-eclampsia and eclampsia and are a major cause of adverse perinatal outcomes.[1,2] Both mother and child are affected equally with serious implications. In addition to elevated blood pressure, proteinuria, and convulsions these disorders are further characterized by ominous impaired liver function, increased serum uric acid, decreased platelet count and signs and symptoms such as headache, visual disturbance, epigastric pain and pulmonary odema.[3] Though endothelial dysfunction and vasospasm have been considered central in pathophysiology of pre-eclampsia, our understanding of its causal factors and etiology is still minimal.[4] Stipulated theories include abnormal trophoblastic invasion of uterine vessels, discordance of immunologic tolerance between placental and fetal tissues, genetic and dietary factors.[5]

As evident from vast medical literature, homocysteine, a sulfur containing amino acid has been implicated in the causal pathway of these hypertensive disorders of pregnancy. Normally, as pregnancy progresses, serum homocysteine falls due to hemodilution, increase in estrogen and increased demand for methionine by both mother and fetus.[6] However, in hyperhomocysteinemia due to causes such as genetic defects in enzymes involved in homocysteine metabolism and deficiency of folic acid and vitamin B12 which are involved in its biochemical pathways; homocysteine undergoes auto-oxidation to produce reactive oxygen species which inactivate nitric oxide and thrombomodulin which leads to endothelial damage and dysfunction.[7] Disturbances in the intracellular homocysteine metabolism lead to elevated homocysteine concentration. In addition, it further interferes with fibrinolytic system adding to pathophysiology of preeclampsia and eclmapsia. Elevated homocysteine causes enhanced risk of severe preeclampsia, abruption, intrauterine growth restriction, recurrent pregnancy loss, intrauterine death and prematurity.[8] Elevated homocysteine is a risk factor for vascular disease. Causes of hyperhomocystenemia are genetic defects in enzymes involved in homocysteine metabolism and deficiency of folic acid and vitamin B12.

To further cement homocyteine in the causal route, homocysteine lowering therapies in the

form of folic acid and vitamin B6 have benefitted patients suffering from pre-eclampsia and eclampsia.[9] Various studies have provided direct and indirect evidence and strengthened the association. Such association has been studied regionally and region specific data and evidence is also available. Such studies have further highlighted that degree of severity of pregnancy induced hypertension is proportionate to the levels of homocysteine.[10,11] These studies have shown association of homocysteine with abruption, Posterior Reversible Encephalopathy (PRES) and Post Partum Haemorrhage (PPH) in the mother. Various fetal and neonatal complications like Respiratory Distress Syndrome (RDS), Transient Tachypnoea of Newborn (TTPN), neonatal jaundice, Intrauterine Growth Restriction (IUGR), low Appearance, Pulse, Grimace, Activity, Respiration (APGAR) score and stillbirths are seen more often in mothers with raised homocysteine levels. It is further well evident that degree of severity of pre eclampsia is proportionate to the levels of homocysteine.

More robust data from region specific cohort studies or randomised control trials are needed to recommend the estimation of homocysteine as a routine investigation as a part of prenatal screening and in normal pregnancy. As various factors determine the level of homocysteine like folic acid, vitamin B12 and vitamin B 6 or genetic defect of enzyme Methylene Tetra Hydro Folate Reductase (MTHFR), interventional studies are required to show whether dietary replacement with these will decrease the incidence of hyperhomocystenemia which in turn will decrease the incidence of adverse pregnancy outcome associated with it.

After generating the evidence, the next step is to translate into action. Routine estimation of homocysteine levels prior to pregnancy may help to correctly predict and prevent further development of preeclampsia and eclampsia, if timely countermeasures are undertaken. But even after the passage of so much time, still homocysteine is nowhere to be seen among battery of antenatal investigations. Incorporation of homocysteine in standard antenatal investigation package through means of maternal health programmes can be a valuable aid and can definitely have positive impact on maternal and neonatal health. An additional inclusion can avert huge burden of morbidity and mortality.

In the current era of women empowerment and free of cost maternal care, it is strongly recommended that the women with a history of adverse pregnancy outcome undergo the screening for hyperhomocystenemia. This will further enrich our arsenal in fight against maternal and neonatal morbidity and mortality concluding in improved mother and child health. Simple yet impactful steps can help us in quality maternal and child health services, achieving universal health care and ensuring sustainable development which is need of the hour.

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