HELLP Syndrome and the Effects on the Neonate

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Abstract

HELLP syndrome is most often diagnosed between 27 and 37 weeks gestation. It is also a diagnosis that can be seen during the postpartum period. The effects of HELLP syndrome on the neonate can be significant. Recognizing the risks to the neonate can assist the clinician in preparing for the neonate prior to delivery. In doing so, the mortality and morbidity rates can be reduced.

Keywords: HELLP syndrome; neonate

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The purpose of this article is to review the perinatal and neonatal effects of maternal HELLP syndrome and provide recommendations for monitoring and management.

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HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome is a complicated maternal condition consisting of a variety of symptoms of differing severities. HELLP syndrome is diagnosed and characterized by three main factors: hemolysis (abnormal peripheral smear), elevated liver enzymes (serum aspartate aminotransferase [AST] >70 units/L), and a low platelet count (platelet count <100,000/mcL).[1] The gestational age of onset at which pregnant women develop HELLP syndrome varies. The average onset often occurs between 27 and 37 gestational weeks, while postpartum period onset begins within the first 48 hours after birth.[1] According to the Preeclampsia Foundation,[2] approximately 48,000 women develop HELLP syndrome each year. HELLP syndrome occurs in approximately 10–20 percent of women with pregnancy-induced hypertension (PIH) or preeclampsia as well as another 10–20 percent of women without gestational hypertensive disease.[3] Using the Mississippi classification system, HELLP syndrome is classified into three categories, which are described in Table 1. This classification system allows practitioners to determine the severity of the disease.

HELLP syndrome may include one or more of the following physical symptoms: headache, nausea, vomiting, indigestion with pain after eating, epigastric tenderness, substernal tenderness, right upper quadrant pain, shoulder pain, bleeding, visual disturbances, swelling, elevated blood pressure, and protein in the urine.[2] Although these signs and symptoms are more often associated with PIH, they can also be early signs of HELLP syndrome. If left untreated, HELLP syndrome can progress to liver rupture and/or stroke, which results in a critically ill mother or maternal death.

MATERNAL PATHOPHYSIOLOGY

The pathophysiology of HELLP syndrome is poorly defined, although microvascular endothelial activation and cell injury is thought to be the main cause.[4] During the 16th–22nd week of pregnancy, there is defective remodeling of the vasculature which results in inadequate placental perfusion.[4] The placenta then becomes hypoxic and releases vascular endothelial growth factor (VGEF) receptor-1, which then binds VEGF and placental growth factor, preventing them from binding to endothelial cell receptors.[4] This causes the symptoms of hypertension, proteinuria, and platelet activation/aggregation.[4] Once this occurs, the coagulation cascade is activated, and platelets are consumed as well as hemolysis from the shearing of erythrocytes traveling through the capillaries.[4]

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TABLE 1 ■ Mississippi Classification System[2]

Class	Severity	Platelet Count
Class 1	Severe thrombocytopenia	Below 50,000/mcL
Class 2	Moderate thrombocytopenia	50,000–100,000/mcL
Class 3	Mild thrombocytopenia	100,000–150,000/mcL

ADDITIONAL PATHOPHYSIOLOGY THEORIES

Multiple theories exist such as preeclampsia precedes HELLP syndrome and HELLP syndrome is in fact a variant of preeclampsia, so the pathophysiology is therefore the same.[4] Another potential cause of HELLP syndrome arises from maternal immune rejection when the maternal cells contact the fetus and there is an immune imbalance resulting in endothelial dysfunction, arterial hypertension, and platelet activation/aggregation. This theory is based on data collected by Ibdah and colleagues.[5]

An additional theory includes inborn errors of metabolism (IEM) of the fetus, causing maternal liver damage and placental-instigated acute inflammatory conditions in a fraction of HELLP syndrome cases.[4] According to Ibdah and colleagues,[5] there is significant evidence suggesting that long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) is associated with HELLP syndrome. Mothers often show significant improvement once the infant is delivered, which leads to the belief that the fetus is causing a toxic effect on the mother similar to those with inborn errors of fatty acid oxidation (FAO).[6]

LCHAD deficiency is the result of a mutated HADHA gene that is autosomal recessive inherited.[7] The infant is unable to break down long-chain fatty acids into ketones with low levels of 3-hydroxyacyl-CoA dehydrogenase.[7] The resulting buildup of fatty acids may cause anorexia, vomiting, abdominal pain, and jaundice during the third trimester, leading to HELLP syndrome or acute fatty liver of pregnancy.[7] Regardless, multiple theories remain, and the true pathophysiology of HELLP syndrome continues to be unknown. As a result, it is considered a complex disorder.[4]

IMPACT ON THE FETUS

Perinatal mortality and morbidity are higher in the fetus than the mother.[1] The effect on the infant is directly related to the gestational age at birth. If infants are born <32 weeks of gestation, they are at the highest risk with a mortality of 32 percent, while infants >32 weeks have a mortality rate of 8 percent.[1]

The leading causes of perinatal mortality associated with HELLP syndrome are prematurity, intrauterine growth restriction (IUGR), asphyxia, placental insufficiency, and abruption.[1] Neonatal thrombocytopenia occurs in between 15 and 38 percent of maternal HELLP syndrome cases.[1] This results in a significant risk factor for both interventricular hemorrhage (IVH) and long-term neurologic complications.[8] According to the Preeclampsia Foundation,[2] the stillbirth rate is 51 per 1,000 HELLP syndrome pregnancies with a 7.7–60 percent perinatal mortality (combined stillbirth and neonatal deaths) in developed countries.

Although these are recognized as potential fetal complications of HELLP syndrome, it is also suggested that the mortality is based not on the HELLP syndrome itself but more on the complications associated with the gestational age at birth. During a five-year study, Murray and colleagues[9] concluded that the neonatal morbidity was closely related to the gestational age of the infant at birth and did not increase based on the diagnosis of maternal HELLP syndrome. Therefore, an infant born at 32 weeks gestational age with a maternal HELLP syndrome risk factor is not at increased risk for mortality compared with an infant born at 32 weeks to a healthy mother.

NEONATAL CLINICAL MANIFESTATIONS AND DIAGNOSTIC EVALUATIONS

As stated previously, infants of mothers with HELLP syndrome can face prematurity, placental insufficiency (IUGR), asphyxia, abruption, thrombocytopenia, and IVH.[1] All of these complications come with their own risks.

Prematurely born infants face multiple complications, which include respiratory distress syndrome, electrolyte imbalances, metabolic problems, infection, necrotizing enterocolitis, patent ductus arteriosus (PDA), apnea, bradycardia, anemia, and IVH.[10] In addition, long-term complications include but are not limited to chronic lung disease, retinopathy of prematurity, visual problems, hearing impairment, developmental delays, and learning difficulties.[10] Clinical manifestations and diagnostic evaluations are focused on the individual complication associated with prematurity.

IUGR is a prenatal diagnosis caused by reduced blood flow to the placenta, which restricts important nutrients required for adequate growth. Each year, 30 million infants are prenatally diagnosed with IUGR; of these infants, 15 percent are associated with preeclampsia or HELLP syndrome.[2] These infants are at increased risk for complications such as perinatal asphyxia, cold stress, polycythemia, cholestasis associated with parenteral nutrition (PN), and hypoglycemia.[10] Persistent pulmonary hypertension of the newborn (PPHN), respiratory distress, and PDA may also be seen in IUGR infants who experience asphyxia during birth. Diagnostic tests to confirm IUGR are made prior to delivery by ultrasound. During the neonatal period, important lab work to obtain includes central hematocrit, blood glucose, and liver function tests if requiring long-term PN. If PPHN or a PDA is suspected, an echocardiogram will be obtained for confirmation. Respiratory distress will be supported; an arterial blood gas and chest x-ray can be obtained for

diagnostic purposes. A magnetic resonance imaging (MRI) or cranial ultrasound should be obtained to assess the total brain volume, which is known to be reduced and underdeveloped when compared with appropriate for gestational age infants.[11] In addition, in preterm IUGR infants, the brain's white matter and gray matter can also be reduced.[10]

Asphyxiated infants can present with varying degrees of distress at birth. These infants are at risk for hypoxic-ischemic encephalopathy (HIE).[10] Diagnostic tests and treatment for these infants depend on the degree of insult at delivery. Management is focused on supportive care including resuscitation using Neonatal Resuscitation Program guidelines, assisted ventilation as needed, perfusion, acid–base management, fluid management, blood glucose management, and seizure prevention.[10]

Abruption can cause neonatal thrombocytopenia and platelet dysfunction as well as hypovolemia.[10] If an abruption is suspected, recommended diagnostic tests include a complete blood count (CBC) with platelet count and type and cross in preparation for a potential platelet or pure red blood cell transfusion to correct the hypovolemia caused by the abruption.

Neonatal thrombocytopenia is defined as a platelet count <150,000/mcL and can range from mild to severe as well as be symptomatic or asymptomatic. Diagnostic tests include a CBC with differential and platelet count.[10] Treatment for thrombocytopenia is based on treating the underlying cause; in the case of HELLP syndrome, treatment will be based on the platelet count and whether the infant is symptomatic. In addition, a cranial ultrasound will be obtained to assess for IVH. Although there is no relationship between the severity of thrombocytopenia and IVH, it has been shown that, along with other risk factors such as prematurity, asphyxia, and IUGR, infants born to mothers with HELLP syndrome are at an increased risk for IVH.[12]

In addition, HELLP syndrome is associated with IEM with acute onset such as FAO disorders in the infant.[10] FAO disorders include LCHAD and short-chain acyl-CoA dehydrogenase.[10] FAO disorders present with impaired cardiac function and occasional cardiac arrhythmias. Encephalopathy, impaired liver function, rhabdomyolysis, muscle weakness, and/or retinopathy may also be present.[10] As an advanced practitioner, it is important to assess for severe cardiomyopathy resulting in cardiac failure, encephalopathy, myopathy, hepatomegaly with low glucose intake, or intercurrent illness and development of hypoketotic hypoglycemia.[10]

If FAO disorders are suspected, the practitioner should evaluate for liver dysfunction, although it may be mild in comparison with other IEM; hypoalbuminemia and coagulopathy may be seen.[10] Hyperammonemia may present if liver dysfunction progresses, and urine organic acids may have tyrosine metabolites present.[10] An acylcarnitine profile is typically included in the newborn screen and helps to determine the levels of fatty acid metabolites with different carbon lengths for diagnosis. A total and free carnitine plasma level can be obtained for diagnostic purposes.[10]

THERAPEUTIC APPROACHES AND TREATMENT OPTIONS

Managing HELLP syndrome involves careful assessment of both the mother and the fetus. Common treatment approaches include glucocorticoids, intravenous magnesium sulfate, systolic blood pressure control, and delivery within 24–72 hours of diagnosis.[13] According to American College of Obstetricians and Gynecologists,[14] the following management is recommended:

- Refer to a tertiary care facility if the gestational age is <35 weeks.
- Admit to labor and delivery unit for maternal/fetal monitoring.
- Administer intravenous magnesium sulfate.
- If systolic blood pressure is ≥160 mmHg or the diastolic blood pressure is ≥105 mmHg, an antihypertensive will be administered.

The decision to deliver the infant is based on a series of questions. If the provider can answer yes to any of the following questions, delivery is imminent.

- Is the infant <23 weeks or >34 weeks?
- Is the infant in fetal distress?
- Is there maternal distress?
  - Eclampsia
  - Abruption
  - Disseminated intravascular coagulation
  - Renal failure
  - Respiratory distress
  - Suspected liver hematoma

If all of the mentioned questions can be answered with a no and the infant is 23–34 completed weeks, the mother will receive a steroid course with 24–48 hours latency, followed by delivery.

EVIDENCE-BASED PRACTICE

Glucosteroid administration initially was administered for the benefit of the fetus to reduce hyaline membrane disease and respiratory distress syndrome (RDS); however, it was discovered that not only did it benefit the infant but it also proved to stabilize the mother's disease process in both undelivered and postpartum mothers.[13]

Intravenous magnesium sulfate is administered to the mother for a multitude of benefits. Magnesium sulfate causes central and peripheral microvascular dilation while reducing systemic vascular resistance. It also protects the blood–brain barrier by reducing cerebral edema and causing a neuroprotective/anticonvulsant action for the mother.[13]

The careful control of systolic blood pressure is a result of multiple studies demonstrating that cerebral hemorrhage was the most important single cause of maternal death with

HELLP syndrome.[13] The Copenhagen Heart Study concludes that the risk for hemorrhagic stroke is directly related to systolic blood pressure alone.[13]

Once the diagnosis of HELLP syndrome is made, delivery should occur within 24–72 hours.[13] While awaiting delivery, careful control of systolic blood pressure, intravenous magnesium sulfate, and glucocorticoids are used to support the patient. In addition, platelet transfusion prior to a cesarean section for Class 1 HELLP syndrome patients is recommended as well as for a vaginal birth with a platelet count lower than 25,000.[1]

ECONOMIC, EMOTIONAL, AND SOCIAL IMPLICATIONS ON THE FAMILY UNIT

HELLP syndrome has an economic, emotional, and social impact on the family. The burden is not only associated with the financial and emotional requirements of the mother's diagnosis but also related to the potential complications of the infant.

The health of women during pregnancy and childbirth affects the health, development, and well-being of the entire family economically, emotionally, and socially.[15] The obstetric complication of HELLP syndrome increases the risk for morbidity and physical and mental disabilities, which in turn increases the economic and social burden. Such burdens can further increase through impoverishment, violence, isolation, divorce, and remarriage.[15] Following a severe obstetric complication, there are secondary consequences such as mental health problems, loss of physical strength, family stability issues, loss in community status, and impoverishment.[15]

As the infant's gestational age decreases, the financial and emotional burden significantly increases.[16] It is important to recognize the perspective of the family in relation to the direct medical costs, nonmedical costs, indirect costs, and intangible costs HELLP syndrome has on the family.[16] Intangible costs include emotional distress and reduced quality of life.[16]

Actual neonatal hospital costs vary according to the complications and degree of illness. March of Dimes Foundation estimates the average NICU stay is $76,164, whereas infants born <32 weeks gestational age average increases to $280,811, which is approximately 9 times more than the cost of an infant born at 37–41 weeks.[17] Additional costs include travel expenses if the NICU is not in their town, child care for siblings, overnight accommodations, and long-term medical care.

In addition to the financial burden and stress of an infant in the NICU, Hodek and colleagues[16] recognize that the emotional stress significantly increases with decreasing gestational age. The emotional burden of an infant in the NICU does not cease once the infant is discharged home; in fact, the largest part of the burden occurs once the infant is discharged home.[16]

CONCLUSION

Although the exact pathophysiology of HELLP syndrome is still unknown and multiple theories exist, it is important to recognize the potential factors that contribute to HELLP syndrome. Early recognition and diagnosis of HELLP syndrome is important in the management of both the mother and infant to reduce complications, mortality, and morbidity. Understanding the impact of HELLP syndrome on the fetus, the clinical manifestations and diagnostic evaluations of the neonate, as well as therapeutic approaches and treatment options help the neonatal team to care for the infant after delivery. As an advanced health care provider, it is also important to recognize the emotional, economic, and social implications that are associated with a maternal illness and/or an infant in the NICU. Understanding the entire illness allows the providers to provide the best and most appropriate care to the mother, infant, and family.

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