Corticosteroid Therapy for Management of Hemolysis, Elevated Liver Enzymes, and Low Platelet Count (HELLP) Syndrome: A Meta-Analysis

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Background: Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome is a severe condition of pregnancy that is associated with significant morbidity and mortality. Corticosteroid (CORT) therapy is common in the management of HELLP syndrome. This study evaluates the efficacy of CORT therapy to patients with HELLP Syndrome.

Material/Methods: A literature search was carried out in multiple electronic databases. Meta-analyses of means difference and odds ratio were carried under the random-effects model.

Results: Fifteen studies (675 CORT treated and 787 control HELLP patients) were included. CORT treatment significantly improved platelet count (mean difference between CORT treated and controls in changes from baseline, MD: 38.08 [15.71, 60.45] ×10^9; p=0.0009), lactic dehydrogenase (LDH) levels (MD: –440 [–760, –120] IU/L; p=0.007), and alanine aminotransferase (ALT) levels (MD: –143.34 [–278.69, –7.99] IU/L; p=0.04) but the decrease in aspartate aminotransferase (AST) levels was not statistically significant (MD: –48.50 [–114.32, 17.32] IU/L; p=0.15). Corticosteroid treatment was also associated with significantly less blood transfusion rate (odds ratio, OR: 0.42 [0.24, 0.76]; p=0.004) and hospital/ICU stay (MD: –1.79 [–3.54, –0.05] days; p=0.04). Maternal mortality (OR: 1.27 [0.45, 3.60]; p=0.65), birth weight (MD: 0.09 [–0.11, 0.28]; p=0.38) and the prevalence of morbid conditions (OR: 0.79 [0.58, 1.08]; p=0.14) did not differ significantly between both groups.

Conclusions: Corticosteroid administration to HELLP patients improves platelet count, and the serum levels of LDH and ALT, and reduces hospital/ICU stay and blood transfusion rate, but is not significantly associated with better maternal mortality and overall morbidity.

MeSH Keywords: Enzyme Activators • Gestational Age • HELLP Syndrome • Hemolysis • Pregnancy Complications

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Background

Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome is a severe manifestation of a hypertensive disorder of pregnancy called pre-eclampsia. It affects about 10% to 20% of pregnant women and causes significant maternal and mortality, which increases in accordance with the severity of this syndrome [1,2]. This syndrome is associated with increased maternal risk of developing morbidities, including cerebral vascular accidents, hemorrhage, pulmonary edema, retinal detachment, hematoma/ hepatic rupture, acute renal failure, liver failure, intravascular coagulopathy, placental abruption, and sepsis [3–5].

Perinatal/infant morbidity and mortality rates are higher in pregnant women with HELLP syndrome [6,7]. The preterm delivery rate is about 70% in HELLP syndrome patients compared with about 15% of cases requiring parturition before the 27th week of gestation [8]. HELLP syndrome has been found to incur long-term consequences as well. Sufferers may refrain from further pregnancies and need psychological support, and those who attempt further pregnancies have higher risk of gestational hypertension [9,10].

Previously, immediate delivery was indicated for patients diagnosed with HELLP syndrome, which often resulted in significant maternal and neonatal morbidity and/or mortality. Later it was recognized that antepartum administration of high-dose corticosteroids can stabilize the disease indicators and prolong the gestation [11]. Although many studies have demonstrated that CORT use helps raises the platelet count and reduces elevated liver enzymes, results are not consistent across all studies. Moreover, evidence regarding the role of corticosteroids in improving maternal morbidity and mortality is not clear. The present study, therefore, carried out a systematic review of the relevant studies and performed a meta-analysis of all related parameters for the sake of evaluating the efficacy of CORT therapy observed in studies with controlled designs.

Material and Methods

Important features of the method used for the present study are summarized in Table 1. Several electronic databases were searched for the acquisition of required study reports by using the most relevant MESH and keywords in different logical combinations and phrases. The inclusion criterion was the studies examining the efficacy of CORT therapy to treat HELLP patients either in a prospective or retrospective controlled design. Some studies were, however, excluded by the following exclusion criteria (Table 1). Important information including outcome measures and outcomes, dosage and mode of administration of CORT, and obstetric and demographic characteristics were obtained from identified papers and organized on datasheets. Meta-analyses of mean difference and odds ratio were carried out under the random-effects model. Publication bias was assessed by visual examination of funnel plots.

Results

Fifteen studies [12–26] fulfilled were eligible and were included in the meta-analysis. A flowchart of the study screening and selection process is presented in Figure 1. Of the included studies, 8 were randomized controlled trials and 7 were retrospective analyses. The overall population of this meta-analysis is 675 CORT treated and 787 control HELLP patients. Age of the CORT treated and control patients as mean ±sd (range) was 26.94±5.8 (23.2±6–33.5±4) years and 26.35±5.7 (23.1±6–30.9±3) years, respectively. Gestation duration was 32.27±3.7 (29.1±3.5–35.1±2.9) weeks in CORT treated and 32.42±3.8 (27.6±3.3–35.5±2.6) weeks in control HELLP patients. In the CORT treated group, 42% of women were nulliparous, whereas 61% were nulliparous in the control group. Other characteristics of the included studies are presented in Supplementary Table 1. Least asymmetry was visible from the visual inspection of the funnel plots, indicative of almost no publication bias in this area of research (Figure 2).

Main findings of the meta-analysis are presented in Table 2. Corticosteroid treatment significantly increased platelet count in HELLP patients. The mean difference [95% confidence interval] in the change from baseline between CORT treated patients and controls was 38.08 [15.71, 60.45]×10^9/L; p=0.0009 (Figure 3). On the other hand, CORT treatment significantly decreased LDH and ALT levels. The mean differences in the changes from baseline between CORT treated and controls were −0.44 [−0.76, −0.12] IU/mL; p=0.007 for LDH (Figure 4) and −143.34 [−278.69, −7.99] IU/L; p=0.04 for ALT. However, the decrease in AST levels was not statistically significant in CORT-treated patients in comparison with controls (−48.50 [−114.32, 17.32] IU/L; p=0.15; Table 2).

Blood transfusion rate was significantly lower in CORT-treated patients (odds ratio [95% CI]: 0.42 [0.24, 0.76]; p=0.004. Hospital/ICU stay was also significantly lower in CORT-treated patients (mean difference: −1.79 [−3.54, −0.05]; p=0.04). There was no significant difference between CORT-treated and control patients in the incidence of cesarean deliveries (odds ratio [95% CI]: 1.25 [0.95, 1.63]; p=0.11), prevalence of infections (0.78 [0.19, 3.15]; p=0.73; Table 2), birth weight (mean difference: 0.09 [−0.11, 0.28]; p=0.38), infant respiratory distress incidence (odds ratio: 1.13 [0.50, 2.53]; p=0.78) and maternal mortality (odds ratio: 1.27 [0.45, 3.60]; p=0.65) (Table 2). Among the included studies, infant mortality was 23% in CORT-treated patients and 8.3% in controls [14] and 4% in CORT-treated
patients and 0% in controls [23]. Perinatal death was 0% in CORT-treated patients and 3% in controls [23].

Despite lower frequency of morbid conditions in HELLP patients treated with CORT (318 vs. 418), there was no significant difference in the incidence of overall morbidity between the groups (odds ratio: 0.79 [0.58, 1.08]; p=0.14). Morbid complications observed in 1 or more studies included pulmonary edema (3.6%) [12], intraventricular hemorrhage (18% [14,23], disseminated intravascular coagulation (15%) [18,22,26], endomyometritis (9%) [20], ascites (13.3%) [22], hematoma (3.3%) [22], acute renal failure and other renal pathologies (14% [17,18,22], necrotizing colitis (12% [23], bronchopulmonary dysplasia (80%) [23], intraventricular hematoma (20%) [23], infant thrombocytopenia (13%) [26], Apgar score less than 7 (18%) [14,23], and other hematological (36%) [17,22], neurological (12%) [17], and cardiopulmonary complications (33%) [17].

### Discussion

This meta-analysis of the studies with variable research designs revealed that in comparison with controls, CORT therapy significantly improved the platelet count, LDH, and ALT, as well as reducing AST levels non-significantly in patients with HELLP syndrome. Moreover, blood transfusion rate and hospital/ICU stay were significantly lower in CORT-treated patients. However, there was no significant difference in the maternal mortality, overall morbidity, birth weight, or infant respiratory distress between CORT-treated and control patients.
Platelet count and serum LDH levels are reliable indicators of HELLP severity, and recovery and longer recovery time is required for more severe cases [27,28]. Corticosteroids are thought to prevent platelet consumption and erythrocyte destruction by stabilizing the vascular endothelium and effectually reducing blood product administration requirements.

### Supplementary Table 1. Characteristics of the included studies.

| Study                  | Design  | Time         | n     | Gestation (CORT) | Gestation (controls) | Percent nulliparous |
|------------------------|---------|--------------|-------|------------------|----------------------|---------------------|
|                        |         |              |       | Week             | sd                   | CORT               | Control             |
| Fonseca 2005           | RCT     | Antepartum   | 66    | 34.4             | 4.8                  | 30.9               | 7.3                 | 33                 | 49                 |
| Katz 2008              | DB-RCT  | Postpartum   | 56    | 30.7             | 4.9                  | 32.8               | 4.7                 | 0                  | 15                 |
| Magann 1994a           | RCT     | Antepartum   | 12    | 33.7             | 3.1                  | 30.9               | 4.5                 |                    |                    |
| Magann 1994b           | RCT     | Postpartum   | 20    |                  |                      |                    |                     |                     |
| Martin 1997            | Retrospective | Postpartum | 43    | 29.1             | 3.5                  | 34.5               | 3.75                | 7                  | 80                 |
| Martin 2003            | Retrospective | Peripartum | 288   | 31.8             | 4.1                  | 33                 | 4.4                 | 25                 | 71                 |
| Meccai 2001            | Retrospective | Postpartum | 20    | 32               | 3.5                  | 34.5               | 3.75                | 7                  | 80                 |
| Nunes 2005             | Retrospective | Peripartum | 35    | 31.8             | 4.1                  | 33                 | 4.4                 | 25                 | 71                 |
| O’Brien 2000           | Retrospective | Antepartum | 11    | 32               | 3.5                  | 36                 | 2                   |                    |                    |
| O’Brien 2002           | Retrospective | Antepartum | 46    | 32.4             | 3.4                  | 34.8               | 4.8                 | 36                 | 65                 |
| Ozer 2009              | RCT     | Antepartum   | 30    | 32.4             | 4.5                  | 33.1               | 3.7                 | 15                 | 60                 |
| van Runnard Heimel 2006| DB-RCT  | Peripartum   | 15    | 27.4             | 1.4                  | 27.6               | 3.3                 | 14                 | 81                 |
| Varol 2001             | Retrospective | Postpartum | 9     | 33.5             | 3.3                  | 32.5               | 3.1                 |                    |                    |
| Vigil-De Gracia 1997   | RCT     | Postpartum   | 17    | 32.8             | 3.4                  | 34.41              | 2.81                |                    |                    |
| Yalcin 1998            | RCT     | Postpartum   | 15    | 35.1             | 2.9                  | 35.5               | 2.6                 | 10                 | 60                 |

**Figure 1.** PRISMA flowchart of study screening and selection process.
The recovery of platelets is reported to start as early as 12 hours after CORT administration [31].

The HELLP syndrome, especially in the postpartum period, is associated with high maternal morbidity [32]. Class 1 HELLP syndrome patients are at higher risk of maternal mortality, and delay in the diagnosis worsens prognosis [33]. Despite improvements in biological parameters of HELLP syndrome, most of the studies reported that CORT treatment does not reduce maternal morbidity [34]. The present study also found no significant difference between CORT-treated and control HELLP patients in the incidence of overall morbidity in a meta-analysis of 8 studies presenting 15 morbid conditions. However, the frequency of events was considerably less in CORT-treated patients. Data were not sufficient for the evaluation of all morbid conditions individually. There was also no significant difference between both the groups in maternal mortality. The morbid conditions observed in the present study were also reported by many studies not included in this meta-analysis [32,33]. The morbidities not reported herein include abruptio placenta, retinal detachment, adult respiratory distress syndrome, and hypoxic ischemic encephalopathy [32,33].

The etiology of the HELLP syndrome is poorly understood. It is believed that an imbalance between proangiogenic and antiangiogenic factors and increased proinflammatory cytokines play an important role in women with preeclampsia and HELLP syndrome.

Table 2. Main findings of the meta-analysis.

| Parameter                  | Studies/patients | Mean difference [95% CI]     | p      | I²/I² after sensitivity analysis |
|----------------------------|------------------|------------------------------|--------|----------------------------------|
| Platelet count (×10⁹/L)    | 10/1315          | 38.08 [15.71, 60.45]         | p=0.0009 | 99%/82%                         |
| LDH (IU/mL)                | 10/1162          | -0.44 [-0.76, -0.12]         | p=0.007 | 94%/76%                         |
| AST (IU/L)                 | 8/755            | -48.50 [-114.32, 17.32]      | p=0.15  | 92%/90%                         |
| ALT (IU/L)                 | 4/179            | -143.34 [-278.69, -7.99]     | p=0.04  | 99%/87%                         |
| SBP (mm Hg)                | 3/125            | 2.10 [-7.71, 11.91]          | p=0.67  | 63%/21%                         |
| DBP (mm Hg)                | 3/125            | -2.88 [-8.24, 2.47]          | p=0.29  | 60%/23%                         |
| Birth weight (kg)          | 3/116            | 0.09 [-0.11, 0.28]           | p=0.38  | 63%/21%                         |
| Hospital/ICU stay (days)   | 7/410            | -1.79 [-3.54, -0.05]         | p=0.04  | 64%/30%                         |
| Cesarean delivery          | 9/1142           | 1.25 [0.95, 1.63]            | p=0.11  | 0%                              |
| Overall morbidity*         | 8/866            | 0.79 [0.58, 1.08]            | p=0.14  | 53%                             |
| Infant respiratory distress| 5/1000           | 1.13 [0.50, 2.53]            | p=0.78  | 78%                             |
| Maternal mortality         | 7/893            | 1.27 [0.45, 3.60]            | p=0.65  | 0%                              |

ALT – alanine aminotransferase; AST – aspartate aminotransferase; CI – confidence interval; DBP – diastolic blood pressure; I² – between study statistical heterogeneity index; ICU – intensive care unit; IU/L – international units per liter; LDH – lactic dehydrogenase. * Morbid conditions are described in results section.
A rather longer postpartum recovery period may be required for patients with progressively worsening HELLP syndrome [27]. Corticosteroid therapy is a cost-effective medication that can be administered via different routes and reduces the length of hospitalization as compared to other treatments, such as platelet transfusion [3]. In the present study, on average, CORT therapy reduced hospital/ICU stay by about 3 days in comparison with controls and this difference was statistically significant in the meta-analysis of 7 studies. Thus, corticosteroids can be beneficial in carefully selected HELLP patients without apparent adverse effects to mother or fetus/neonate.

This meta-analysis has some important limitations. Firstly, studies with varying designs were included because none of a particular design could make sufficient data available. Secondly, clinical and methodological heterogeneity of the sample population in the form of factors such as the severity of HELLP syndrome, time of CORT administration, and dosage and duration of CORT administration in recruited patients may have

### Table 1: Forest graph showing the effect of CORT on platelet count in individual studies and the overall effect of the meta-analysis.

| Study or subgroup | Platelet count (Mean, SD, Total) | Weight | Mean difference (IV, Random, 95% CI) | Mean difference (IV, Random, 95% CI) |
|------------------|---------------------------------|--------|-------------------------------------|-------------------------------------|
| Katz 2008        | 119 ± 16.9 (56)                 | 7.9%   | 0.50 (–5.39, 6.39)                  |                                    |
| Magann 199a      | 18.8 ± 5.83 (12)                | 7.2%   | 64.20 (38.85, 89.55)                |                                    |
| Magann 199b      | 15.2 ± 3.22 (12)                | 7.9%   | 68.10 (61.85, 74.35)                |                                    |
| Martin 1997      | 32 ± 16.4 (43)                  | 7.9%   | 8.00 (2.68, 13.32)                  |                                    |
| Martin 2003      | –5 ± 1.52 (208)                 | 7.9%   | 81.00 (76.41, 83.59)                |                                    |
| Meccal 2001      | 90.9 ± 3.31 (32)                | 6.9%   | 60.10 (29.77, 90.43)                |                                    |
| Nunes 2005       | 61.19 ± 3.75 (31)               | 7.8%   | 64.10 (55.09, 73.11)                |                                    |
| O’Brien 2000     | 60.8 ± 7.5 (58)                 | 6.0%   | 73.60 (28.26, 118.94)               |                                    |
| O’Brien 2002     | –4 ± 5.9 (46)                   | 7.4%   | 11.00 (–10.00, 32.00)               |                                    |
| Ozer 2009        | 64.5 ± 9.7 (32)                 | 5.3%   | –12.90 (–68.87, 43.49)              |                                    |
| van Rannard Heimel 2006 | 49 ± 4.9 (15) | 6.8% | 7.93 (–24.36, 40.22) |                                    |
| Vazol 2001       | 51 ± 10.5 (9)                   | 7.7%   | 33.99 (21.82, 46.16)                |                                    |
| Vigil-De Gracia 1997 | 98.2 ± 9.8 (17) | 5.8% | 73.85 (25.85, 121.85) |                                    |
| Yalcin 1998      | 28.5 ± 16.8 (15)                | 7.6%   | –1.73 (–19.23, 15.77)               |                                    |

Total (95% CI): 601 – 714 100.0%: 38.08 (15.71, 60.45)

### Figure 3. Forest graph showing the effect of CORT on platelet count in individual studies and the overall effect of the meta-analysis.

### Table 2: Forest graph showing the effect of CORT on LDH in individual studies and the overall effect of the meta-analysis.

| Study or subgroup | LDH (Mean, SD, Total) | Weight |Mean difference (IV, Random, 95% CI) | Mean difference (IV, Random, 95% CI) |
|------------------|-----------------------|--------|-------------------------------------|-------------------------------------|
| Katz 2008        | 149 ± 16.9 (56)       | 11.5%  | 0.00 (–0.22, 0.23)                  |                                    |
| Magann 199a      | 0.76 ± 0.312 (12)     | 11.7%  | –1.22 (–1.42, –1.02)                |                                    |
| Magann 199b      | 0.75 ± 0.321 (12)     | 4.7%   | –1.15 (–1.89, –0.41)                |                                    |
| Martin 1997      | 0.75 ± 0.303 (43)     | 11.5%  | –0.20 (–0.40, 0.00)                 |                                    |
| Martin 2003      | 0.808 ± 0.408 (288)   | 7.7%   | –0.55 (–1.24, 0.15)                 |                                    |
| Meccal 2001      | –0.029 ± 0.245 (12)   | 10.3%  | –0.12 (–0.52, 0.27)                 |                                    |
| Nunes 2005       | –0.326 ± 0.280 (35)   | 11.9%  | –0.05 (–0.20, 0.09)                 |                                    |
| O’Brien 2000     | –0.355 ± 0.22 (31)    | 11.4%  | –0.66 (–0.90, –0.43)                |                                    |
| Ozer 2009        | –0.407 ± 0.239 (30)   | 12.1%  | 0.06 (–0.04, 0.16)                  |                                    |
| van Rannard Heimel 2006 | 0.275 ± 0.3518 (15) | 4.5% | –1.38 (–2.57, –0.19) |                                    |

Total (95% CI): 514 – 648 100.0%: –0.44 (–0.76, –0.12)

### Figure 4. Forest graph showing the effect of CORT on LDH in individual studies and the overall effect of the meta-analysis.
affected overall outcomes. Although, the random-effects model was used to interpret the results, but multi-center randomized controlled trials will be required for clarification of these results. Thirdly, the effect of some statistical procedures used to impute missing data may also have had a slight impact, as not all studies provided measures of dispersal values of the effect size of change in indicators following CORT/placebo treatments.

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Conclusions

Corticosteroid administration to HELLP patients improves platelet count and the serum levels of LDH, besides reducing hospital/ICU stay and blood transfusion rate. However, these indices do not significantly associate with maternal mortality and overall morbidity prevalence.

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