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HELLP Syndrome: Incidence and Management

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Objective: To estimate the incidence of HELLP syndrome in the Bahrain Government Hospitals.

Design: A retrospective analytical study of all patient deliveries between 1st January, 2001 and 30th April, 2002 was undertaken.

Setting: Salmaniya Medical Complex, Jidhafs and Muharraque Maternity Hospitals. Additionally the Sitra, Riffa and Western Region Maternity Units were surveyed.

Methods: All patients admitted for delivery to Salmaniya Medical Complex together with the other satellite maternity units from the 1st January, 2001 until 30th April, 2002 were reviewed. Since none of the peripheral Government maternity hospitals would deal with such complicated cases, the four cases reported are truly representative of the incidence of HELLP syndrome in the Government Maternity Hospitals in Bahrain.

Results: A total of 16,060 patients were delivered in this period. Of these there were four cases of HELLP syndrome in the hospitals surveyed which indicate that

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incidence is 0.025% among those surveyed. Two patients were local Bahrainis and two were Indian. One case was admitted at 27 weeks of gestation, the second at 34 weeks, the third at 38 weeks, and the last manifested the symptoms in the peripartum period. In all cases there was an initial delay in the diagnosis and all required intensive care.

Conclusions: There was no maternal mortality and all babies are alive and healthy. The authors are of the opinion that there were some cases of HELLP syndrome that were not accurately diagnosed prior to delivery, and therefore not managed as aggressively as current thinking would recommend. A management protocol must be developed for this serious condition.

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Weinstein first described HELLP syndrome in 1982[1]. This acronym is used to describe a set of preeclamptic women who develop haemolysis, elevated liver enzymes and low platelets. The syndome has been considered a variant of preeclampsia, but it can occur on its own or in association with preeclampsia. Because the condition is serious and all too often is associated with poor maternal and foetal outcomes, obstetric care providers need to be aware of HELLP syndrome so that it can be identified early[2,3].

HELLP syndrome occurs according to Western European and North American statistics in approximately 0.2 to 0.6 percent of all pregnancies. In comparison, preeclampsia occurs in 5 to 7 percent of all pregnancies. Superimposed HELLP syndrome develops in 4 to 12 percent of women with preeclampsia or eclampsia[4]. When preeclampsia is not present, diagnosis of the syndrome is often delayed[5].

To date, the pathogenesis of HELLP is not fully understood. The findings of this multisystem disease are attributed to abnormal vascular tone, vasospasm and coagulation defects. So far, no common precipitating factor has been found. The syndrome seems to be the final manifestation of some insult that leads to microvascular endothelial damage and intravascular platelet activation. With platelet activation, thromboxane A and serotonin are released, causing vasopasm, platelet agglutination and aggregations, and further endothelial damage[2]. Thus begins a cascade that is only terminated with delivery[5].

Since the optimal management in these cases is dependent upon early diagnosis and adequate tertiary care, it was decided to carry out this study to estimate the incidence of HELLP syndrome in Bahrain government hospitals, to analyze the difficulties encountered with the diagnosis, and to discuss the therapeutic challenges associated with the management.

METHODS

Labour room registries of all patients admitted for delivery to Salmaniya Medical Complex together with those at the other satellite maternity units from the 1st January,

2001 until 30th April, 2002 were reviewed. The Intensive Care Unit (ICU) records were also examined for any missing cases of HELLP syndrome during this period. A total of four cases of HELLP syndrome were diagnosed and treated. Since none of the peripheral Government Maternity Units would deal with such complicated cases, the four cases are truly representative of the incidence of HELLP syndrome in the Government Maternity Hospitals in Bahrain. The cases are reported and described in detail with particular emphasis on difficulties in diagnosis along with the theraputic challenges.

Case No. 1

KSM is a 27-year-old Bahraini woman (Gravida 2, Para 0, Abortion 1) admitted via the Emergency Room at 27 weeks of gestation with a history of retrosternal pain, chest pains, malaise, and a loss of appetite of a few days duration. The fundal height corresponded to 24 weeks. The foetus was alive, lying in the longitudinal position and presenting by the head. The blood pressure (BP) was 140/90 mmHg and urinalysis revealed heavy albuminuria (three plus). Haematological investigations revealed a Hb of 10.5 Gm%, a platelet count of 34,000/mm^3, uric acid 226 μmol/L, urea 2 mmol/L and creatinine 45 μmol/L. Liver function tests, total protein, albumin and globulin levels were normal. The alanine aminotransferase (SGPT) 92 U/L, alkaline phosphatase 60 U/L and aspartate aminotransferase (SGOT) 351 U/L were also within normal limits.

A platelet transfusion of six units was begun. Haemoglobin electrophoresis, peripheral blood smear and lupus antigen test were normal. The following day, despite the platelet transfusion, the platelet count remained critical at 17,000/mm^3. The coagulation profiles however were normal. Treatment with platelet transfusions and fresh frozen plasma was continued. There was no evidence of renal impairment. Liver enzymes became high - alanine aminotransferase (SGPT) 984 U/L and aspartate aminotransferase (SGOT) 2906 U/L, and the BP was 156/92 mmHg. Urinary protein was found to be three pluses. A diagnosis of HELLP syndrome was made. Treatment continued with a fresh frozen plasma transfusion and plasmaphoresis through a Vascat in the femoral vein. The urinary output dropped to less than 250 mL/24 hours and laboratory findings of urea 8.4 mmol/L, platelets 39,000/mm^3, Hb 9.8 Gm% and BP 190/110 mmHg were determined. Non-stress test (NST) was normal. It was decided to induce premature labour. This was performed with prostaglandin (PGE_2) vaginal tablets. At this time she developed marked vulval oedema. She progressed into a spontaneous vaginal delivery of a premature and growth-retarded baby. The Apgar scores were nine and ten after one and five minutes. After delivery she was treated with hydralazine (Apresoline) 25 mg bid, lasix (Frusemide) 40 mgs I.V. The urinary output was closely monitored.

Three days post-delivery, she was taking hydralazine (Apresoline) tds, lasix (Frusemide) tablet 20 mg bid, methyldopa (Aldomet) tablets 500 mg tds and methyl prednisolone 250 mg daily along with cefuroxime (Zinnat) tabs 500 mg tds. On the twelth postnatal day she was still on hydralazine (Apresoline), methyldopa (Aldomet) and lasix (Frusemide). Her general condition improved and she was discharged. Because of persistent albuminuria she underwent a renal biopsy which revealed lupus nephritis class II. Her child was alive and healthy.

Case No. 2

SMH is a 33-year-old Bahraini woman (Gravida 4, Para 3, Abortion 0) who was admitted at 37 weeks gestation. She complained of upper abdominal pain, headaches and vomiting. Her previous obstetrical history included three normal spontaneous vaginal deliveries at term of live, healthy babies. The antenatal care during this pregnancy was normal and her investigations were as follows: blood group A rhesus positive, sickle cell trait, hepatitis B negative, and she had a glucose 6 phosphate dehydrogenase (G6PD) deficiency.

On admission the patient was restless and pale. There was no evidence of cyanosis or jaundice; the BP was 200/127 mmHg and urinalysis revealed proteinuria three plus. She had frequent uterine contractions. The foetal lie was longitudinal with cephalic presentation at the pelvic brim. The foetal heart rate was 140 beats/minute, regular in rate and rhythm. Ophthalmoscopy was done which revealed a blurred optic disk but no evidence of papilloedema. Blood vessels and macula were normal. Because of Hb 9.0 Gm%; WBC 8,000/mm3; platelets 5,000/mm3, the patient was started immediately on magnesium sulphate (Mg SO4) first as a four Gm bolus dose and then as an I.V. drip. She was also put on a hydralazine (Apresoline) drip. The BP gradually settled to 140/90 mmHg and the patient was induced with prostaglandins (PGE_2) (half tablet) vaginally. She had a spontaneous vaginal delivery of a live and healthy female baby weighing 2300 grams. The Apgar scores were nine and ten. The third stage of labour was uncomplicated.

After delivery the reports indicated elevated liver enzymes, (SGPT of 890 U/L, SGOT of 1450 IU/ L), low platelet count, 60,000/mm3, and a raised bilirubin level, (direct 143 mol/L); alkaline phosphatase 130 U/L, gamma glutamyl transferase (GGT) 36 U/L. The coagulation profile was normal (PT 18/12, PTT 23/30). Jaundice and a palpable liver were detected. HELLP syndrome was diagnosed. She was managed initially with two units of packed red cells transfusion as her Hb had dropped to 6.9 Gm%, plasmaphoresis once daily and then according to the platelet count and lactic dehyrogenase (LDH), methylprednisolone 20 mg twice daily, ranitidine (Zantac) 300 mg daily and cefuroxime (Zinnat) 500 mg twice daily. After three days her condition had improved - Hb was 8.2 Gm%, platelet count was 171,000/mm^3, serum total bilirubin was 19 mol/L, blood urea 19.4 mmol/L, and uric acid was 586 μmol/L. Ultrasound of kidney, ureter and bladder revealed no abnormality. Two days later she was discharged.

She was followed up in the outpatient clinic over the next three months. The baby was alive and healthy. The BP was 130/85 mmHg; the Hb, WBC, platelet count, urea, uric acid, creatinine, liver enzymes and bilirubin were all normal.

Case No. 3

LKP is a 36-year-old Indian woman (Gravida 2, Para 1, Abortion 0) admitted at 33 weeks of gestation because of generalised oedema and severe pregnancy induced hypertension

(PIH), which manifested at 31 weeks of gestation. She gave a history of a Caesarean section in 1999 due to foetal distress. During this pregnancy, she developed hypertension, BP of 150/90 mmHg, ten days prior to her admission. She was given dietary advice and prescribed methyldopa (Aldomet) 250 mg tablets thrice daily.

On admission her general condition was satisfactory apart from mild hypertension. The urinalysis was free of albumin. Liver function tests (total bilirubin 17 mol/L, direct bilirubin 14 mol/ L, AST 35 Iu/L, ALT 50 Iu/L, total protein 52 G/L, albumin 22 G/L, globulin 30 G/L) and fibrin degradation products (less than 1,000) were normal. However the uric acid was high at 453 μmol/L. Fundoscopy was within normal limits. She remained in the hospital for two weeks with fluctuating blood pressures despite medication. She had also undergone regular tests of foetal well-being - non-stress tests (NST) twice weekly and a biophysical profile once weekly. At 35 weeks of pregnancy, she developed severe nausea and epigastric pain. Her investigations revealed elevated liver enzymes; LDH (1564 U/L), SGPT (1460 U/L) and elevated urea (14.6 mmol/L), but the platelet count was normal at 280,000/mm^3. Urine revealed only a trace of albumin. Her BP remained at 160/90 mmHg, but there were positive plantar reflexes. The clotting profile was normal. She was diagnosed to have early signs of eclampsia. Urinalysis revealed heavy albuminuria. Non-stress test (NST) of the foetus showed poor beat-to-beat variation. The bilirubin 18 mol/L was borderline. Uric acid and liver enzymes were still elevated. The Hb level and platelet count however remained normal.

On the 16^{th} day of her hospitalization she underwent a lower segment Caesarean section because of foetal distress. A live 3.5 kg baby male was born, but the patient had a postpartum haemorrhage of 1800 mL. She responded to a blood transfusion and oxytocin drip. Her laboratory results still suggested HELLP syndrome. The patient gradually improved and her BP, liver enzymes, serum proteins, serum total bilirubin and creatinine all returned to normal. The patient was discharged on the 26^{th} day following admission.

Case No. 4

SB, a 31-year-old Indian woman (Gravida 3, Para 2, Abortion 0) was admitted at 38 weeks gestation with a history of right upper quadrant abdominal pain of two weeks duration, generalized weakness, malaise, anorexia and diarrhoea. Initially she was admitted as a case of urinary tract infection. She complained of pain in the right loin and hypochondrium. There was no history of pruritis, urinary symptoms or bleeding tendency. Eight years earlier, she had been treated for pulmonary tuberculosis in India. There were no significant antenatal complications. She gave a history of a previous vaginal delivery and a Caesarean section because of foetal distress. On admission, she was conscious, oriented but pale and icteric. There was no oedema and the vital signs were normal. Examination of the cardiovascular and respiratory systems revealed no abnormality. The foetus was alive in a cephalic presentation.

Urinalysis was negative for albumin; Hb 13.8 Gm%, WBC 7,000/mm^3, platelets 120,000/mm3 decreasing very rapidly, urea normal (4.5 mmol/L), uric acid 480 μmol/day and increasing, and with a bicarbonate of 17 mmol/L. The liver function tests showed

elevated total bilirubin (17.4 mol/L) and high direct bilirubin (98 mol/L). The alkaline phosphatase was high (603 U/L) and liver enzymes SGPT (1248 U/L) and LDH (1860 U/L) were elevated. A non-stress test (NST) was done and only mild, irregular contractions were detected. The foetal heart beat was regular in rate and rhythm. Coagulation and hepatitis profiles were normal. The following morning she progressed to a normal spontaneous vaginal delivery of a live male infant weighing 2820 grams. The Apgar scores were eight and ten at one and five minutes respectively. The third stage of labour was complete with minimal blood loss. A vaginal pack was inserted at the episiotomy site due to excessive bleeding.

Five hours following delivery the patient was observed to be deeply jaundiced; the vaginal pack was removed and a local vaginal haematoma was observed at the site of the episiotomy. It was therefore reopened and a significant blood clot removed. Because of continuous leakage of blood from the episiotomy, it was decided to leave it open.

The case was diagnosed as HELLP Syndrome with associated DIC. Peripheral blood smear, Hb 9.8 Gm%, and a coagulation profile were normal. She was given Tazocin 4.5 grams 8 hourly, Metronidozale 500 mg I.V. eight hourly, and ranitidine (Zantac) one tablet daily. Hydration was increased due to decreasing urinary output (200 mL/5 hours); fresh frozen plasma (FFP) was given at the rate of two units every six hours. The patient continued to be jaundiced with increased bleeding tendencies. She received five units of blood and 12 units of FFP. Haematology revealed Hb 7.2Gm%, WBC 22.9/mm^3, alkaline phosphatase 327 U/L, PT 27/12, PTT 49/29, INR 2.3.

On the fourth day of her admission, the patient became disoriented with altered sensorium. Her reflexes were exaggerated which was assumed to be due to hepatic encephalopathy. She later suffered a convulsion which lasted for 45 seconds. The BP was 160/100 mmHg. She was given an injection of valium (Diazepam) 10 mg IV along with a $MgSO_4$ bolus dose of four grams. Fundoscopy was done but no evidence of vascular changes or papilloedema was seen. The following three days she was monitored continuously, and given Neomycin 500 mg qid and Vitamin K ten mg for three days. Besides that, she was treated with phenytoin 100 mg tds, ranitidine (Zantac) 150 mg bid, and methyldopa (Aldomet) 250 mg tds. Her condition improved and she had no further convulsions. An MRI revealed no area of ischaemia and no venous thrombosis. She continued with the above treatment and received a total of six units of packed red cells, 16 units of FFP and two units of cryoprecipitate. Laboratory values showed Hb 8.7 Gm%, platelets 260,000/mm^3, WBC 40,900/mm^3 mostly polymorphs, blood urea of 2.6 mmol/L, and liver function tests to be normal.

Later the Vitamin K and the Neomycin were discontinued. The episiotomy was resutured and she was discharged with her baby on the 20th day following admission.

DISCUSSION

HELLP syndrome is associated with poor maternal and foetal prognosis[1-4]. Maternal mortality ranges from 3.5% to 24%[5]. These patients are at greater risk for complications

such as liver rupture, disseminated intravascular coagulation, abruptio placentae and acute renal failure[6,7]. Perinatal mortality is equally high, ranging from 100 to 367 per 1000 live births. It can be due to large placental infarcts, abruptio placentae, intrauterine growth retardation, intrauterine asphyxia, and prematurity. HELLP syndrome occurs in 0.2-0.6% of all pregnancies[5]. In this series however, the incidence is significantly less. This may be due to a genuine difference or even misdiagnosis of milder cases. In our opinion, the latter cannot explain the marked difference.

There is minimal data regarding subsequent pregnancies and the long-term prognosis after the syndrome of haemolysis, elevated liver enzymes, low platelets and acute renal failure[2,6-8]. Sibai and Ramadan[8] in a study of 32 parturients with HELLP syndrome, indicated that patients have an increased risk of developing preeclampsia in subsequent pregnancies. However, pregnancy outcome and long term prognosis are usually favorable in the absence of preexisting chronic hypertension. Risks were significantly increased for both mother and foetus if the parturient had pre-existing chronic hypertension. This study recommends that parturients with preexisting chronic hypertension who have had HELLP syndrome be counseled regarding the high likelihood of severe preeclampsia and poor foetal outcome in subsequent pregnancies[8].
Inadequate uterine perfusion has an important role in the etiology of pregnancy induced hypertension (PIH) and HELLP syndrome. A possible mechanism initiating the process could be a developmental defect of the spiral arteries of the uterus. Typically, with early trophoblastic invasion the muscular walls of the spiral arteries lose their ability to contract. In patients with PIH however, this process is incomplete and the spiral arteries retain some of their contractability. This is thought to result in the ischaemic process producing placental necrosis with subsequent release of tissue thromboplastin and renin into the maternal circulation[9].

An alteration of the renin-angiotensin system occurs producing vasospasm with generalized tissue hypoxia and vascular endothelial damage. Aldosterone secretion is increased, resulting in sodium and water retention. Activation of the maternal coagulation system and enhanced platelet aggregation resulting from vascular endothelial damage produces fibrinoid deposits in the basement membranes of smaller vessels, especially those of the placenta. Overall, a generalized "capillary leak" causes a fluid shift into the extracellular space. The decrease in colloid oncotic pressure (COP), hypovolemia, haemocentration, and increased blood viscosity develop secondary to the accompanying loss of albumin[10].

With HELLP syndrome, striking hepatic changes occur. Hepatic blood flow is obstructed when hepatic sinusoids develop fibrin deposits. The liver becomes swollen and engorged stretching Glisson's capsule, producing epigastric and/or right upper quadrant pain and tenderness. Haemorrhagic periportal necrosis, subcapsular haemorrhage, and in severe cases, spontaneous hepatic rupture, could occur. The liver enzymes become elevated and the SGOT value can be 700 U/mL or more. Infrequently, acute hepatic failure and jaundice will appear[11]. Maternal hypoglycemia associated with HELLP syndrome is a particularly grave laboratory finding. However, the aetiology of the value is still obscure.

Because of misdiagnosis and less than optimal treatment is not uncommon with HELLP syndrome, proper management relies on a thorough understanding of its differential diagnosis. The non-specific, mostly gastrointestinal symptoms of HELLP lead many to suspect gastrointestinal diseases, including hepatitis, gastritis, pancreatitis, cholecystitis, and appendicitis. When considering these diagnoses in pregnant patients, the physician should obtain liver function enzyme values and a platelet count[12-14]. Supportive signs of preeclampsia, such as mild hypertension or oedema, should influence the physician to seriously consider HELLP and preeclampsia. Hepatitis often presents with a higher liver enzyme level and rarely with a significant thrombocytopenia of HELLP.

The haemolysis associated with HELLP syndrome is consistent with a microangiopathic haemolytic anaemia. Vascular endothelial damage with fibrin deposition results in red blood cell fragmentation. The peripheral blood smear reveals crenated and distorted red cells with spiny projections along the borders (Burr cells)[10]. Also present are schistocytes, which are small, irregularly shaped red cell fragments. The low platelet counts associated with HELLP syndrome appear to be caused by increased peripheral vascular destruction. Bone marrow studies reveal an increase in megakaryocytes which suggest rapid platelet turnover. In addition, recent studies suggest an associated platelet activation as well as platelet dysfunction[11].

The management goals of HELLP are based on optimizing the maternal condition while weighing the perinatal risks of premature delivery[15]. Care is primarily supportive and anticipatory with the focus on determining the safest timing and route of delivery. The first task is to confirm or exclude HELLP or preeclampsia from the other diseases included in the differential diagnosis. A chemistry panel including blood urea nitrogen (BUN), creatinine, liver function enzymes including alanine and aspartate aminotransferases, LDH, glucose, and uric acid should be obtained. A complete haematological evaluation needs to be accomplished through a complete blood count with platelets and peripheral smear, PT, PTT, and fibrinogen[2,10,12-16]. The laboratory parameters of HELLP syndrome are not independent risk factors for adverse maternal outcome[17,18].

Again, definitive therapy for the patient with HELLP syndrome is delivery. Prior to delivery, aggressive control of the disease is the goal. Pregnancy is usually allowed to continue as long as there is no apparent evidence of foetal and/or maternal compromise. Obstetric management is directed toward stabilizing the cardiovascular system, improving intravascular volume, preventing intracranial haemorrhage, and controlling central nervous system irritability. As noted previously, obstetric management of the patient presenting with HELLP syndrome is less clearly defined. Predicting the ultimate disease severity is difficult because it depends on numerous factors, particularly the aggressiveness and timely pregnancy interruption, which should be early in the terminal phase of accelerated disease progression[4].

Although uterine irritability is frequently present, and the cervix is often "ripe" for induction, a significant number of these patients undergo an operative delivery due to foetal distress. In Weinstein's series of 57 patients with HELLP syndrome, 29% of the

multiparous patients and 79% of the primigravida patients were delivered by Caesarean section[13].

Proposed new therapies to permit prolonging preterm pregnancy and foetal maturation include vasodilation therapy using fluids and antihypertensives and intensive corticosteroid therapy used intravenously, administered as high-dose dexamethasone, usually ten mg every twelve hours. The latter theory appears to improve foetal and maternal health with the added benefit of accelerating postpartum recovery from HELLP syndrome[19].

The reasons for the use of invasive monitoring are based upon the following criteria:
1) these patients are critically ill and should be managed as such; 2) the severity of disease is often not clinically apparent; and 3) many of these patients will deliver operatively and haemodynamic alterations can be more effectively controlled. Close attention to fluid status and parenteral fluids could help prevent pulmonary oedema. Central haemodynamic monitoring with a pulmonary artery catheter could be required should there be refractory pulmonary oedema or oliguria[17-20].
The four cases reported demonstrate the need for a high index of suspicion for the disease because the presentations vary from one case to another. The D-dimer test is a more sensitive indicator of subclinical coagulopathy, and could be positive before coagulation studies become abnormal[17]. In addition to the need for early diagnosis, it seems that the cases treated with corticosteroids were resolved more quickly[19]. Tertiary care and ICU management are imperative in these cases as the condition may deteriorate very quickly. One of our cases was diagnosed as thrombocytopaenia and several units of platelet transfusions were given without improvement. In fact recent reports have shown that this treatment is useless for cases of HELLP syndrome[16,17,20].

The last case was complicated by DIC and cholestasis which contributed to the intial delay in diagnosis. In the light of the need for a multidisciplinary tertiary approach for these patients, it is vital that each Obstetric Department have a detailed protocol for the management of HELLP syndrome. The protocol must then be regularly updated.

CONCLUSION

There is significant maternal and foetal risk of morbidity and mortality associated with HELLP syndrome. Prompt diagnosis and appropriate treatment is crucial to optimize outcome. Patients with HELLP syndrome should be treated in tertiary care centres that are prepared to handle a multitude of associated maternal and foetal complications, particularly management of these new-born infants at risk for perinatal asphyxia and a potential for long-term neurologic sequelae. Because HELLP syndrome occurs frequently at premature gestational ages, the obstetrician is faced with deciding the optimal timing and route for delivery. Guidelines for the supportive care before delivery and postpartum have been suggested. Review of the recurrent risks in subsequent pregnancies, selection of effective contraception, and consideration of preventative strategies must be considered for a patient who has had HELLP syndrome.

The four cases presented here had no mortality. Having reviewed the records of the 16,060 deliveries in this study however, the authors are of the opinion that there were some cases of HELLP syndrome that were not accurately diagnosed prior to delivery; and therefore not managed as agressively as current thinking would recommend. A management protocol must be developed for this serious condition.

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