HELLP syndrome: Incidence and Clinical management in the Tropics

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ABSTRACT

The continuum of pre-eclampsia/eclampsia accounts for about one third of maternal deaths in developing countries[1]. There is multi-systemic involvement in preeclampsia/eclampsia and haemolysis, abnormal liver function tests and thrombocytopaenia have been recognized as complications of pregnancy for many years.

The acronym HELLP syndrome was coined by Weinstein (1982) [2] when he described 29 cases of severe pre-eclampsia/eclampsia complicated by haemolysis, elevated liver enzymes and low platelets. He proposed that HELLP syndrome was a severe consequence of hypertension in pregnancy and that women were being misdiagnosed.

HELLP syndrome is a life-threatening complication of pre-eclampsia. Both conditions may occur during the latter stages of pregnancy, during parturition or in the puerperium.

Differential diagnoses that have to be considered are haemolytic uraemic syndrome, thrombotic thrombocytopaenic purpura, hepatic encephalopathy, viral hepatitis and disseminated intravascular coagulopathy from other aetiologies[3]. In the Tropics, the co-existence of severe malaria with HELLP syndrome may further darken maternal prospects for survival [4,5].

EPIDEMIOLOGY

HELLP syndrome occurs across all ethnicities, races, socio-economic classes and age ranges. It may develop both in the primigravidae and multigravidae and its incidence ranges between 0.2- 0.6% of all pregnancies[6,7]. In the USA, Sibai et al identified the syndrome in 2- 20% of pre-eclamptic patients and in 10% of eclamptic patients[8]. In Indonesia, the syndrome accounted for 22.2% of maternal mortality cases in 2002[9].

Loki et al (1995) reported an incidence of 2.96% among primigravidae in Congo Brazzaville[10] while in Mali in 2005, HELLP syndrome was responsible for 0.58% of Intensive Care Unit admission and 6.2% of obstetrical emergencies and was diagnosed in 18% of patients with toxaemia of pregnancy and was responsible for 33.3% of maternal deaths[10].In a recent study in Ile-Ife, Nigeria, Makinde et al found that six (17.6%) of 34 consecutive cases of severe pre-

eclampsia/eclampsia in a one-year period developed HELLP syndrome. In that study, four (33%) of the 12 eclamptics developed HELLP syndrome and all died and were all unbooked patients; only 1/10 (10%) of the cases of imminent eclampsia and 1/12 (8.3%) of severe pre-eclampsia developed the syndrome and none of these latter cases died[11].

PATHOPHYSIOLOGY

The aetiology and pathogenesis of pre-eclampsia and HELLP syndrome remains unclear. However, it is believed that the basic pathology in the development of both is endothelial cell injury. The injury is believed to cause vascular constriction within multiple organ systems, activation of the coagulation system, increased capillary permeability, and platelet activation with platelet consumption in the microvasculature, all resulting in hypertension, proteinuria, oedema, and thrombocytopaenia. Why certain women with severe pre-eclampsia develop HELLP syndrome is unclear, but it has been postulated that these women may have more endothelial injury with greater activation of the coagulation system. Immunologic factors have also been proposed as the underlying iniator of pre-eclampsia and HELLP syndrome. Maternal cell-mediated immune response to pregnancy with cytokine-mediated endothelial damage may be an important factor.

In HELLP syndrome, there is intravascular platelet activation resulting in the release of Thromboxane A_2 and serotonin. Thromboxane and serotonin cause vasospasm, platelet aggregation and further enhances endothelial damage already present in pre-eclampsia. The fact that thrombocytopaenia occurs secondary to increased platelet consumption or destruction is in concurrence with the finding of increased megakaryocytes in bone marrow studies[13].

CLASSIFICATION

Criteria to establish the diagnosis of HELLP syndrome generally accepted are as follows:

- Haemolysis: abnormal peripheral smear, increased Bilirubin > 1.2 mg/dl, and increased lactic dehydrogenase >600 iu/L.
- Elevated liver enzymes: aspartate aminotransferase(AST) $\geq$ 72iu/L.
- Thrombocytopaenia: platelet count < 100000/mm^3.

The platelet count has been found to be moderately predictive of the severity of cases of HELLP syndrome. Martin et al[7], developed the **Mississippi triple class system** to classify cases that developed the syndrome. Thus, **class 1** is defined by the presence of micro-angiopathic haemolytic anaemia and hepatic dysfunction in addition to a maternal platelet count $\leq$ 50000/mm^3. **Class 2** is defined by a platelet nadir >50000 to $\leq$ 100000mm^3. **Class 3** is defined by a platelet nadir > 100000 to $\leq$ 150000mm^3.

HELLP syndrome may also be classified into complete and partial based on the distinguishing feature of platelet count[14]. There **is complete HELLP syndrome** if there is a mean platelet count of 52000/UL and **it is partial** if the mean platelet count is 113,000/UL. Sibai[8] reported 2(3.4%) out of 59 patients having **recurrent HELLP syndrome in subsequent pregnancies.**

CLINICAL FEATURES

The clinical presentation of most cases of HELLP syndrome usually does not differ from others that have only pre-eclampsia/eclampsia. Thus pain both epigastric and in the right upper quadrant of the abdomen, headache, blurred vision, nausea, vomiting, anorexia, malaise, jaundice and low grade fever were the common symptoms. Other uncommon symptoms are haematuria and evidence of gastrointestinal bleeding. In the presence of eclampsia, the patient may present in coma.

Since there is multisystemic involvement in pre-eclampsia/eclampsia, there may be maternal complications like pleural effusion, pulmonary oedema, laryngeal oedema, adult respiratory distress syndrome, cerebral oedema, retinal detachment leading to blindness, ascites, abruptio placenta, disseminated intravascular coagulopathy, subcapsular liver haematoma and rupture and ultimately maternal death.

The foetus may also present with features suggestive of intra-uterine growth restriction, foetal distress and ultimately foetal demise.

MANAGEMENT

The most important factor for successful management of patients with HELLP syndrome is meticulous medical management in a tertiary centre by a skilled multi-disciplinary team comprising the obstetrician, the neonatologist, the anaesthesiologist, the internists and Intensive-care nurses who are familiar with the clinical manifestations of HELLP syndrome. Efforts should be geared by appropriate health-care authorities in the Tropics to prevent treatment delays which may lead to substandard care of patients.

Since HELLP syndrome co-exists with pre-eclampsia/eclampsia, the modalities of management that would

be highlighted would address the triad.

- **Control/Prevention of seizures**. Magnesium sulphate is the drug of choice (gold standard) for the prevention and control of seizures. As an anti-convulsant, magnesium sulphate has been found to be superior to both diazepam and phenytoin. While being used, the patient's respiratory rate, tendon reflexes and urinary output have to be closely monitored to prevent magnesium toxicity.
- **Control of hypertension**. The objective of anti-hypertensive therapy is to avoid vascular damage due to blood pressure elevation without causing excessive reduction in blood pressure that would critically affect uteroplacental perfusion. The most commonly used threshold for treatment is a sustained diastolic blood pressure of 110mmHg or higher. There are several anti-hypertensive drugs that may be used during pregnancy. Oral anti-hypertensive agents that may be used in less acute situations include methyl-dopa, β-blockers like labetalol and calcium channel blockers like nifedipine.

In acute situations, intravenous agents like hydralazine and β-blockers like labetalol may be used. Drugs belonging to angiotensin converting enzyme inhibitors (ACEI) group are contraindicated in pregnancy because of the possibility of foetal nephropathy. The choice of anti-hypertensives during pregnancy should depend on the experience and familiarity of the individual clinician with a particular drug and on what is known about adverse maternal and foetal side effects.

- **Corticosteroids**. The use of corticosteroids was recommended after the observation that its administration for inducing foetal lung maturation exerted a temporary beneficial effect on the laboratory parameters of HELLP syndrome in the mother such as the platelet count. Studies have shown that high dose corticosteroids (dexamethasone) administration in the mother stabilized the condition of the patients to facilitate the transfer to a tertiary care centre and also expediting patients' recovery after delivery [13,15].
- **Volume expansion**. Prior to delivery, women with severe pre-eclampsia/HELLP syndrome often have a contracted circulating intravascular volume; it is therefore reasonable that plasma volume expansion should be carried out in order to improve maternal systemic and utero-placental circulation. However, a cautionary note must be sounded about volume expansion in the puerperium to prevent maternal circulatory overload as the venous volume rises during the period. Furthermore, while volume expansion is being carried out, close monitoring of maternal and foetal conditions must be done.
- **Prostacycline**. Prostacyclin given intravenously is a powerful vasodilator and the most potent inhibitor of platelet aggregation. Bolte et al used prostacyclin successfully in some patients with thrombocytopaenia and HELLP syndrome[13].
- **Serotonin (S_2-receptor blockers).** Pre-eclampsia has been recognized as an endothelial disease resulting in increased platelet aggregation. The selective blockade of the vasoconstrictor and platelet aggregating effects of serotonin mediated by its serotonin (S_2)- receptor may provide an attractive pharmacotherapeutic option in the management of severe pre-eclampsia. Blockade of the S_2-receptor with ketanserin may counteract serotonin dependent vasoconstriction and increased platelet aggregation that is characteristic of pre-eclampsia**. Ketanserin** when administered to a patient with HELLP syndrome brings about a rise in platelet count and a marked relief of epigastric pain.[13].
- **Plasma exchange therapy**. The use of fresh frozen plasma (exchange plasmapheresis) has been advocated in the treatment of HELLP syndrome, haemolytic uremic syndrome and thrombotic thrombocytopaenic purpura, all disease states in which microangiopathic haemolysis occurs. However, because exchange plasmapheresis is an invasive and expensive procedure of questionable benefits and that there is a high risk of plasma transmitted infections, it's use is not generally recommended [13,16].
- **Management of HELLP syndrome co-existing with severe malaria in pregnancy**. Malaria is endemic in the tropics. Due to diminished immunity in the pregnant woman, both humoral and cellular, malaria tends to be worse off in the pregnant female especially the primigravida and more so in the second trimester. Diallo et al (2005) and Chobli et al (1998) reported that when severe malaria co-exists with HELLP syndrome in the same patient the prognosis for the patient is further darkened. To further highlight

the problem of the two disease states co-existing, both may present with non-specific symptoms and signs. The physician working in the tropics should carry out confirmatory tests for malaria such as the rapid diagnostic test or standard microscopy and thereafter treat with effective antimalarials such as the **Artemisinin based combination therapy (A.C.T.)** when indicated and safe. Other strategies in the **Roll-Back Malaria initiative are the usage of combination of Sulphonamide/Pyrimethamine as Intermittent Preventive Therapy (I.P.T) to combat a presumed load of parasitaemia and** the usage of treated mosquito nets **(I.T.N)** by the pregnant female [18].

PREVENTION

The continuum of pre-eclampsia to eclampsia may be further complicated by HELLP syndrome. Makinde et al (2008) in Ile-Ife, Nigeria found out that 76.5% of cases of severe pre-eclampsia/eclampsia were unbooked and that all the cases of HELLP syndrome that died and all the perinatal deaths recorded were all among unbooked patients. In an environment like this, the Pre-eclampsia Community Guideline (PRECOG) recommendations when adhered to would go a long way in minimizing the incidence and complications of pre-eclampsia and eclampsia, the precursors of HELLP syndrome. The PRECOG provides an evidenced based risk assessment with criteria for early referral for specialist input, a 2-tiered schedule for monitoring women in the community after 20 weeks gestation for stepped-up care. Thus, any of the following risk factors for pre-eclampsia: maternal age greater than 35 years, nulliparity, interval of more than 10 years between pregnancies, previous pre-eclampsia, family history, multiple pregnancy, elevated blood pressure at booking and medical conditions such as pre-existing hypertension ,renal disease ,body mass index >35 kgm^{-2} and auto-immune disease should be identified before 20 weeks of gestation. Thereafter, there should be referral for specialist care before 20 weeks if there is history of previous eclampsia, multiple pregnancy, underlying medical conditions previously stated and occurrence of proteinuria > 300mg/24 hours. Lastly, after 20 weeks of gestation, and at every assessment, the following signs and symptoms should be identified and prompt and appropriate action taken: hypertension and proteinuria developing for the first time, symptoms of headache, visual disturbance or both, reduced foetal movement and a small for gestational age foetus. Should HELLP syndrome occur, substandard care consequent to treatment delays should be avoided.

CONCLUSION

The most important factor for successful management of HELLP syndrome is prompt and meticulous management in a tertiary centre by a skilled multi-disciplinary team familiar with the clinical manifestations of the syndrome.

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