# CORTICOSTEROIDS FOR HELLP SYNDROME – AN INCURSION IN SUSPICIOUS SCIENCE

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***Background***

In 1980's, several case reports emerged implying that administration of corticosteroids for fetal maturation in pregnancies complicated by HELLP syndrome may be followed by improvement in clinical and laboratory markers.[1] It has been hypothesized that the underlying mechanism for such observations resides in the antiinflammatory and immunosuppressive effects of corticosteroids.

Preeclampsia is characterized by endothelial dysfunction as part of an inappropriate maternal systemic inflammatory response.[2] The inflammatory response is stimulated in turn by placental hypoxia resulting from poor placentation at an early gestational age. The degree of inappropriate inflammatory activation seems to be greater in earlier cases of preeclampsia, which will bear the greatest maternal and perinatal risks.[3] In addition to inflammation, immune mechanisms may also play an important role in preeclampsia.[4]

HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome is a type of severe preeclampsia, featuring specific manifestations of endothelial dysfunction, with variable degrees of hepatic damage, microangiopathic hemolytic anemia, and thrombocytopenia. Its presence is associated with increased maternal morbidity and mortality. Immediate delivery is required to reverse the ominous course of this condition, with the resulting iatrogenic prematurity contributing to a very high rate of perinatal morbidity and mortality.

The long-acting fluorinated corticosteroids used for fetal maturation, dexamethasone (DXM) or betamethasone (BTM), have an antiinflammatory activity 25 to 30 times more potent than that of cortisol.[5] As the underlying molecular mechanisms, it is known that corticosteroids decrease the gene transcription of various cytokines: interleukins-1 to 6, interleukin-8, interleukins-11 to 13, interferon gamma, and tumor necrosis factor alpha. Moreover, corticosteroids upregulate gene transcription of lipocortin-I, an antiinflammatory protein and interleukin-1 receptor antagonist.[6] Corticosteroids can also diminish tissue edema by decrease of blood vessel diameter and permeability,[7] and a stabilizing effect of corticosteroids on endothelial cells has been reported.[8] In addition, corticosteroids inhibit the infiltration of inflammatory leukocytes[9] and platelet aggregation.[10] One can see that, at least theoretically, corticosteroids have the ability to modify the proinflammatory features of severe preeclampsia.

***Antepartum treatment with corticosteroids in HELLP syndrome***

After a few retrospective and prospective observational reports in the literature, Magann and his colleagues at the University of Mississippi published in 1994 the results of the first randomized trial comparing the use of high-dose DXM to no treatment for antepartum stabilization of HELLP syndrome.[11] The study was small, including only 12

subjects in the intervention group and 13 controls, and suffered from a plethora of methodological problems. In spite of randomization, the study groups were not comparable on several criteria, including racial distribution, and more importantly, severity of disease. The mean baseline platelet count at randomization in the corticosteroid group was 69,300/microL significantly different from 106,800/microL in the control group. It is easier to overestimate the effect of an intervention when the intervention group is sicker than the control group. Benefit from an intervention increases with the baseline disease risk, and the sicker individuals are expected tobenefit most.[12] Platelet count values in excess of 100,000/microL, as the mean value recorded in the control group, does not even satisfy the widely accepted diagnostic criteria for HELLP syndrome proposed by Sibai in 1990: aspartate aminotransferase (AST) > 70 IU/L, lactic dehydrogenase (LDH) more or equal to 600 IU/L, and platelet count < 100,000.[13] The researchers from the University of Mississippi used their own diagnostic criteria based on a triple classification of HELLP syndrome in 3 classes: class 1 with nadir platelet count < 50,000, class 2 with a platelet nadir between 50,000 and 100,000, and class 3 with platelet nadir > 100,000.[14] For class 3, the AST, and alanine aminotransferase (ALT) cut-off value is 40 IU/L, curiously in normal range for pregnancy. We recognize that classifications or strict cut-off values are often arbitrary, but common and precise diagnostic criteria are essential to enable scientific reporting and communication. It is interesting that the researchers from Mississippi themselves recognized later that identifying class 3 HELLP patients has little clinical significance.[15] Unfortunately, the inclusion of an undisclosed number of class 3 patients in the study, patients without a severe abnormality, and the exclusion from the study of those most concerning cases from class 1, makes the interpretation of results more difficult and possibly unreliable.

The mean gestational age at randomization was 30.7 +/- 4.9 weeks in the steroid group and 32.8 +/- 4.7 in the control group. Although the numbers are not significantly different, we can see that some patients, especially in the control group had gestational ages between 34 and 37 weeks. Since the study protocol requested immediate delivery at 34 weeks, the interpretation of the interval from randomization to delivery (mean of 41 hours in the steroid group and 15 hours in the control group) also becomes problematic. It might not reflect a treatment effect, but rather the fact that more patients in the control group had to be delivered immediately by protocol, with no motivation for temporization at a gestational age of 34 weeks or more.

The predicted hourly rate of improvement by simple linear regression in platelet count, LDH, AST, and urinary output indicated a significant difference in favor of the treated group. This suggestion of a potential maternal benefit was lost shortly after discontinuation of treatment, and in the absence of postpartum treatment, there was no difference in rapidity of reaching recovery. In both groups resolution of clinical and laboratory abnormalities was evident by 96 hours postpartum, indicating that antepartum treatment did not modify the natural history of the syndrome.

There were no significant differences in neonatal outcomes such as mean birth weight, respiratory distress syndrome (RDS), need for ventilator support, intracerebral hemorrhage, necrotizing enterocolitis, or Apgar score <7 at 5 minutes, probably because the number of neonates at less than 32 weeks in the study was too small. More than suggestions, it is difficult to identify any definite outcome improvements in the results of

this study. Even the questionable gain in interval to delivery, was not more than approximately one day.

A troubling aspect of the study is that the control group could not receive any corticosteroids and was denied the benefits of standard antenatal steroids for fetal maturation. Three of the neonates in this group died of prematurity complications, while in the treatment group there was only one neonatal death. A study that intentionally withholds effective treatment from one group of patients is ethically suspect. Moreover, the study has no external validity, because in the real world patients at less than 32-34 weeks gestation would always receive corticosteroids for fetal maturation.

Based on a single randomized study of 25 patients, and as we have seen, a study with many methodological and interpretative deficiencies, many practitioners all over the world were quick to adopt this treatment. At the Institute of Obstetrics and Gynecology of the University of Florence, Italy, heparin had been used since 1990 for the treatment of HELLP syndrome. In 1996, heparin was no longer administered, and was replaced with a new protocol of high dose DXM. A retrospective study compared 12 patients treated with DXM with 20 historical controls treated with heparin.[16] The only significant differences observed were more cases of disseminated intravascular coagulation (DIC) developing after the diagnosis of HELLP, with hemorrhage requiring transfusion and renal failure in the heparin group. This study can hardly be interpreted as supporting the beneficial effect of corticosteroids, but rather the inadvisability of heparin treatment for HELLP syndrome.

It has been reported that the hematological effects of BTM in pregnancy last only 48 hours.[17] When corticosteroids are used antepartum in HELLP syndrome, in at least 60% of cases, in 24-48 hours after discontinuation of treatment, the hematological and biochemical abnormalities rebound, which is probably the result of persistent mediators of disease.[18] In a case report from Nuremberg, Germany, of a pregnancy affected by HELLP syndrome at 25 weeks gestation, there was clinical and laboratory parameters improvement after the initial high-dose methylprednisolone treatment (40 mg iv) for 6 days, with rebound deterioration upon discontinuation of treatment.[19] With reinstitution of corticosteroids, the authors were able to prolong the pregnancy for 33 days. Five years later, Qureshi and Tomlinson used the same protocol in a case of HELLP syndrome at 26 weeks gestation.[20] After the initial 6 days treatment, there was no rebound deterioration, and the patient was discharged with twice weekly antepartum testing. In spite of this surveillance and normalization of laboratory parameters, fetal demise occurred at 28 weeks.

In a personal communication at the 14$^{th}$ World Congress of the International Society for the Study of Hypertension in Pregnancy, Vienna, Austria, 2004, Pieter van Runnard Heimel from the University Medical Center, Utrecht, the Netherlands reported on a randomized, placebo-controlled trial of 31 women who developed HELLP syndrome before 30 weeks gestation. Fifteen were treated with 50 mg prednisolone iv twice daily, and 16 were treated with placebo iv. The clinical and laboratory parameters were comparable between the groups. The mean interval to delivery was 6.9 days in the steroid group, and 8.0 days in the placebo group. At 2 years follow up, only 10 children were alive in each group. Although there was no demonstrable benefit in prolongation of pregnancy or long-term infant survival, the steroid treatment appeared to be protective short-term. In contrast, in the placebo group, there were 3 severe cases of maternal

morbidity/mortality (one liver hematoma and two cases of hepatic rupture, one lethal), 2 cases of fetal demise, and 2 neonatal deaths in the first week of life. No such cases were recorded in the steroid group. This is another example of an ethically suspect study. The ultimate goal of an alternative approach in HELLP syndrome should be a better balance between the risks for prematurity complications and the risk for maternal complications including death. Corticosteroids for disease modification in women with HELLP syndrome should be compared to a similar group managed with immediate delivery, the current gold standard, not with expectant management and placebo, which can be a death sentence for up to 20% of women and an experiment in itself.

***Concerns related to the use of high-dose antepartum corticosteroids***

The high dose of DXM introduced in the original randomized study from the University of Mississippi,[11] was chosen arbitrarily based on doubling of the conventional fetal maturation protocol.[21] It was subsequently confirmed that a greater improvement in laboratory values can be achieved with such doses compared to the standard corticosteroid dosage for fetal maturation.[18] Although the intention of the investigators was to treat the mother, the choice for treatment was almost always DXM or BTM, synthetic preparations that are only minimally inactivated by 11-beta-hydroxysteroid dehydrogenase and cross the placenta in significant amount, exposing the fetus to inordinately high amounts of corticosteroids. Furthermore, preeclampsia is a condition associated with reduced placental 11-beta-hydroxysteroid dehydrogenase 2 function,[22] already favorizing excessive fetal exposure to corticosteroids, including endogenous ones. Experimental evidence with invasive monitoring of the healthy term sheep fetus demonstrated that exposure to corticosteroids even at doses equivalent to the usual clinical dose for fetal maturation induced fetal hypertension,[23] reduced cerebral blood flow,[24] and increased fetal lactate levels.[25] Real, well-founded concerns have also been expressed regarding the prolonged or repeated exposure to antenatal corticosteroids in humans, even at the standard intramuscular doses.[26,27] In contrast, the intravenous administration of high-dose antenatal corticosteroids has never been sufficiently evaluated for safety. Even the originators of the antepartum corticosteroid treatment for HELLP syndrome, the investigators from the University of Mississippi, by now consider that “antenatal high-dose corticosteroid use for maternal indication [has] the potential for...adverse effects on the fetus and child....The antepartum treatment...should be as brief as possible to achieve maximal maternal benefit and minimize any potential adverse perinatal impact”.[21]

***Antenatal corticosteroids and fetal growth restriction***

Recent evidence suggests that severely growth-restricted fetuses may have a poor response to antenatally administered corticosteroids. Such a context represents another hazard when corticosteroid treatment is entertained for cases of HELLP syndrome, because preeclampsia is frequently associated with fetal growth restriction (FGR). Moreover, in severe preeclampsia there may be increased umbilical artery and placental vascular resistance. Wallace and Baker reported in a small retrospective study in1999 that the administration of BTM for fetal maturation in cases of increased placental vascular resistance, as evidenced by absent end-diastolic flow (AEDF) in the umbilical artery, was associated with a transient return of end-diastolic flow in a majority of cases.[28] The return

of end-diastolic flow with corticosteroids was confirmed in 70% of cases in a subsequent prospective cohort study.[29] The phenomenon was also noted in 50% of multiple pregnancies discordant for AEDF.[30] The flow return is transient though, an average of 3 to 5 days, and Adamson and Kingdom warned that the return of end-diastolic flow does not necessarily equate with improved gas exchange.[31]

Evaluation of umbilical artery Doppler waveform in presumed growth restricted fetuses is routinely used. It improves fetal surveillance, assists in timing of delivery, and reduces perinatal mortality.[32] If the assessment is performed shortly after corticosteroid administration, falsely reassuring and misleading results may be obtained.

In a prospective study, Simchen et al observed a better outcome in growth-restricted fetuses with AEDF that responded to corticosteroid administration with return of the diastolic flow compared to those fetuses with persistent AEDF (40% vs 89% acute deterioration or demise).[33] The fact that even in the first group 40% of fetuses manifested acute deterioration suggests poor tolerance of corticosteroids in severely growth-restricted fetuses as a whole. The authors recommended caution in using corticosteroids for growth retarded fetuses with AEDF.

***Postpartum treatment with corticosteroids in HELLP syndrome***

Three randomized trials compared high-dose DXM with no treatment for postpartum stabilization of HELLP syndrome.[34-36] Their size was small (30 to 40 participants), none was placebo-controlled, in one study[34] the loss to follow up was 37%, and different diagnostic criteria for HELLP syndrome were used.

In the Vigil-De Gracia and Garcia-Caceres study,[35] conducted in Mexico, the postrandomization groups were not comparable with regards to platelet count (lower counts in the treatment group). As discussed relative to the Magann et al antepartum study,[11] such a difference would overestimate the intervention effect and cast doubt on the interpretation of results, especially when the only maternal outcome difference was in the rate of increase in platelet count. There were no differences in urinary output, LDH, AST, ALT, or blood pressure values. Even the mean platelet count was never below 50,000/microL during the study period of 72 hours postpartum, raising questions about the clinical significance of any putative difference between the groups. No magnesium sulfate prophylaxis was used in this study and one death was recorded in the control group due to eclampsia, platelet count 23,000/microL before seizure, and massive cerebral hemorrhage. It is unlikely that the outcome of this severe case could have been averted by the addition of corticosteroids only, in the absence of seizure prophylaxis.

Similar deficiencies can be identified in the Yalcin et al study,[36] conducted in Turkey. The randomization and blinding method are not stated, the number of class 3 HELLP patients included in the study is undisclosed, and the platelet count at randomization is not comparable between the groups (significantly lower in the treatment group).

The conclusion independently reached by all these studies was that corticosteroids treatment was associated with a significantly more rapid recovery in laboratory parameters, mean arterial pressure, and urinary output. But preeclampsia, including HELLP syndrome always subsides in postpartum without any treatment other than supportive. All the available evidence so far with corticosteroids in cases of HELLP syndrome has never demonstrated any benefit in clinically important maternal outcomes

such as pulmonary, renal, hepatic complications, or the need for blood products.[35] When all the available antepartum and postpartum randomized studies were analyzed in aggregate in a Cochrane review, no benefit could be demonstrated in terms of maternal and perinatal morbidity and mortality.[38]

Furthermore, the recently published results of another randomized trial conducted at the University of Mississippi place significant doubts on the previous claim that high-dose DXM would be effective in the treatment of HELLP syndrome. This time, high-dose DXM was given in 4 doses at 0, 12, 24, and 36 hours postpartum in women with severe preeclampsia, but without elements of HELLP syndrome.[39] No benefit could be detected in relation to the DXM treatment. It is hard to find even a speculative explanation why the DXM would be effective in HELLP syndrome, a form of severe preeclampsia, and would be unable to modify in any way the clinical course of other cases of severe preeclampsia. Inflammatory dysfunction of the endothelium is presumably present in all the cases of severe preeclampsia, and some similarity in response should be present.

***Conclusion***

The available evidence does not support the hypothesis that corticosteroids, either antepartum and/or postpartum can improve the outcome of pregnancies affected by HELLP syndrome. More research is needed, but until more convincing data become available, corticosteroids for disease modification in women with preeclampsia should not be used outside the setting of a clinical trial.

REFERENCES


1. Clark SL, Phelan JR, Allen SH, Golde SR. Antepartum reversal of hematologic abnormalities associated with HELLP syndrome. A report of three cases. J Reprod Med 1986;31:70-2
2. Redman CW, Sacks GP, Sargent IL. Preeclampsia: an excessive maternal inflammatory response to pregnancy. Am J Obstet Gynecol 1999;180:499-506
3. von Dadelszen P, Magee LA, Roberts JM. Subclassification of preeclampsia. Hypertens Pregn 2003;22:143-8
4. Sacks GP, Sargent IL, Redman CW. An innate view of human pregnancy. Immunol Today 1999;20:114-8
5. Melby JC. Drug spotlight program: systemic corticosteroid therapy: pharmacology and endocrinologic considerations. Ann Intern Med 1974;81:502-12
6. Barnes PJ. Anti-inflammatory actions of glucocorticoids: molecular mechanisms. Clin Sci (London) 1998;94:557-72
7. Schleimer RP. An overview of glucocorticoid anti-inflammatory actions. Eur J Clin Pharmacol 1993;45 (suppl 1):S3-S7
8. Boumpas DT, Chrousos GP, Wilder RL, et al. Glucocorticoid therapy for immune-mediated diseases: basic and clinical correlates. Ann Intern Med 1993;119:1198-208
9. Pitzalis C, Pipitone N, Perretti M. Regulation of leukocyte-endothelial interactions by glucocorticoids. Ann N Y Acad Sci 2002;966:108-18

10. Glass F, Lippton H, Kadowitz PJ. Effects of methylprednisolone and hydrocortisone on aggregation of rabbit platelets induced by arachidonic acid and other aggregating substances. Thromb Haemost 1981;46:676-9
11. Magann EF, Bass D, Chauhan SP, et al. Antepartum corticosteroids: disease stabilization in patients with the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP). Am J Obstet Gynecol 1994;171:1148-53
12. Glasziou PP, Irwig LM. An evidence based approach to individualizing treatment. BMJ 1995;311:1356-9
13. Sibai BM. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): much ado about nothing? Am J Obstet Gynecol 1990;162:311-6
14. Martin Jr JN, Blake PG, Perry Jr KG, McCaul JF, Hess LW, Martin RW. The natural history of HELLP syndrome: patterns of disease progression and regression. Am J Obstet Gynecol 1991;164:1500-9
15. Martin Jr JN, Rinehart BK, May WL, Magann EF, Terrone DA, Blake PG. The spectrum of severe preeclampsia: comparative analysis by HELLP (hemolysis, elevated liver enzyme levels, and low platelet count) syndrome classification. Am J Obstet Gynecol 1999;180:1373-84
16. Mecacci F, Carignani L, Cioni R, et al. Time course of recovery and complications of HELLP syndrome with two different treatments: heparin or dexamethasone. Thrombosis Research 2001;102:99-105
17. Wallace EM, Ekkel K, Cotter T, Tippett C, Catalano J. Haematological effects of betamethasone treatment in late pregnancy. Aust N Z J Obstet Gynaecol 1998;38:396-8
18. O'Brien JM, Milligan DA, Barton JR. Impact of high-dose corticosteroid therapy for patients with HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. Am J Obstet Gynecol 2000;183:921-4
19. Schlembach D, Munz W, Fischer T. Effects of corticosteroids on HELLP syndrome: a case report. J Perinat Med 2000;28:502-5
20. Qureshi NS, Tomlinson AJ. Prenatal corticosteroid therapy for elevated liver enzyme/low platelet count syndrome. J Reprod Med 2005;50:64-6
21. Martin Jr JN, Thigpen BD, Rose CH, Cushman J, Moore A, May WL. Maternal benefit of high-dose intravenous corticosteroid therapy for HELLP syndrome. Am J Obstet Gynecol 2003;189:830-4
22. Schoof W, Girstl M, Frobenius W, et al. Decreased gene expression of 11beta-hydroxysteroid dehydrogenase type 2 and 15-hydroxyprostaglandin dehydrogenase in human placenta of patients with preeclampsia. J Clin Endocrinol Metab 2001;86:1313-7
23. Derks JB, Giussani DA, Jenkins SL, et al. A comparative study of cardiovascular, endocrine and behavioural effects of betamethasone and dexamethasone administration to fetal sheep. J Physiol 1997;499:217-6

24. Schwab M, Roedel M, Anwar MA, et al. Effects of betamethasone administration to the fetal sheep in late gestation on fetal cerebral blood flow. J Physiol 2000;528:619-32
25. Bennet L, Kozuma S, McGarrigle HHG, Hanson MA. Temporal changes in fetal cardiovascular, behavioural, metabolic and endocrine response to maternally administered dexamethasone in the late gestation fetal sheep. BJOG 1999;106:331-9
26. Vidaeff AC, Mastrobattista JM. Controversies in the use of antenatal steroids for fetal maturation. Semin Perinatol 2001; 25:385-96
27. Vidaeff AC, Doyle NM, Gilstrap LC. Antenatal corticosteroids for fetal maturation in women at risk for preterm delivery. Clin Perinatol 2003; 30:825-840
28. Wallace EM, Baker LS. Effect of antenatal betamethasone administration on placental vascular resistance. Lancet 1999;353:1404-7
29. Edwards A, Baker LS, Wallace EM. Changes in umbilical artery flow velocity waveforms following maternal administration of betamethasone. Placenta 2003;24:12-16
30. Barkehall-Thomas A, Thompson M, Baker LS, Edwards A, Wallace EM. Betamethasone associated changes in umbilical artery flow velocity waveforms in multiple pregnancies with umbilical artery absent and diastolic flow. Aust N Z J Obstet Gynaecol 2003;43:360-3
31. Adamson SL, Kingdom J. Antenatal betamethasone and feto-placental blood flow (letter). Lancet 1999;354:255-6
32. Sivan E, Dulitzky M, Lipitz S, et al. The clinical value of umbilical artery Doppler velocimetry in the management of intrauterine growth retarded fetus before 32 weeks' gestation. Gynecol Obstet Invest 1995;40:19-23
33. Simchen MJ, Alkazaleh F, Adamson SL, et al. The fetal cardiovascular response to antenatal steroids in severe early-onset intrauterine growth restriction. Am J Obstet Gynecol 2004;190:296-304
34. Magann EF, Perry Jr KG, Meydrech EF, et al. Postpartum corticosteroids: accelerated recovery from the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP). Am J Obstet Gynecol1994;171:1154-8
35. Vigil-De Gracia P, Garcia-Caceres E. Dexamethasone in the post-partum treatment of HELLP syndrome. Int J Gynaecol Obstet 1997;59:217-21
36. Yalcin OT, Sener T, Hassa H, et al. Effects of postpartum corticosteroids in patients with HELLP syndrome. Int J Gynaecol Obstet 1998;61:141-8
37. Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. Obstet Gynecol 2004;103:981-991
38. Matchaba P, Moodley J. Corticosteroids for HELLP syndrome in pregnancy. Cochrane Database Syst Rev 2004;1:CD002076

39. Barrilleaux PS, Martin JN, Klauser CK, Bufkin L, May WL. Postpartum intravenous dexamethasone for severely preeclamptic patients without hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome: a randomized trial. Obstet Gynecol 2005;105:843-8