RENAL FUNCTION DERANGEMENT IN HELLP SYNDROME
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ABSTRACT

BACKGROUND
HELDP is the acronym for haemolysis, elevated liver enzymes and low platelet count. HELLP syndrome is a form of severe preeclampsia with an incidence of 0.2-0.6% of all pregnancies.

The aim of our study is to evaluate the trend of renal dysfunction in HELLP syndrome patients.

MATERIALS AND METHODS
This is a cross-sectional observational study conducted in Department of Obstetrics and Gynaecology, Institute of Maternal and Child Health, Government Medical College, Kozhikode, during the period of 12 months from January 2013 to December 2013. All patients with HELLP syndrome were included in the study and their renal function tests monitored.

RESULTS
Results were renal dysfunction prevalence in HELLP syndrome patients is 77%. The renal impairment recovered by 6 days on an average. All had normal renal function tests at the time of discharge. Patients with renal function derangement had a mean duration of hospital stay and transfusion requirements more than the patients without renal function derangement, which was statistically significant (p value 0.036). Haemodialysis required for one out of 60 patients. One maternal mortality due to acute renal failure.

CONCLUSION
As the prevalence of renal dysfunction is high, some amount of renal impairment maybe a part of the HELLP syndrome disease spectrum itself. Though the incidence of progression to acute renal failure and dialysis is less, this is the important cause of morbidity and mortality in HELLP syndrome patients.

KEYWORDS
Renal Function Tests, HELLP Syndrome, Renal Dysfunction, Haemodialysis.

Abnormal Trophoblastic Invasion
The primary wave of trophoblastic invasion is partly impaired and the secondary wave of trophoblastic invasion fails to occur resulting in reduced uteroplacental flow and placental hypoxia.

Angiogenic imbalance due to increased soluble Fms-like tyrosine kinase sFlt-1 and soluble endoglin (ENG), also decrease in Vascular Endothelial Growth Factor (VEGF), which are released by trophoblast. Trophoblast produces at least two anti-angiogenic peptides that enter the maternal. Hypoxia is a potent stimulus for the induction of VEGF genes expression leading to preeclampsia.

Other major theories include endothelial cell dysfunction and vasosospasm disruption of prostaglandin thromboxane homeostasis, consumption of clotting factors and platelets. Genetic factors include MTHFR C677T polymorphism has been found to be associated with HELLP syndrome.7 Caspases 3, 8 and 9 are all required to effect apoptotic cell death and active forms of all 3 are detected in liver extracts of HELLP patients. Blocking of CD95 signaling reduces the hepatocytotoxic activity of HELLP serum. Thus, systemic CD95L is involved in the pathogenesis of HELLP syndrome. In a secondary analysis of information collected in the ECLAXIR study in France suggests that ethnic origin may have an effect on the severity of the preeclampsia.

Normal implantation of placenta is characterised by extensive remodeling of the spiral arterioles within the decidua basalis. Endovascular trophoblasts replace the vascular endothelial and muscular linings to enlarge the vessel diameter. In cases of preeclampsia, incomplete trophoblastic invasion occurs.8 With this, myometrial vessels remain unchanged and their mean external diameter is only half that of normal placenta (Fisher, 2014). Endothelial activation causes vascular constriction with increased resistance, hence hypertension. Endothelial cell damage causes interstitial leakage, so platelets and fibrinogen are deposited subendothelially. Suzuki and co-workers (2003)9 described ultrastructural changes in the subendothelial region of resistance arteries in preeclamptic women leading to decreased blood flow causing ischaemia, necrosis, haemorrhage and other end-organ disturbances characteristic of the syndrome. Haemolysis is microangiopathic haematocrit anaemia evidenced by elevated serum lactate dehydrogenase levels and decreased haptoglobin levels. Other evidence comes from schizocytosis, spherocytosis and reticulocytosis in peripheral blood (Cunningham, 1985; Pritchard, 1954, 1976).

Renal perfusion and glomerular filtration are reduced mainly from increased renal afferent arteriolar resistance that maybe elevated up to fivefold (Conrad 2014, Cornelis 2011).10,11 Diminished filtration causes serum creatinine levels to (Lindheimer, 2008a).12 Abnormal values usually begin to normalise 10 days or later after delivery (Spaan, 2012a).13,14 Plasma uric acid concentration elevate. 10 to 15 percent of women with HELLP syndrome did not have proteinuria at presentation (Sibai, 2004). In another report, 17 percent of eclamptic women did not have proteinuria by the time of seizures (Zwart, 2008).

MATERIALS AND METHODS
Study Design- Cross-sectional observational study.
Study Setting- Institute of Maternal and Child Health, Medical College, Kozhikode.
Study Group- All patients with HELLP syndrome in IMCH from January 2013 to December 2013 were included in the study.
Sample Size- 60.
Inclusion Criteria
All patients with HELLP syndrome were included in my study, both complete HELLP and partial HELLP syndrome.
Exclusion Criteria
Patients with history of chronic renal disease or any form of preexisting kidney disease were excluded from the study.

Kirshon and co-workers (1988) proposed intensive intravenous fluid therapy is not indicated as “treatment” for preeclamptic women with oliguria. 90% of the patients present with generalised malaise. 90% right upper quadrant tenderness, 87% proteinuria, 85% hypertension, 9% bleeding and 5% jaundice. HELLP is diagnosed by Mississippi and Tennessee classification. The first step is to anticipate and make the diagnosis. This may be difficult because patient presentation may not suggest preeclampsia, but merely a nonspecific illness. Once HELLP is suspected, appropriate laboratory tests are indicated. If gestational age <24 weeks or >34 weeks, foetal or maternal distress, DIC, immediate eclampsia, delivery is the treatment. If above are absent, 2 doses of steroid to be given before delivery. Maternal wellbeing monitored with complete blood count, liver and renal function test. Serial monitoring of platelet count and LDH. Coagulation profile to be done, if platelet count <1 lakh. Control of hypertension by labetalol and hydralazine. To prevent eclampsia, magnesium sulphate regime as intravenous infusion regime or IM regime. Fluid intake 80-125 mL/hour, urine output at least 30 mL/hr. Platelet count to be maintained at 20,000 to 40,000 for vaginal, caesarean, respectively. If <20,000 platelet transfusion to be given. Vaginal delivery is attempted in patients in active labour less than 30 weeks with ruptured membranes or with a Bishop score 5 or more in the absence of obstetric contraindications. Major maternal complications encountered are DIC 15%, abruption 10-15%, massive ascites 10-15%, acute renal failure 3% and death 1%. Patients with HELLP syndrome usually recover completely. Normalisation of renal function after a HELLP syndrome pregnancy was reported by Jacquemyn’s Belgian group. Incidence of subsequent hypertension requiring treatment was 3 times higher than controls. 15 to 20 percent of women with preeclampsia who undergo renal biopsy have evidence of chronic renal disease (Chesley, 1978) Spaan and co-workers (2009) noticed on long-term follow up of 20 years following delivery, preeclamptic women were significantly more likely to be chronically hypertensive.
AIM OF THE STUDY
1. To study the prevalence of renal function derangement in HELLP syndrome patients.
2. The impact of the renal function derangement over maternal morbidity and mortality.

RESULTS
The incidence of hypertensive disorders in our institute during my study period was 11.8%. The incidence of preeclampsia was 2.9%. The incidence of HELLP syndrome was 0.38% (Chart 1). The most common presenting complaint was epigastric pain (50%) followed by headache (21%).
- 67% of patients who presented with headache had renal function derangement.
- 89% of the patients who presented with epigastric pain had renal function derangement.
- 90% of patients with ascites had renal function derangement.
- 100% of the patients who presented with seizures and all patients who presented with decreased urine output had renal function derangement.

The mean value of urea in my study is 34.38 ± 19.5 mg/dL. There is clustering of values between 30-50 mg/dL. The mean value of creatinine in my study is 1.19 ± 0.568 mg/dL. There is clustering of values between 0.9-1.5 mg/dL. The mean value of uric acid in my study is 6.53 ± 1.59 mg/dL. There were 4 patients with isolated elevated uric acid level. Operative delivery is not significantly different between the patients with and without renal function derangement. The mean transfusion requirement for patients with renal function derangement was 3.67 (Chart 11) (Table 3). There was one patient who developed acute renal failure with DIC requiring haemodialysis and she succumbed to death.

Chart 1. Incidence of Complete and Partial HELLP

Chart 2. Prevalence of Renal Function Derangement

Chart 3. Renal Function Derangement in Complete Vs. Partial HELLP

Chart 4. Age Wise Distribution of Renal Function Derangement

Chart 5. Obstetric Score and Renal Function Derangement
Chart 6. Gestational Age Wise Distribution

Chart 7. Gestational Age at Detection of Hypertension and Renal Function Derangement

Chart 8. Histogram Showing the Distribution of Urea Nitrogen Values
Chart 9. Histogram Showing the Creatinine Values

Chart 10. Histogram Showing Distribution of Serum Uric Acid

Chart 11. Transfusions and Renal Function Derangement
DISCUSSION
The prevalence of renal function derangement in our study is 77%, which means 77% of the HELLP syndrome patients have some form of abnormal renal function test, blood urea nitrogen or creatinine or uric acid (Table 2). The prevalence of renal dysfunction in HELLP syndrome has been in a wide range in various studies from 33% to 54% (Chart 2).

Table 1. Incidence of Complete and Partial HELLP

<table>
<thead>
<tr>
<th>Complete HELLP Syndrome</th>
<th>Partial HELLP Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 (32%)</td>
<td>41 (68%)</td>
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</tbody>
</table>

Table 2. Normal Values of Renal Function Tests in Pregnancy

<table>
<thead>
<tr>
<th>Creatinine (mg/dL)</th>
<th>Urea nitrogen (mg/dL)</th>
<th>Uric acid (mg/dL)</th>
</tr>
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<tbody>
<tr>
<td>0.5-0.9</td>
<td>7-20</td>
<td>2.5-5.6</td>
</tr>
<tr>
<td>0.4-0.7</td>
<td>7-12</td>
<td>2-4.2</td>
</tr>
<tr>
<td>0.4-0.8</td>
<td>3-13</td>
<td>2.4-4.9</td>
</tr>
<tr>
<td>0.4-0.9</td>
<td>3-11</td>
<td>3.1-6.3</td>
</tr>
</tbody>
</table>

Table 3. Transfusions and Renal Function Derangement

<table>
<thead>
<tr>
<th>Number of Transfusions</th>
<th>Total</th>
<th>Number of Patients With Renal Function Derangement</th>
<th>Number of Patients Without Renal Function Derangement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nil</td>
<td>13</td>
<td>8 (62%)</td>
<td>5 (38%)</td>
</tr>
<tr>
<td>&lt;4</td>
<td>27</td>
<td>23 (85%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>5-10</td>
<td>17</td>
<td>12 (71%)</td>
<td>5 (29%)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>3</td>
<td>3 (100%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Adapted from appendix I of William’s Obstetrics 24th Edition.
The prevalence of renal function derangement in complete HELLP syndrome and partial HELLP syndrome is almost similar (79% vs. 76%) (Table 1). Partial HELLP syndrome is almost as grave as HELLP syndrome. All morbidities have almost equal prevalence in partial and complete HELLP syndrome (Chart 3). This is in consensus with the observations of Al-Ameen et al (2014). RFT impairment was more or less than 20 years and more than 40 years of age (Chart 4).

All morbidities due to hypertensive disorders are more severe in primigravidae, so is the renal function derangement in my study (Chart 5). This is similar to the observations of M.L. Miranda et al (2011). Early onset hypertension and early onset preeclampsia have more severe a disease pattern than the late onset ones (Chart 6). This is seen in my study also. The group of patients who were detected to have hypertensive disorder at <28 weeks of gestational age had the maximum percentage of renal function derangement (Chart 7). The most common presenting complaint was epigastric pain (50%) followed by headache (21%). This is almost the same percentage reported by many authors including Vigil de Gracia et al (2001) and Sibai. The mean value of creatinine in my study is almost similar to the results of Mehmet et al of Turkey (2006) 95 who found it to be 1.29 ± 0.49 mg/dL (Chart 9).

The uric acid level is slightly lower than the mean uric acid level in the study done by Miranada et al (2011) where it was 7.3 mg/dL. Hence, uric acid is a poor predictor of maternal complications as also evidenced by the study of Thangaratinam et al of UK (Chart 10). Among the 46 patients with renal function derangement, 48% of the patients had 3+ proteinuria. Among the 14 patients without renal function derangement, 58% of the patients had trace in dipstick test. When comparing patients with >3+ proteinuria and patients <3+ proteinuria, renal dysfunction was as high as 89% in patients with >3+ proteinuria and P value is 0.03, statistically significant.

Among the HELLP syndrome patients with renal function derangement, 65% of the patients had 300 mg-1 g proteinuria in 24 hours, whereas in patients with no renal function derangement, 64% of them had proteinuria <300 mg in 24 hours. Proteinuria >1 g was not seen in patients without renal dysfunction. Of the total 60 patients, 28 patients had IUUG and 32 patients had no IUUG. In the group of patients with IUUG, 86% of them had renal function derangement. This finding recapitulates the fact that there is end-organ damage in HELLP (severe preeclampsia). Operative delivery is not significantly different between the patients with and without renal function derangement. This is similar to the findings of Al-Ameen et al (2014). Among the 46 patients who had renal function derangement, 54% of the patients had their investigations normalised by 5 days, 35% patients by 6-10 days, only 11% of patients took >10 days for their renal function tests to be normalised (Chart 12). All patients had normal renal function tests at the time of discharge.

Similar normalisation of renal function after a HELLP syndrome pregnancy was reported by Jacquemyn's Belgian group (2004). The incidence of acute renal failure in my study is 1.6%. This is the same range quoted by many authors in different studies.

The mortality rate according to my study is 1.6%, which is almost the same as many other studies done by different authors including Sibai and L. Weinstein.

SUMMARY AND CONCLUSION

1. The incidence of HELLP syndrome in my institute during my study period was 0.38%.
2. The prevalence of renal function derangement in HELLP syndrome according to my study was 77%.
3. The prevalence of renal dysfunction in complete HELLP syndrome was 79% and partial HELLP syndrome was 76%.
4. Of the 46 patients with renal function derangement 50% were primigravida.
5. Early onset hypertensive disorder and high BP at the time of admission has direct correlation with the renal function derangement, p value is 0.03.
6. The mean value of blood urea nitrogen in my study was 34.38 mg/dl (Chart 8).
7. The mean value of uric acid was 6.53 mg/dl.
8. The mean value of creatinine was 1.19 mg/dl.
9. The percentage of operative delivery was not significantly different among patients with and without renal dysfunction.
10. The mean requirement of transfusion was 3.67 in patients with renal dysfunction and 2.85 in patients without renal dysfunction (Chart 11).
11. The mean duration of hospital stay was 11.47 in patients with renal dysfunction and 8 in patients without renal dysfunction and it was statistically significant, p value=0.036.
12. The mean duration to resume normal renal function test was 6 days.
13. The incidence of acute renal failure requiring haemodialysis support was 1.6%.
14. There was one case of maternal mortality (incidence 1.6%). Cause of death was acute kidney injury/cardiorespiratory arrest.
15. As the prevalence of renal dysfunction is high as 77%, some amount of renal impairment maybe a part of the HELLP syndrome disease spectrum itself. Though the incidence of progression to acute renal failure and dialysis is less, this is the important cause of morbidity and mortality in HELLP syndrome patients.

REFERENCES


