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The Lack of Neonatal Consequences in Pre eclampsia, Eclampsia and HELLP Syndrome; a surprising finding.

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Abstract

Introduction

Knowledge of the correlation between maternal conditions, especially during pregnancy and fetal outcomes is paramount to optimal care in pediatrics. One which has not been frequently commented on in the literature is pre-eclampsia, eclampsia and hemolysis, elevated liver enzymes and low platelets (HELLP). This spectrum, which starts as pre eclampsia involves hypertension and proteinuria in the pregnant mother. The transition to eclampsia occurs with seizures. Finally, 10-20% of severe cases result in HELLP, which carries a 1% mortality to the mother. Preterm delivery is increased in pre-eclampsia and HELLP at 25.5% and 50% respectively. Intuitively, a disease which is caused by deranged blood flow and coagulation factors must have an effect on the developing fetus. This begs the question, why is there a paucity of information about these diseases and the consequences to the child?

Methods

A retrospective review of all documented cases of pre-eclampsia, eclampsia and HELLP was done at a community Regional Neonatal Center. Over a five year period, 291 mothers were diagnosed with one of the three diseases and gave birth to 318 children. The children were stratified for gestational age and birth weight. Selected conditions were screened for in the medical record over the first year of life.

Results

Of the 318 neonates, two were still births and one mother died from intracranial hemorrhage in the face of HELLP. Two hundred and twelve (66.67%) were born before 37

weeks, which is higher than the expected rate for these conditions. A total of 114 neonates were low birth weight (36%), while 75 were very low birth weight (23%). None of the conditions appeared significantly different for their suspected incidence when stratified for gestational age and birth weight.

Discussion

Eclampsia and HELLP are serious conditions in the pregnant patient, which significantly increase rates of preterm delivery, as well as correlates with low birth weights. As with all maternal conditions, thought must be given to the effect of these derangements on the developing fetus. Conditions such as necrotizing enterocolitis (NEC) caused by low flow sates and intestinal atresias, thought to occur with vascular incidents, were not seen at a higher rate in these patients once stratified for gestational age and birth weight. The authors conclude that although pre-eclampsia, eclampsia and HELLP are a risk factor for prematurity and low birth weight; they are not themselves an independent risk factor for any identifiable neonatal surgical condition.

Introduction

Various pediatric conditions are related to maternal health problems. During fetal development, several challenges face mothers and healthcare providers. These include managing pre-existing medical conditions (which can become increasingly difficult during this time), evaluating for teratogenic occupational and social exposures, and managing any conditions that develop as a result of pregnancy.

One such set of conditions that has been demonstrated to have significant deleterious effects is pre-eclampsia, eclampsia and HELLP syndrome. These conditions affect 3.4% of pregnancies in the United States, and are more common in first pregnancies.[1] Pre-eclampsia is defined as new onset hypertension with signs of end organ dysfunction, usually proteinuria, after 20 weeks of gestation. Eclampsia occurs when the symptoms of Pre-eclampsia are compounded with seizures.[2] HELLP syndrome is characterized by hemolysis, elevated liver enzymes and low platelets, and affects 0.2-0.8% of pregnancies, as well as 10-20% of cases of severe pre-eclampsia.[3]

The proposed pathogenic mechanism of these hypertensive disorders of pregnancy stems from abnormal development of the placenta. This theory has been demonstrated in experimental trials, and is supported by the fact that the placenta is necessary for development of disease, but not the fetus,[4,5] and that delivery of the placenta results in complete resolution of symptoms. The underlying placental abnormalities result in hypoxia of the placenta and an increase in maternal circulating factors that lead to endothelial dysfunction and ultimately symptoms characteristic of pre-eclampsia. Defective placentation has been implicated in not only pre-eclampsia, but also other conditions like spontaneous abortion, intrauterine growth restriction, preterm labor and placental abruption.[6] However, what has been poorly studied in the literature are the perinatal conditions and congenital defects that neonates born to mothers with these hypertensive disorders face. One would reasonably assume that a process that causes such disorders for the mother would have a significant effect on fetal development.

In the present study, the authors conduct a retrospective chart review of neonates born to mothers afflicted with pre-eclampsia, eclampsia and HELLP syndrome to determine whether these conditions serve as independent risk factors for congenital defects and perinatal conditions in the neonate. The neonatal data obtained and incidence of congenital defects and perinatal conditions was compared to that of the general population when stratified for birth weight and gestational age.

Materials and Methods

This is a retrospective chart review examining the incidence of neonatal anomalies born to mothers affected by pre-eclampsia, eclampsia and HELLP syndrome. IRB approval was first obtained. The research team, which consisted of residents and a medical student identified the electronic medical records of 291 mothers over a seven-year period extending from 2008-2015 diagnosed with pre-eclampsia, eclampsia or HELLP. These charts were identified by IDC-9 codes. These mothers gave birth to 318 children, indicating some multiple gestations. The medical record of each mother was examined for risk factors relating to the diagnosis of pre-

eclampsia, eclampsia and HELLP, as well as for pre-term birth. These factors included maternal age, hypertension, diabetes, first pregnancy, multiple gestation, smoking and drug use.

The medical record of the child was then examined for all pulmonary, and gastrointestinal abnormalities within the first year of life. Cardiac and renal issues were eliminated because they were too heterogeneous to compare. The rates of these abnormalities were then compared to incidence of the general population as best reported from the updated at large literature. Next, their statistical significance determined when adjusting for birth weight using Z-test and chi square analysis. (This is our statistics method). Comparisons were made after groups were separated out by week gestation and weight at birth since prematurity and low birth weight have different incidences of the respective conditions. The primary endpoint of this study was to determine if pre-eclampsia, eclampsia or HELLP syndrome are independent risk factors for the development of neonatal abnormalities when compared with average risk patients.

Results

During the seven years under review, 318 neonates born to 291 mothers were analyzed for medical conditions and their association with pre-eclampsia, eclampsia, and HELLP syndrome. Of the 318 neonates, there were 12 sets of twins and one set of triplets. Two neonates were stillborn and one mother passed away from intracranial hemorrhage secondary to HELLP syndrome.

The neonates were stratified by week's gestation at birth and birth weight. 215 (67.6%) neonates were born premature, defined as prior to 37 weeks gestation. 114 neonates (36%) were categorized as having low birth weight, while 75 neonates (23.5%) were very low birth weight; the remaining 129 neonates (40.5%) were categorized as normal birth weight.

The incidences of gastrointestinal conditions (including intestinal atresia, necrotizing enterocolitis and pyloric stenosis), abdominal wall defects (including hernias, Gastroschisis and omphalocele), and pulmonary conditions (including respiratory distress syndrome (RDS)) were recorded. The main clinical data of the two groups (stratified for birth weight and stratified for maturity) are shown in tables 1 and 2.

The authors found that when stratified according to birth weight, 80% of neonates <1500g, 40% of neonates 1500-2500g, and 16% neonates >2500g were found to have conditions. This reinforces the established correlation between birth weight and incidence of neonatal conditions. This is reflected in table 3 below.

Gastrointestinal

Necrotizing Enterocolitis (NEC) was seen in two patients. Both patients were VLBW. As seen in Tables 3 and 4, the incidence in this study was lower than that of the at large population (2.6% vs 6-7% for VLBW[7]). Intestinal atresia was seen in one patient who was premature. Pyloric stenosis was seen in one patient who was normal birth weight. There were 15 inguinal hernias diagnosed in the study population. Of these 15 patients, 12 were very low birth

weight and 3 were low birth weight. 14 of these 15 patients were born premature, and one was born full term. There were no neonates born with gastroschisis or omphalocele.

Pulmonary

There were 50/75 (67%) VLBW neonates with pulmonary conditions. Of these patients, 45 (60%) were diagnosed with Respiratory Distress Syndrome (RDS). 47/114 (41%) LBW neonates had pulmonary conditions at birth, 36 (31.5%) developed RDS. 15/129 (12%) of normal weight neonates had pulmonary conditions, while 12 (9.3%) developed RDS.

When stratified for maturity, 106/215 (49%) of pre-term neonates had pulmonary conditions. Of those, 92 (43%) developed RDS. 6/103 (5.8%) neonates born full-term developed pulmonary conditions, with one patient (1%) developing RDS.

Discussion

While it is well established that the maternal hypertensive conditions outlined in this study can lead to lower birth weights and preterm delivery, their independent risk for the development of neonatal conditions has not been well studied. The trend seen amongst the neonatal conditions was surprising, given the pathogenesis of these conditions and the significant symptoms observed in the mother. It appears that the patients in this study were at increased risk for complications of prematurity and early delivery, but that these maternal conditions conferred no additional risk for the development of perinatal conditions. Each organ system is discussed below.

Gastrointestinal

NEC is a broadly studied and feared complication of prematurity. It is the second most common cause of morbidity in premature infants, and the most commonly diagnosed gastrointestinal emergency[8]. This disease can cause necrosis of the neonate's intestine, intolerance to feeds, abdominal distention, possible intestinal perforation and resulting sepsis. The disease process has been theorized to result from a combination of the infant's immature intestines combined with host factors of inflammation[9]. Ischemia can play a role in this disease process, possibly implicating maternal conditions such as the conditions described in this study. A fetus' developing enteral tract may be compromised by constricted blood flow or deranged coagulation, and the underlying pathogenesis of the maternal conditions in this study would seem to confer a higher risk for developing NEC.

Two patients developed NEC from this cohort. Both were premature and VLBW. This data gives a 2.6% incidence of NEC in this study. A recent systematic review demonstrated an association between NEC, prematurity and low birth weight. This association was especially pronounced in children with birth weights 1000-1499g (183.2 vs 119.3/10000, p=0.006) and 1500-2499g (22.7 vs 14.7/10000, p=0.006). NEC is rare in term infants, in whom it is usually associated with congenital anomalies, sepsis, or hypotension[10]. The data obtained in this study does not appear to be statistically different from the general incidence of NEC.

Duodenal and more distal atresias of the small bowel are another well-studied aspect of neonatal disease. Duodenal atresias occur in 1/10,000 live births (.01%) and encompass 25-50% of all intestinal atresias. Duodenal atresias are thought to occur because of the failure of recanalization of the lumen following endodermal proliferation[11], while jejuno-ileal atresias are attributed to vascular accidents and subsequent infarction and reabsorption of the affected bowel[12,13]. Both subsets are associated with LBW and prematurity, while duodenal atresias are associated with cardiac conditions, malrotation, annular pancreas, renal anomalies, tracheoesophageal fistulas and anorectal problems. Previous studies have demonstrated vasoconstrictive drugs and substances to be implicated in intestinal atresias[14]. By the same logic, the maternal conditions in this study would put the fetus at similar risk for the development of atresias. However, there was only one neonate in this study with intestinal atresia, who was born premature to a mother who admitted smoking during pregnancy. The expected incidence of intestinal atresia would be no higher than a few patients, but the maternal conditions in this study failed to show any increase in risk for intestinal atresia.

Hypertrophic pyloric stenosis is seen in 2-3/1000 live births in the United States. It is most common in whites, followed by African Americans, then Asians. It is 4-6 times more common in the first born male of a family[15]. The disease is usually not present at birth and rare in stillbirths, therefore it most likely develops after birth. Although prenatal factors could theoretically predispose the neonate to the condition, pyloric stenosis would not intuitively have an association with a prenatal circulation disorder.

According to one study, 2.7% of males and 3% of females with VLBW developed pyloric stenosis. In males and females with LBW, pyloric stenosis is diagnosed in 4.4% and 2.8% respectively[16]. The one neonate in this study with pyloric stenosis was of normal birth weight. When compared to the general population at 0.1-0.3%[15], this number is not statistically significant. The maternal conditions discussed in this paper do not seem to add independent risk for development of pyloric stenosis.

There were 15 total inguinal hernias, 12 neonates with VLBW, 3 neonates with LBW, and none in normal birth weight neonates detected in the first year of life. A study performed at Case Western Reserve University School of Medicine in Cleveland, Ohio, 222 of 1,391 (16%) neonates that were VLBW and who survived past 28 days after birth, had inguinal hernias[16]. When compared to the general population, no significant difference was found in the rate of inguinal hernia.

When stratified for gestational age, 14 neonates with inguinal hernias were born pre-term. According to one study the incidence of inguinal hernias in preterm infants of 32 WGA or less was 9.34% (65/696). About 3-5% of healthy, full-term babies may be born with an inguinal hernia and one third of infancy and childhood hernias appear in the first 6 months of life[17]. The number of hernias found in this study appear to agree with the at large data. The maternal conditions in this study appear to lead to lower birth weight and premature delivery which in turn lead to higher percentage of inguinal hernias, but the conditions themselves do not seem to increase the rate of inguinal hernias.

Pulmonary

The previously reported incidence of RDS in the population of VLBW, LBW and normal birth weight neonates is 39%, 6.7% and 0.1%, respectively[18]. In the present study these rates were found to be 60%, 31.5% and 9.3% in patients with very low birth weight, low birth weight and normal birth weight, respectively. The association of neonatal respiratory distress in children born to mothers with pre-eclampsia, eclampsia and HELLP syndrome in this study is intriguing, as the patients in this study suffered from a significantly higher rate of RDS than other neonates when stratified for weight and maturity. Further studies specifically directed at evaluating the existence of correlation between RDS and the three eclampsia-related disorders should be performed to further evaluate this association.

Conclusion

This study was a retrospective review analyzing how maternal pre-eclampsia, eclampsia and HELLP syndrome may affect perinatal health. Multiple neonatal conditions were analyzed in the first year of life. The incidence of prematurity and lower birth weights was higher for infants born to mothers with these conditions, which had been established from previous studies. Although the underlying pathophysiologic mechanism of these conditions may seem to predispose neonates to a more hostile environment when compared to other neonates of similar gestational age or birthweight, the present study failed to establish these conditions as independent risk factors for the development of these neonatal conditions. This study did however find that the incidence of RDS was higher when compared to another study population. The studied population failed to show any difference from the at large data to correlate these maternal conditions with an increased risk for neonatal problems. Increasing the sample size and incorporating multiple neonatal centers may show increased incidences if they truly exist. Longitudinal studies following children born to mothers diagnosed with pre-eclampsia, eclampsia, and HELLP syndrome are needed to ascertain if these children require greater amounts of surgical and medical intervention for health conditions than their counterparts born to mothers without these conditions.

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