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Case Review

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Nutritional Management in Pre Eclampsia-Gestosis

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Introduction

Preeclampsia (PE) is a common medical disorder during pregnancy with many immediate and long-lasting adverse influences to the mothers as well as the new-born health. The incidence is found to be 5 to 10 percent overall in India [1] and HDP-Gestosis as it should be appropriately named contributes to significant perinatal morbidity and mortality. The physiopathology of preeclampsia is thought to involve an abnormal placentation, diffuse endothelial cell dysfunction and increased systemic inflammation characterized by deficient trophoblast invasion resulting in narrow spiral arterioles leading to hypoxia, endothelial dysfunction [2,3]. Role of maternal nutrition is well established in the placental development and, disruption in the processes of placentation is directly associated with foetal growth restriction and challenges to the maternal habitus if not properly prepared before conception and during pregnancy (Figure 1).

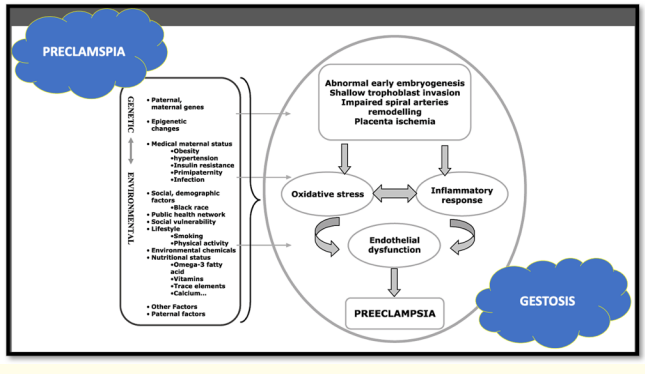

Figure 1: Pathophysiology of preclampsia-gestosis mechanisms vastly influenced by maternal medical and nutritional status as well as nutritional status.

As micronutrients play a key role in placental endothelial function, oxidative stress and expression of angiogenic factors, periconceptional micronutrient supplementation has been proposed to reduce the risk of preeclampsia. Recent studies reported conflicting results and this is a reflection of lack of robust studies in the nutritionally affected populations in the world. Indian women as a norm embark on pregnancy with calcium, iron and energy deficient conditions and thus risking the possibility of conditions such as Gestosis.

Factors such as obesity, diabetes, dyslipidaemia, insulin resistance, hypothyroidism, anaemia have been found to be risk factors linking to the possible association of malnutrition as a common pathway.

Malnutrition (poor nutrition) refers not only to inadequate intake of macronutrients (energy and protein undernutrition), but also to inadequate intake or increased losses of single or multiple vitamins and minerals (micronutrient malnutrition), such that the body's requirements are not met. Malnutrition can result from over-consumption of non-nutritive energy and underconsump-

tion of nutrient-dense foods. A good diet is more than a matter of food quantity—quality is critical.

The pathogenesis of HDP-gestosis which seems to be aggravated in the setting of oxidative stress leading to or as a consequence, immunological maladaptation, endothelial dysfunction and related abnormalities point to associated nutritional elements being deficient or malfunctioning. This has made us explore the role of nutrition in the management of preeclampsia. The REVAMP study [4] conducted at our institution revealed that the dietary deficiency of long chain polyunsaturated fatty acids (LCPUFA) and their metabolites play an important role in implantation and are required at various stages of placental development and function and can be a part of PE pathogenesis. Also ensuring the availability of these in maternal nutrition can act as therapeutic approach in treatment or prevention of PE. The plausible mechanism of reduced intake of LCPUFA (ALA: alpha linolenic acid; DHA: docosahexaenoic acid) is demonstrated in figure 2.

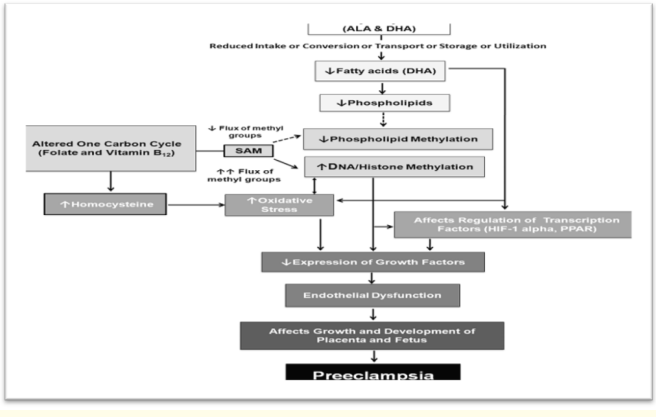

Figure 2: Proposed Mechanism of Altered Maternal Nutrition Leading to Preeclampsia.
ALA: Alpha Linolenic Acid; DHA: Docosahexaenoic Acid; DNA: Deoxyribonucleic Acid; HIF-1 Alpha: Hypoxia Inducible Factor – 1 Alpha; PPAR: Peroxisome Proliferator-Activated Receptor; SAM: S-adenosylmethionine.

In this write up we will consider the two broader aspects of nutritional management in PE:

- Nutritional management in women affected by preeclampsia
- Nutritional management to prevent preeclampsia or HDP gestosis

Preeclampsia is a type of hypertensive disorder which is classified as abnormal blood pressure after 20 weeks of gestation with proteinuria and the severe disease is associated with systemic involvements such as hepatic, renal and/or haematological. PE occurring before 34 weeks has been identified as severe type of the disease than the one occurring after 34 weeks. Women with chronic hypertension are at higher risk of developing PE and gestational hypertension (GHT) has been found to be preceding PE 40% of the times. Many women present with hypertension intrapartum or postpartum de-novo and therefore the term Gestosis seems appropriate to accommodate the entire spectrum of the disorder. Inflammatory response is the common pathway leading to endothelial dysfunction and multisystemic affection and much of this seems to be driven by nutritional factors. Also the pathogenetic pathways are similar and point towards oxidative stress and other factors.

Preeclampsia pathogenesis, nutritional basis

Several studies have drawn attention to associations between nutrition and preeclampsia and following factors are responsible for occurrence of preeclampsia

- High caloric consumption especially fortified and added sugars
- Increased dietary trans fats especially the PUFA
- Anaemia and lower ferritin levels
- Protein energy malnutrition
- Vitamin D and calcium deficiency
- Deficient micronutrients such as folates, Vitamin E & B12
- Lower fibre intake.

Maternal weight, obesity or high BMI especially periconceptional are risk factors for development of gestosis. Excessive weight gain during pregnancy has higher incidence of PE compared to mothers with normal weight gain or for that matter to those obese women with normal weight gain. Such a weight gain can be a result of excessive water retention. Higher the BMI, higher the blood pressure and especially positive correlation of weight with systolic blood pressure is observed. Surprising enough women with GHT have been observed to have a reduced fat percentage depicting low energy intake and reduced stored energy. Increased weight is the

result of on the total body water and extracellular water in pregnant women with gestational hypertension. Additionally higher intracellular fluids due to fluid retention is contributory. This is a result of low energy and low protein intake [5].

Macronutrients are an important part of the nutritional planning and comprise of the proteins, carbohydrates and fats and are essential to optimise the increase energy needs of the pregnancy. Proteins, rightly referred to as the building blocks are much needed during pregnancy to contribute to the increased tissue formation for the foetus, placenta, and the mother. Embarking on a pregnancy with a setting of protein deficient diets and its consequence is similar to a "kwashiorkor" like situation further aggravated by pregnancy and its demands (Figure 1).

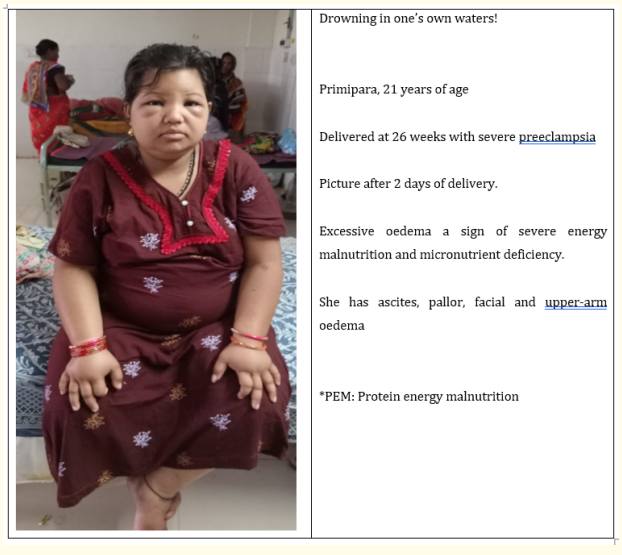

Figure a: Severe preeclampsia mother post-delivery with severe oedema and PEM* facies (Figure 1).
Courtesy: Dr Indira Palo, Associate Professor, Behrampur, Odisa, India.

Abnormalities in the carbohydrate metabolism leading to gestational diabetes or overt diabetes are associated with pregnancy hypertension. Perinatal outcomes of pregnant women with mild glucose intolerance or GDM show significantly higher rates of preeclampsia [6]. The rate of preeclampsia has been found to correlate with the level of glycaemic control with 7.8% with FPG <105 mg/dL compared to 13.8% that is nearly the double quantum with FBL >105 MG/DL[6]. Compared with nondiabetics, women with diabetes are at considerably higher risk for HDP to an extent that 20% of pregnant diabetic women will develop GHT and/or preeclampsia. Associated risk factors identified are underlying microvascular complications, pre-existing hypertension, poor glycaemic control [7]. Hyperinsulinemia and or excess free fatty acids have been proposed to activate an enzyme, the vascular superoxide producing nicotinamide adenine dinucleotide phosphate reduced oxidase which has a prominent role to play in oxidative stress and inflammation. Lipids are found to be increased during pregnancy in the maternal blood and these changes are profound in women who develop PE. Increased triglycerides and low high density lipoproteins (HDL) have been reported in women with PE. Dyslipidaemia is also a result of high carbohydrate and fatty acids containing diets. Low dietary fibre intake contributes to the occurrence of all the above metabolic abnormalities and leads to hypertension.

Micronutrient deficiencies have been identified to contribute to the occurrence of gestosis and diet fortification or supplements have shown beneficial result. Hyperhomocysteinemia is a result of folate, vitamin B12, vitamin B6, and choline regulation and is linked to cardiovascular disease and other adverse effects if present in elevated levels. Vitamin B6 is involved in this pathway as a cofactor for homocysteine metabolizing enzymes. In pregnancy, elevated homocysteine can increase the risk of placental vascular disorders, preterm birth, low birth weight, and small-for-gestational-age infants and influence levels of DNA methylation, thereby epigenetically influencing gene expression which can be responsible for transgenerational disease presentation (Figure 3).

The malady continues further as these neonates borne in the environment of stress and deprivation are phenotypically programmed as SGA babies programmed to serious lifestyle disorders in the future such as diabetes, cardiovascular morbidity, coronary heart disease. chronic kidney disease. All this seems to be a result of reduced adiposity, pancreatic cells, nephrons and high insulin resistance (Figure 4).

Dietary deficiency of calcium and vitamin D has been found to be associated with occurrence of gestosis. Reduced calcium stimulates the parathyroid gland to secrete parathyroid hormone (PTH). Along with vitamin D, PTH causes increase intracellular calcium by increasing the cell membrane permeability. Calcium influx in

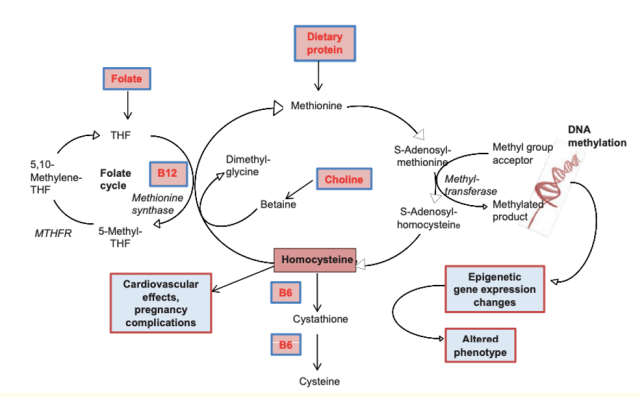

Figure 3: Dietary factors influencing homocysteine metabolism and DNA methylation. Folate, vitamin B6, vitamin B12, choline, and methionine from dietary protein all interact to maintain appropriate levels of homocysteine and regulate DNA methylation. Epigenetic processes including such DNA methylation modify phenotypic outcomes, with long-term effects on health and disease (The International Federation of Gynecology and Obstetrics (FIGO) recommendations on adolescent, preconception, and maternal nutrition: "Think Nutrition First).

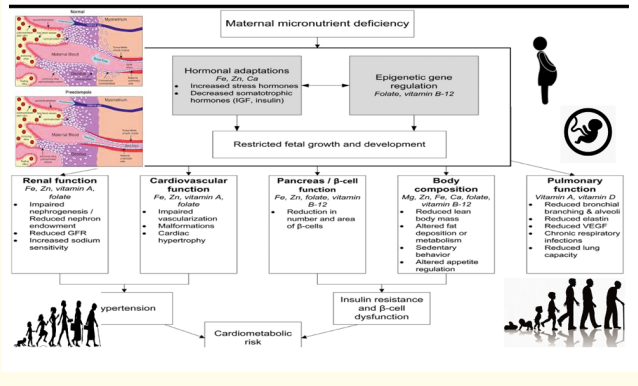

Figure 4: Maternal micronutrient deficiency leads to FGR and consequent modification in the phenotype of the bay and programming for future metabolic diseases in adult life.

the intracellular space causes vascular smooth muscle contraction leading to vasoconstriction resulting in raised blood pressure [8]. Maternal vitamin D deficiency at 23-28 weeks gestational age is strongly associated with occurrence of severe PE [9]. Vitamin D intake is postulated to help maintain calcium homeostasis thus help in regulating blood pressure [10] and may directly suppress the vascular smooth muscle cells proliferation [11]. Vitamin D is acts as a powerful endocrine suppressor of renin biosynthesis. The renin-angiotensin system is known to influence the blood pressure regulation [12] adipokines are known to modify the endothelial and vascular health and vitamin D contributes in their synthesis [13]. Nifedipine is a potent antihypertensive used in hypertensive crisis and acts as a calcium channel blocker. Vitamin D supplementation potentiates the action of nifedipine by shortening the time to blood pressure control, and prolong the action thus preventing the occurrence of hypertensive crisis and this action is brought about by immunomodulatory mechanism [14]. Magnesium contributes in similar pathway by releasing the prostacyclin from the endothelial cells. Prostacyclin causes vasodilatation and inhibition of platelet activation [15].

To thwart the endothelial dysfunction and prevention of the oxidative stress dietary or supplementary anti-oxidants can be effective and such benefits have been demonstrated especially in women with low dietary anti-oxidants. Lower rate of preeclampsia after antioxidant supplementation in pregnant women with low antioxidant status [16].

Anaemia is reduced oxygen carrying capacity and is a risk factor for occurrence of gestosis through its effect on inducing an inflammatory response and oxidative stress. This association however is conflicting in case of preeclampsia where the haemoglobin level may be increased due to relative haemoconcentration ones the disease is overt. It's a good practice to interpret this correctly in view of the fact that after delivery women with preeclampsia present with severe anaemia disproportionate to the blood loss representing haemoconcentration during the antenatal period.PE mothers are known to have lower intravascular volumes due to vasoconstriction and increased endothelial permeability which may be a result of hypoproteinaemia. Additionally anaemia is associated with deficiency of E-CR1 (Human erythrocyte complement receptor type 1) a complement regulatory protein which aids in immune complex clearance mechanism in the human. E-CR1 deficiency is noted in preclampsia [17] similar to in immunological conditions such as

SLE and explains the immunological and inflammatory pathway of HDP-gestosis. Anaemia commonly is a result of iron deficiency and ferritin levels are the reliable markers of iron stores. Serum ferritin levels are significantly high in hypertensive women compared to normotensive women with a positive correlation with both systolic as well as diastolic blood pressure [18]. Increased ferritin levels represent cellular damage or haemolysis and high ferritin levels in the third trimester are associated with poor perinatal outcomes [19]. Due to increase foetal demand in the third trimester the ferritin levels are low in healthy pregnancy [20].

Patient signs and symptoms related to nutritional deficiencies in pregnancy

- Pedal oedema and anasarca: Signs of water retention and protein deficiency and inactivity
- Food cravings, pica: Lack of micronutrients
- Aphthous ulcers, glossitis: B12, iron deficiency
- Muscle and leg cramps, spasms: Calcium, vitamin D and E deficiency
- Geophagia (Pica for soil): Calcium and iron deficiency.
- Excessive thirst: Water retention, starvation, diabetes, metabolic syndrome

Interestingly women practising geophagia have been observed to have remarkably low levels of haemoglobin, haematocrit, ferritin levels and calcium levels [21]. These indicate iron deficiency responsible for adverse perinatal outcomes [22]. Geophagia is associated with lead and arsenic poisoning and helminthiasis and should be looked for and discouraged.

Controversies in nutritional studies in preeclampsia [24]

Study from Denmark concluded that calcium, magnesium, folate, vitamin C, D, E or milk, did not affect the risk of hypertension. Similar study form the USA failed to associate nutrition with hypertensive disorders of pregnancy. Magnesium supplementation haven't showed beneficial effect in reducing hypertension in pregnancy [23]. Data from recently updated Cochrane reviews did not support routine supplementation of vitamins C, E or D for either the prevention or treatment of preeclampsia. Evidences are also poor to support zinc or folic acid supplementation for preeclampsia prevention

Nutritional recommendations in management of preeclampsia

The World Health Organization recommends the administration of 1.5-2.0g of elemental calcium to pregnant women for the prevention and treatment of hypertension in pregnancy, in areas where dietary intakes of calcium are low. Dietary inclusion of fibre or more than 20-30 g per day as consumption of at least 21.2g of total fibre/day reduced the risk of developing hypertension by 67%. This also was seen to be associated with reduction in triglycerides and increase in the HDL-cholesterol. Dark chocolate, flavonoid-rich food, and long-chain polyunsaturated fatty acids might also be candidates for prevention of preeclampsia. Overall the recommended increase in protein intake is 10-25g per day above the pre-pregnancy recommendation of 60g per day, thus equalling 75-80 g as recommended by the FIGO; though there is no significant increased need in the first trimester. The WHO recommends an increase of 1, 9, and 31 g per day in the first to third trimesters, respectively. Protein supplementation studies have produced varying/conflicting results. Balanced protein/energy supplementation, in which protein accounts for no more than 25% of total dietary energy, can improve maternal health.

The protein story and the rational of increased protein intake

There is a logic behind recommendation of increased protein intake during pregnancy. Amino acids, the breakdown products of proteins are the true building blocks necessary for optimising the maternal adaptation that occurs in response to pregnancy and to provide for the foetal growth. There is approximately 50-60% increase in the maternal blood volume. The protein needed for this change is manufactured in the liver as albumin. If albumin is deficient the plasma in the blood gradually migrates to the third compartment which presents first as water retention, then as oedema of various grades and excessive maternal weight gain. Additionally if the maternal diet is deficient in calories (approximate 2600-2800 kcal based on the formula of 20-25kcal/per kg bodyweight in women with normal BMI) the proteins are used for energy production and nothing is available for the production of albumin. This results in the reduction of the plasma volume in women with preeclampsia-gestosis leading to haemoconcentration. This reduction of blood volume signals the renal- angiotensin system as depletion of the intravascular volume leading to vasoconstriction and increased blood pressure. The kidney tries to reabsorb as much as water and salt to ensure optimum blood volume but lack of albumin in the blood further causes osmotic gradient toward the extravascular compartment. This further gets affected if the woman starts practising salt restriction. Thus there is further weight gain, oedema and hypertension. This cycle in its early stages can be broken by

adequate protein intake of 1gram per kg bodyweight in the earlier parts of pregnancy and may act as therapeutic approach to treat pregnancy oedema and prevent hypertension and reduce its consequences.

Preconceptional optimisation and nutritional guidance to prevent HDP-Gestosis

Optimization of BMI through weight loss in the obese and weight gain in the lean by proper planning of the energy consumption is essential. Ideal BMI for the Indian women recommended is 19-26 kg/M^2. Food frequency assessment to detail about the dietary composition meeting the macro and micronutrient needs and avoidance of junk food, excess sugar intakes, longer hours of starvation and water intake. Question about pica, constipation, gastro-colitis, dyspepsia, pica, obesity surgeries, helminthiasis etc. Screening for anaemia, hypothyroidism, hypoproteinaemia, insulin resistance, diabetes and correction of these disorders. Encouraging heathy nutrition and physical activity for at least 30-40 minutes daily. Supplements of calcium Vitamin D, DHA, folic acid.

Nutritional assessment and guidance is the mainstay of the antenatal counselling and has to be considered preconceptionally as well as at periodic intervals in each trimester to ensure proper dietary practices to prevent serious disorders such as gestosis.

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