Corticosteroids for HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome in pregnancy

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There is insufficient evidence to support the inclusion of corticosteroids in the standard therapy for HELLP syndrome. When administered antenatally, corticosteroids had a positive effect on secondary outcomes such as platelet count, aspartate transaminase, alanine transaminase, lactate dehydrogenase, and urinary output, but they did not have any effect on substantive clinical outcomes for the mother and the baby.

RHL Commentary by Amorim M and Katz L

1. INTRODUCTION

HELP (haemolysis, elevated liver enzymes, low platelets) syndrome is one of the most severe forms of pre-eclampsia which adversely affects the prognosis for both the mother and her baby (1, 2). There is no specific treatment for the syndrome and historically the treatment has been limited to control of blood pressure, prophylaxis against convulsions and resolution of pregnancy either by delivery or by termination (1).

Observational studies had suggested that corticosteroids may help improve the condition of the mother with HELLP syndrome by stabilizing her clinical and laboratory status, thereby permitting the pregnancy to be maintained until the woman is in the ideal clinical condition and location for delivery. However, two recent randomized controlled trials evaluating the use of corticosteroid therapy to accelerate maternal postpartum recovery in women with HELLP syndrome have not confirmed the findings of the observational studies (3, 4). The present Cochrane review (5) sought to assess the effects of corticosteroids on women with HELLP syndrome and their babies.

2. METHODS OF THE REVIEW

The authors carried out a comprehensive search, without any language restriction, to identify trials from the Cochrane Pregnancy and Childbirth Group’s Trial Register, MEDLINE, EMBASE, CINAHL and MIDIRS (December 2010).

The selection criteria for studies included all published, unpublished, and ongoing randomized controlled trials involving comparisons in women with HELLP syndrome of any corticosteroid versus placebo, no treatment, or another drug, or comparison of a corticosteroid versus another corticosteroid or comparison of different dosages of corticosteroids. Quasi-randomized trials were excluded.

The primary outcomes studied for the mother were maternal death or severe maternal morbidity and for the
baby perinatal death and severe perinatal morbidity. Secondary outcomes included for the mother were the presence of liver haematoma or rupture or liver failure, pulmonary oedema, renal failure, placenta abruptio, eclampsia, cerebrovascular accident, elective delivery (induction of labour or elective caesarean section), caesarean section, caesarean section performed under general anaesthesia, postpartum haemorrhage, platelet count or rate of change in platelet count, side-effects or adverse events, use of hospital resources and woman's experience and views of the interventions.

The secondary outcomes for the baby were time from enrolment to birth, respiratory distress syndrome, intracerebral haemorrhage, necrotizing enterocolitis, care in a special care nursery for seven days or more, preterm birth, very preterm birth, extremely preterm birth, infection, retinopathy of prematurity, Apgar score at five minutes, use of hospital resources, and long-term growth and development.

The authors used fixed-effect inverse variance meta-analysis for combining data where trials examined the same intervention and the trials’ populations and methods were judged to be sufficiently similar. When there was clinical or methodological heterogeneity between studies to suggest that treatment effects may differ between trials, the random-effects meta-analysis method was used. The standardized mean difference (SMD) was used to combine trials that measured the same outcome, but used different methods. Where data were available, subgroup analyses was planned for gestation at trial entry, type of intervention (type or class, dose, or duration of corticosteroid) and corticosteroid versus no treatment, corticosteroid versus placebo.

### 3. RESULTS OF THE REVIEW

A total of 13 trials were included in the review. Eleven trials (550 women) had compared corticosteroids (dexamethasone, betamethasone or prednisolone) with placebo or no treatment. In two studies two different corticosteroids had been compared (dexamethasone versus betamethasone). All of the included studies had recruited women with a diagnosis of haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome.

In five of the 13 studies, pregnant women had been recruited and treatment started in the antenatal period. In one study women had been recruited and treatment started both antenatally and postnatally. In seven studies corticosteroid treatment had been started just after delivery or in the postnatal period (although the diagnosis of HELLP syndrome may have been made before delivery). In most of the studies it was stated that women also received other standard treatments as required, including magnesium sulfate and anti-hypertensive drugs, as well as, in some studies, standard doses of corticosteroids antenatally for fetal lung maturation.

There was clear evidence of an effect on platelets (expressed as platelet counts following treatment, or the rate of change in platelet counts per hour) in women who received corticosteroids versus women who received placebo or no treatment. The overall effect showed a SMD of 0.67 with a 95% confidence interval (CI) of 0.24–1.10).

The strongest evidence of this was found in the group of women who had commenced treatment antenatally; there was no clear evidence of an effect on platelet count in women who had started treatment postnatally (one study, 17 women, SMD in platelet count at 72 hours postpartum 0.47, 95% CI 0.21 to 1.16). In contrast, in the group in which treatment had commenced antenatally, there was evidence of an effect (SMD 0.80, 95% CI 0.25–1.35).

It was also found that for non-prespecified outcomes (aspartate transaminase, alanine transaminase, lactate dehydrogenase, and urinary output) there were significantly greater improvements in women receiving corticosteroids.

Despite the above finding, there was no clear evidence of any treatment effect of corticosteroids on substantive clinical outcomes. There was no evidence of any effect of corticosteroids in women with HELLP syndrome with regard to outcomes such as maternal death, maternal morbidity or complications, use of
hospital resources, woman's experience and views of the interventions and on the length of stay in hospital. For the baby, no effect of corticosteroids was observed on perinatal death or severe perinatal morbidity.

There were insufficient data available to allow the review authors to carry out subgroup analysis by gestation at trial entry, dose and duration of the intervention, and corticosteroid versus no treatment and corticosteroid versus placebo.

**DISCUSSION**

**4.1. APPLICABILITY OF THE RESULTS**

There is insufficient evidence to support the inclusion of corticosteroids in the standard therapy for HELLP syndrome. When administered antenatally, corticosteroids had a positive effect on secondary outcomes such as platelet count, aspartate transaminase, alanine transaminase, lactate dehydrogenase, and urinary output, but they did not have any effect on substantive clinical outcomes for the mother and the baby.

The positive effects of corticosteroid therapy observed in laboratorial results do not translate into clinical benefits. For instance, the rise in platelet count from corticosteroid therapy did not lead to lower incidence of haemorrhagic complications and need for transfusions of blood products, which in turn would result in decrease in maternal morbidity and mortality and duration of hospital stay. One possible explanation for this may be that the numbers of women in the studies was enough to demonstrate difference in the secondary quantitative endpoints such as platelet count, but the numbers were insufficient to demonstrate differences in primary qualitative outcomes, such as complications.

Another issue that needs to be considered is that, in the studies included in this review, women with different clinical severity of HELLP syndrome were recruited. In the largest trial included, a post-hoc analysis found a faster platelet recovery rate in the subgroup of Class I patients (6). It is possible that if only this subgroup of patients had been analysed, the clinical endpoint could have also been positively impacted by the laboratorial finding. For example, if platelet count rises in a patient from 70,000/mm$^3$ to 90,000/mm$^3$, probably there would be very little clinical impact of this rise. However, if the platelet count rises from 30,000/mm$^3$ to 90,000/mm$^3$, a much greater clinical impact may occur. Therefore it is possible that if only very severe cases are studied one may find a greater impact of corticosteroids on substantive outcomes.

Another interesting point is that the positive effect on secondary outcomes was observed only when the treatment was started antenatally. It is possible that women who demand initiating some type of intervention before interruption of pregnancy represent a more severely ill fraction of patients, in which severe laboratorial findings are detected early. Based on the theory presented above, this would be the group of women who are likely to benefit most from the intervention. However, considering all of the above, there is no justification at the present time to make this intervention a routine practice in all patients with HELLP syndrome.

**4.2. IMPLEMENTATION OF THE INTERVENTION**

Although there is insufficient evidence to include corticosteroids in the standard therapy for HELLP syndrome, some clinicians may consider it appropriate to use them in specific situations related to the treatment of HELLP syndrome cases. For example, in patients with platelet count under 50,000/mm$^3$ (Class I HELLP syndrome), raising the platelet count may be desirable and considered clinically important.

**4.3. IMPLICATIONS FOR RESEARCH**

The improvement found in platelet count, aspartate transaminase, alanine transaminase, lactate dehydrogenase, and urinary output, justifies further studies on the use of corticosteroids in women with HELLP syndrome. In order to obtain sufficiently powerful studies results, it is essential that sample size
calculation is made for clinical endpoints. Future trials should also select women with more severe forms of
the disease, which appear to be the group that would benefit most from the treatment.

There are very limited data suggesting that different types of corticosteroid may have different clinical
effects. After initial studies regarding value of corticosteroids in this clinical situation, further trials should
aim to study different types of corticosteroids and different dosages. Finally, it is also important to analyse
the costs associated with corticosteroid therapy and whether the treatment results in reduced costs for these
patients and for the health system.

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