Management of hyperemesis gravidarum: the importance of weight loss as a criterion for steroid therapy

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Summary

Background: Although the effectiveness of prednisolone therapy for severe hyperemesis gravidarum has been demonstrated, there is no consensus on how to assess severity to justify such treatment, nor any information on whether such therapy affects birth weight.

Aim: To document the effect of prednisolone therapy in women with defined severity of hyperemesis gravidarum.

Design: Single centre, observational study of 30 consecutive pregnancies complicated by hyperemesis and weight loss of >5% of pre-pregnant weight between April 1995 and July 2000. Comparison of birth weight with a contemporaneous control series of women admitted with hyperemesis that was judged insufficiently severe to require steroids.

Results: Treatment with prednisolone 10 mg tid rapid resolved nausea and vomiting, allowing discharge in 3 (range 1–6.5) days. Steroid therapy, which was reduced in a stepwise manner, was discontinued at a median gestation of 20 weeks. Maternal weight gain in pregnancy was restored to normal. Median birth weight in the severe, steroid-treated group was 3.33 (range 2.80–3.27) kg vs. 3.27 (range 3.04–3.53) kg in the less severe group.

Conclusion: Weight loss >5% served as a criterion to define a subset of women with severe hyperemesis gravidarum. In these women, steroid therapy was uniformly successful resulting in the prompt resolution of symptoms. Steroid therapy did not affect birth weight.

Introduction

Hyperemesis gravidarum is a debilitating illness affecting 0.3–2.0% of pregnant women.¹ It is characterized by continuous vomiting, dehydration, ketosis and muscle wasting. Standard anti-emetics are ineffective, and as yet there is no consensus on effective therapy. However, discussion has been clouded by lack of distinction between hyperemesis severe enough to cause significant weight loss, and hyperemesis which although troublesome, does not absolutely prevent food intake. While the former usually requires intravenous fluid for weeks or months and is very rare, the latter settles to a level of nausea and vomiting compatible with maintaining fluid balance. Most cases settle spontaneously between 16 and 22 weeks gestation, irrespective of severity.

Two small case series have described dramatically successful steroid therapy for severe hyperemesis.²,³ In the latter mean weight loss at presentation was documented and was considerable, being 10.5 kg (range 5.4–17.0). A recent multicentre double-blind placebo-controlled trial of prednisolone therapy in hyperemesis demonstrated significant benefit of steroids in respect of well-being.

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food intake and weight gain at 1 week, even though subjects were of variable severity and weight loss was not specified.\textsuperscript{4}

In the Newcastle upon Tyne Obstetric Unit, with 5000 deliveries per year, an average of six cases of severe hyperemesis are seen annually. At least six times that number require admission for intravenous fluids on one or more occasions, but are judged not to require steroid therapy. Since 1994, prednisolone therapy has been used for all cases of severe hyperemesis. This paper reports upon outcomes of pregnancy in the largest single centre consecutive series of such women treated with steroids. Birth weight in this series is compared with that in a series of less severely affected women with hyperemesis gravidarum not requiring steroid therapy.

Methods

Women requiring inpatient treatment for hyperemesis gravidarum in Newcastle upon Tyne between April 1995 and July 2000 were studied. Following a strict protocol, women were offered steroid treatment if they met the criteria listed in Table 1. An information leaflet was provided to all such women.

All women were assessed by a single physician particularly to exclude other possible causes of severe vomiting. A detailed history was taken, ascertaining gestation at which vomiting commenced, lack of other underlying cause, extent of vomiting, effect upon physical activity and family history of hyperemesis. Physical examination was performed to exclude localized epigastric tenderness, signs of hyperthyroidism and to test muscle wasting by observing performance of a squat test.

During the study period, steroid treatment was commenced in a total of 30 pregnancies in 25 women. This includes seven women previously reported\textsuperscript{3} and six recruited to the placebo-controlled double-blind randomized trial of Nelson-Piercy \textit{et al}.\textsuperscript{4} Of these six women, three were randomized to the placebo arm, but persistent symptoms resulted in steroid treatment for each subject following the one-week assessment period.

The treatment protocol was flexible, aiming to control or abolish symptoms using the minimum steroid dose. Oral prednisolone 10 mg 8-hourly was prescribed, replacing traditional anti-emetics. Initial stabilization with intravenous hydrocortisone 50 mg 8-hourly was reserved for those unable to tolerate tablets because of vomiting. Prednisolone dosage was reduced in a stepwise fashion over the subsequent weeks as rapidly as symptoms allowed. Typically, dosage would be decreased to 15 mg daily within 5 weeks, remaining between 12.5 and 15 mg for a further 3–8 weeks. Individual patient-held protocols for step-wise dosage reduction were provided, with instructions to return to the immediately previous dose if vomiting recurred after a dose reduction.

To compare pregnancy outcome, a retrospective series was identified of 25 consecutive women hospitalized for hyperemesis but judged not to require steroid therapy. All required intravenous rehydration, prophylactic thiamine support, and were prescribed traditional anti-emetics (metoclopramide, prochlorperazine maleate, or cyclizine hydrochloride). The Mann-Whitney U test was used to compare differences between groups where appropriate.

Results

Steroid therapy for severe hyperemesis was indicated in 30 pregnancies involving 25 women. Eight women gave a family history of hyperemesis gravidarum and 10 of the 14 multiparas had a previously affected pregnancy. Five were Asian compared with two in the non-steroid-treated group.

The response to steroids was prompt and complete in most women. Although eight women continued intravenous fluid and electrolyte replacement for more than 24 h after starting steroids, only three continued beyond 48 h. The median number of in-patient days pre-steroid treatment was 8 (range 4–14) and after commencement of steroid therapy was 3 (range 1–6.5). The total pre-treatment number of admissions was higher in the steroid-treated group (Table 2), although once steroids were initiated, only four women required readmission. Incomplete initial response in two women necessitated increases in steroid dose to 40 mg and 60 mg, respectively, and this achieved rapid and complete resolution of nausea and vomiting. When ptyalism was present, this symptom persisted for up to 10 days even though appetite had returned and vomiting had ceased.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Criteria for offering steroid treatment</th>
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<tr>
<td>Hyperemesis gravidarum requiring hospital admission plus:</td>
<td>Weight loss &gt; 5 kg and/or evidence of muscle wasting</td>
</tr>
<tr>
<td></td>
<td>Onset of nausea and vomiting before 6 weeks</td>
</tr>
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<td></td>
<td>Ketonuria on admission</td>
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<td>Intravenous fluids for &gt; 1 week or &gt; 24 h if a repeat admission</td>
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<td></td>
<td>Failure of traditional anti-emetic treatment</td>
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<td></td>
<td>Vomiting at least twice per day or severe nausea precluding any oral intake</td>
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<td></td>
<td>Gestation over 8 weeks</td>
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In those managed without steroids, weight loss >5% was only seen in three women. Maximum weight loss was >5% of pre-pregnant weight in every case in the steroid-treated group and symptom onset was earlier. Subsequent weight gain is shown in Figure 1.

The response to oral prednisolone or placebo for the six Newcastle patients included in the randomized double-blind trial is shown in Figure 2. For the one-week duration of the study the prednisolone dosage of 20 mg b.d. was used. It can be seen that the visual analogue data for intensity of nausea show a clear pattern of resolution in the active treatment group. All three placebo treated women subsequently received steroid therapy.

Steroid therapy reduced in-patient management, and most women required out-patient treatment for approximately 10 weeks, the median gestation of treatment cessation being 20 weeks. Three women continued treatment past 30 weeks. There were three pregnancies which were terminated in the first trimester, of which two were in the non-steroid-treated group.

Gestation at delivery and birth weight for term singletons was similar between groups (Table 2). There were two preterm deliveries in each group. Amongst those receiving steroids, one woman delivered a healthy baby girl (1100 g; >5th centile) following an antepartum haemorrhage, and one delivered a healthy baby girl at 35 weeks (2030 g; >10th centile). In the non-steroid-treated group, there were two deliveries during the 36th week (each >10th centile). In both groups, two women delivered term infants weighing less than the 5th centile. In the steroid group, both involved Asian women who had not taken steroids beyond the 21st week, one case being an otherwise uncomplicated twin pregnancy.

### Table 2: Outcome data and patient characteristics for each group

<table>
<thead>
<tr>
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<th>Steroid treated (n = 30)</th>
<th>Non-steroid-treated (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30 (27–33)</td>
<td>26 (24.5–28.5)*</td>
</tr>
<tr>
<td>Primiparous women</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Twins</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Onset of symptoms (weeks)</td>
<td>5.4 (0.9)</td>
<td>7.1 (2.1)*</td>
</tr>
<tr>
<td>Total number of admissions</td>
<td>3 (1–11)</td>
<td>1 (1–7)**</td>
</tr>
<tr>
<td>Maximum weight loss (kg)</td>
<td>6.5 (5–8)</td>
<td>2 (0.8–3.5)**</td>
</tr>
<tr>
<td>Gestation at start of steroid therapy (weeks)</td>
<td>9.6 (8.6–11.1)</td>
<td>–</td>
</tr>
<tr>
<td>Gestation at delivery (weeks)</td>
<td>39 (37–39.4)</td>
<td>39 (38.1–40.6)</td>
</tr>
<tr>
<td>Singleton birth weight &gt;37 weeks (g)</td>
<td>3331 (2800–3760)</td>
<td>3268 (3040–3530)</td>
</tr>
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</table>

Data are means (SD) for gestational age at symptom onset and medians (IQR) for all other parameters. *p < 0.01; **p < 0.005.

### Figure 1

Change in weight with gestation in the steroid-treated group (median, interquartile range and range). The points represent body weight pre-pregnancy, prior to steroid treatment but following rehydration, weight after 5–7 weeks of steroid therapy and weight prior to delivery.

### Figure 2

Data on intensity of nausea from visual analogue scale estimation collected prior to initiation of therapy and at 3 and 7 days of treatment. Symptom severity increases from 0 (no nausea) to 10 (worst possible nausea). Data are shown for each of the six women randomized for the double-blind trial. One woman in the placebo group felt too nauseated to complete the form on day 7, and the value of 10 was assumed for this point (open symbol). All three women in the placebo group subsequently required steroid therapy because of persistence or recurrence of severe vomiting.
Pre-meal blood glucose measurement over the 48 h following steroid initiation was used to screen for impaired glucose tolerance (IGT). Transient increases in plasma glucose (> 6.5 mmol/l) were seen in four women. One underwent formal glucose tolerance testing on steroids and was found to be normal. No serious steroid side-effects were seen.

Discussion

Although steroid therapy for hyperemesis was first reported almost 50 years ago and more recent small case series have reported benefit, the place of steroid therapy has remained contentious. One problem is the widespread belief reflected in most textbooks that the condition is merely a psychological problem. A further difficulty is that the term is applied to a wide spectrum of severity of vomiting. No serious attempt has hitherto been made to categorise severity of hyperemesis, even though untreated, at the extreme end of the spectrum, it is associated with fetal growth restriction, Wernicke’s encephalopathy, central pontine myelinolysis, and maternal death. The social cost of severe hyperemesis, with prolonged hospitalization, is enormous for the small group of families involved. The present study demonstrates a practical approach to defining severe hyperemesis, and reports upon the clinical course of pregnancy complicated by steroid-treated hyperemesis.

Our series illustrates the successful use of steroids for a selected group of women when traditional anti-emetic therapy had failed. The response was characteristically prompt and dramatic. Vomiting stopped and nausea remitted in 6–24 h of starting oral prednisolone and 3–24 h of intravenous hydrocortisone. Intravenous fluids were discontinued in all but three women by 48 h, enabling out-patient management. Once symptoms were controlled, a stepwise reduction in prednisolone dosage was initiated. Typically, the midday dose was reduced by 5 mg at a time followed by the same decrease in the evening then morning dose every 72 h. The typical dose required to maintain remission was 15 mg daily. Expectation of symptom control rather than total suppression of all nausea was explained and this, combined with individualized written protocols for dosage reduction, enabled out-patient steroid withdrawal. It is important to emphasize that although out-patient control of symptoms was quickly obtained, steroids typically need to be continued to the gestation at which the hyperemesis would have resolved (16 to 20 weeks gestation). For the majority, treatment continued for a median of 10 weeks and in a minority was necessary beyond 20 weeks gestation. For an individual woman, there was no doubt when the hyperemesis tendency had ceased, repeated attempts to reduce steroid dose suddenly becoming successful without return of nausea and vomiting.

The recent double-blind, placebo-controlled trial of steroids for treatment of hyperemesis reported significant improvements in appetite, weight gain and well-being after one week. These are highly important observations, even though the trend towards improvement in nausea and vomiting did not achieve statistical significance, probably as a consequence of the study being much smaller than the original power calculation recommended (24 rather than 45 subjects). However, the major difference between the present series and the multicentre study is that there was no requirement for a specified degree of weight loss in the latter. Hence, some subjects in the multicentre study would have had hyperemesis of a lesser degree of severity and could be expected to improve with bed rest and intravenous fluids, making the attainment of a clear difference between active and placebo groups more difficult without larger numbers. An additional point is that time of onset of vomiting was specified as before 12 weeks for the double-blind study, whereas we continue to observe that severe hyperemesis always develops before 6 weeks gestation. The striking decrease in nausea in the three Newcastle subjects randomized to the steroid group, but recruited by our criteria, suggest that severity of hyperemesis is important to consider in planning therapy (Figure 2).

Even though hyperemesis gravidarum of the severity typical of the steroid-treated group is a devastating disorder with profound weight loss and prolonged intravenous therapy, any treatment should present little risk to mother or fetus. Teratogenic evidence for corticosteroids is lacking. Early concerns from animal work of a possible relationship between oral facial clefts and cortisone has not been borne out by recent case-controlled studies. Rodriguez-Pinilla and Martinez-Frias found oral cleft rates did not differ significantly between controls and those taking steroids in the first trimester, and Czeizel and Rockenbauer similarly failed to demonstrate an association with steroid treatment in the second or third month. In a literature review, Fraser and Sajoo concluded that there was little if any teratogenic risk to the fetus. There is no evidence of steroids increasing risks to the fetus when used in the treatment of treating asthma or inflammatory bowel disease. In a recent prospective observational study, severe disease requiring repeated courses of betamethasone was associated with significant reductions in head circumference and birthweight in prematurely delivered infants. Twenty-year follow-up of...
subjects receiving a single course of corticosteroids at 27–32 weeks did not demonstrate any adverse medical or psychological sequelae, but data are lacking for those receiving multiple courses. Dexa- 
methasone and betamethasone are chosen for their efficient transplacental passage when given to improve fetal lung maturity. In contrast, the trans-
placental passage of prednisolone is limited to only 10%, the remainder being metabolized to the inactive form, prednisone.\textsuperscript{20} In our study, although numbers were small, preterm delivery rates and birthweight (including percentage below the 5th centile) were reassuringly similar between groups (Table 2).

The maternal side-effects of long-term steroid therapy are well documented, including osteopa-
penia, prevention of gastric ulcer healing and psychiatric morbidity. However, the commonest 
steroid side-effect in pregnancy is gestational dia-
betes. Although transient increases in plasma glucose were seen, impaired glucose tolerance did not develop in any of the 30 pregnancies reported in the present series. Two patients had pre-existing type 1 diabetes and required the usual 40% increase in insulin dose on starting high-dose steroids. No serious steroid side-effects were seen and in no patient was adrenal suppression observed on withdrawing treatment.

Despite the lack of serious side-effects in our series, clinical prudence dictates that steroid ther-
apy should be reserved for those with the severest symptoms and most likely to be at risk of maternal or fetal complications of severe hyperemesis. Weight loss >5% of prepregnant weight has previously been reported as an index of hyperemesis severity.\textsuperscript{21} The present study confirms this, and suggest that it may be the best objective clinical indicator of severity. This criterion enabled a con-
sistent treatment regimen, and this was important to establish, as observation of successful treatment leads to patient and midwife pressures to broaden the inclusion criteria to some of the much larger group admitted for less severe or shorter duration hyperemesis.

Three pregnancies were terminated, two in those not receiving steroids. It is not possible to determine the extent to which hyperemesis contributed to this decision. Prior to the commencement of steroids, however, at least two further women were considering termination of pregnancy.

In conclusion, prednisolone therapy was effective in a large consecutive series of women with severe hyperemesis gravidarum in abolishing vomiting and restoring nutrition, allowing recovery of muscle mass and muscle strength. This enabled return to normal social functioning. Steroid therapy was not associated with decreased birth weight. By establishing simple criteria to define a group of women with hyperemesis severe enough to justify steroid therapy, some degree of clarity and uniformity in the approach to treatment can be achieved.

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**References**


