MODIFIED MISSISSIPPI PROTOCOL FOR HELLP/PARTIAL HELLP SYNDROME OCCURRING IN THE PERIVIABLE PERIOD: A REPORT OF THREE CASES

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HELLP syndrome is a life-threatening complication of pregnancy that requires immediate delivery. Temporizing management for short durations (24–48 hours) may be an acceptable option. However, there is insufficient information on long-term expectant management (>48 hours) for HELLP syndrome occurring during the periviable period (22–24 weeks of gestation). The Mississippi protocol, which includes high doses of dexamethasone in combination with antihypertensives and magnesium sulphate, is usually used for planned delivery within 48 hours after diagnosis of HELLP syndrome to prevent severe maternal morbidity. Here we present three cases of HELLP/partial HELLP syndrome occurring during the periviable period, which were treated with a modified Mississippi protocol. The modified Mississippi protocol involved administration of three-day, high-dose dexamethasone followed by long-term, low-dose prednisolone (10 mg/day). The modified Mississippi protocol contributed to prolongation of pregnancy (8, 10, and 16 days), and may be a promising therapeutic option especially for periviable HELLP/partial HELLP syndrome.

INTRODUCTION

Haemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome is a life-threatening complication of pregnancy. HELLP syndrome is a severe variant of preeclampsia that occurs in 10–20% of women who have preeclampsia with severe features. Partial HELLP syndrome, which has one or two elements of the triad of HELLP syndrome, is not considered a separate disorder from HELLP syndrome. Although HELLP/partial HELLP syndrome usually occurs in the third trimester of pregnancy or peripartum period, women with preeclampsia can also develop HELLP/partial HELLP syndrome at a periviable gestational age (22–24 weeks of gestation).

The only definitive treatment for HELLP syndrome is termination of pregnancy. However, an obstetrician will face the dilemma of decision-making regarding the optimal timing for delivery of the foetus and the placenta in the management of HELLP syndrome remote from term, especially in the periviable period. Delaying the termination of pregnancy increases the risk of maternal organ dysfunction and mortality, but is beneficial to foetal maturatation. The Mississippi protocol (MP), which is used to treat HELLP syndrome and involves high doses of dexamethasone (Antepartum: 10 mg intravenously every 12 hours within 24–72 hours after diagnosis; Postpartum: two 10-mg doses 12 hours apart followed by two additional doses of 5 mg at 12-hour intervals) in combination with antihypertensives and magnesium sulphate, is known to prevent disease progression and maternal morbidity.

As treatment with MP is generally conducted with planned delivery within 48 hours, the safety is uncertain for women when a more expectant approach is attempted with the aim of reducing the mortality and morbidity of the foetus. Here we present three cases of HELLP/partial HELLP syndrome occurring during the periviable period, which were treated with a modified Mississippi protocol (mMP). The mMP involved intravenous dexamethasone (six 10-mg doses at 12-hour intervals) followed by oral
administration of 10 mg prednisolone every 24 hours until three to four days after delivery. The protocol was approved by the evaluation committee on off-label drug use of Kyoto University Hospital, and long-term corticosteroid treatment was performed after obtaining informed consent.

**Case 1**
A 42-year-old primigravida was transferred to our hospital for severe hypertension (180/107 mmHg) and proteinuria (1.3 g/day) at 24 and 0/7 weeks of gestation. Magnesium sulphate and antihypertensives were administered for the management of preeclampsia with severe features. Blood tests upon admission revealed a normal platelet count (334,000/μL) and no elevation of liver enzymes (aspartate aminotransferase: AST 21 U/L, alanine aminotransferase: ALT 15 U/L) and lactic dehydrogenase (LDH, 221 U/L). At 24 and 1/7 weeks of gestation, she complained of headache and vomiting, and blood tests revealed a slight decrease in her platelet count (273,000/μL) and elevated liver enzymes (AST 104 U/L, ALT 78 U/L) and LDH (450 U/L). The symptoms disappeared and laboratory data indicated an improvement after mMP treatment was initiated upon the diagnosis of partial HELLP syndrome1) (Figure 1). At 24 and 4/7 weeks of gestation, non-invasive positive pressure ventilation was initiated because SpO2 fell to 95%, probably due to pleural effusion and pulmonary oedema. Although adequate oxygenation saturation levels had been maintained and deterioration of liver function was not observed, an emergency caesarean section was performed due to subjective symptoms of severe fatigue at 25 and 2/7 weeks of gestation. A 532-g (−2.1 SD) female infant was delivered. The infant’s cognitive development was normal, and no medical intervention other than thyroid hormone supplementation was needed at age 32 months.

**Case 2**
A 42-year-old primigravida was referred to our hospital for new-onset hypertension (140/90 mmHg) at 23 and 6/7 weeks of gestation. Antihypertensives were initiated at 24 and 0/7 weeks, and magnesium sulphate was thereafter commenced due to development of preeclampsia with severe features including headache, epigastric pain, and visual changes at 24 and 3/7 weeks of gestation. The woman experienced occasional epigastric pain, and blood tests presented a mild decrease in platelet count (176,000/μL) and elevated liver enzymes (AST 154 U/L, ALT 152 U/L) and LDH (366 U/L) at 24 and 6/7 weeks of gestation. The symptoms disappeared and laboratory data indicated an improvement after following treatment with mMP for partial HELLP syndrome (Figure 1). Although maternal condition had been well controlled,
an emergency caesarean section was performed at 26 and 2/7 weeks of gestation due to non-reassuring foetal status determined by reduced foetal movement and decreased foetal heart rate variability. A 628-g (−2.0 SD) female infant was delivered, and the physical growth of the infant was satisfactory at age 16 months. The infant required home oxygen therapy only when she caught a cold.

Case 3
A 41-year-old primigravida was transferred to our hospital for the management of HELLP syndrome at 23 and 2/7 weeks of gestation. On admission, the woman presented with severe hypertension (183/110 mmHg) accompanied by severe features such as severe headache and epigastric pain with visual changes. Blood tests revealed a low platelet count (83,000/μL) and elevated liver enzymes (AST 665 U/L, ALT 386 U/L) and LDH (1,139 U/L). The symptoms disappeared and laboratory data improved immediately after mMP treatment was conducted for expectant management (Figure 1). An emergency caesarean section was performed at 25 and 4/7 weeks due to occasional late decelerations and decreased foetal heart rate variability. A 610-g (−1.6 SD) female infant was delivered. The physical development of the infant was good, although she required home oxygen therapy at age 13 months.

Discussion
To the best of our knowledge, this is the first case series of periviable HELLP/partial HELLP syndrome in which mMP treatment involving long-term corticosteroids resulted in the prolongation of pregnancy. The diagnosis to delivery intervals were 8, 10, and 16 days, respectively, which was important for the infants born around the limit of viability. Moreover, no severe morbidity was observed in the women treated by mMP. Therefore, mMP may help slow disease progression for a relatively long period and reduce neonatal mortality and morbidity, as well as prevent maternal severe morbidity.

Expectant management of preterm preeclampsia with severe features is generally recommended in order to reduce neonatal morbidity without increasing maternal morbidity.5) In HELLP syndrome, however, immediate delivery is the current gold standard. Corticosteroid treatment, including high-dose dexamethasone, can be used in HELLP syndrome before 34 weeks of gestation with the aim of limited prolongation of pregnancy, optimizing maternal condition, and promoting foetal lung maturity before delivery beyond 24–48 hours, whereas systematic reviews have noted the lack of clear evidence that corticosteroids are associated with favourable maternal and perinatal outcomes.6,7) In the present cases, none of the infants showed neurological sequelae during the observation period despite the pregnancies being complicated with periviable HELLP/partial HELLP syndrome, although long-term follow-up is required to confirm their physical, neurologic, and psychological development. Discrepancies regarding perinatal outcomes between previous randomised controlled trials and the present cases may have been due to the striking differences in gestational age. In previous randomised controlled trials, the mean gestational age of participants was 31–32 weeks of gestation,6,7) when foetuses are generally mature enough not to result in severe perinatal/infant morbidity or death. In that context, the risk of severe maternal morbidity due to prolonging the pregnancy usually outweighs the benefits of further foetal maturation. On the other hand, expectant management with mMP at periviable gestation may be an acceptable option if it is performed in intensive care units under close maternal and foetal surveillance.

The mechanism underlying the alleviation of HELLP syndrome upon treatment with corticosteroids remains largely unknown. Wallace et al. reported that high-dose dexamethasone significantly decreased levels of circulating interleukin-6, soluble fms-like tyrosine kinase-1, and soluble endoglin,8) which may lead to unfavourable effects on brain development and birth weight.9,10) Since dexamethasone readily passes through the placenta, mMP involving oral prednisolone (10 mg/day) following high-dose dexamethasone (10 mg/day for three days) was attempted to slow disease progression. With a similar purpose, Van Runnard et al. adopted long-term intravenous high-dose prednisolone administration (100 mg/day) for HELLP syndrome before 30 weeks of gestation.11) They conducted a randomised placebo-controlled trial and reported that long-term, high-dose prednisolone therapy reduced the risk of recurrent HELLP syndrome exacerbations. However, the optimal dosage of prednisolone is at <20 mg/day during pregnancy, and high-dose prednisolone (100 mg/day) administration increases the susceptibility to infections such as Pneumocystis pneumonia. Although the present study showed that low-dose prednisolone (10 mg/day) could prevent rapid deterioration in platelet count, liver function, and clinical symptoms such as headache and epigastric pain, further studies will be needed to determine the optimal dosage of prednisolone for expectant management of HELLP/partial HELLP syndrome.

In conclusion, mMP may alleviate the progression of HELLP/partial HELLP syndrome and may be a possible therapeutic option especially for periviable HELLP/partial HELLP syndrome.
Steroids for periviable HELLP syndrome

Acknowledgments

None to report.

Conflict of interest

None to report.

References