

Termination is not the treatment of choice for severe hyperemesis gravidarum: Successful management using prednisolone

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Summary: Severe hyperemesis gravidarum causes profound maternal morbidity. Termination of pregnancy is still offered before the use of medical therapy. This report describes management of a woman who had undergone two previous terminations for hyperemesis, and additionally presents the dosage profile of prednisolone used to successfully manage a consecutive series of 33 women with severe hyperemesis gravidarum. The treatment protocol is described. The group had a median weight loss in pregnancy of 5.5 kg (range 2.0–12.5 kg), had been admitted on a median of 3.0 (range 0–9) occasions and had spent 7.5 (range 0–25) days on i.v. fluids. Continuing vomiting prevented oral steroid therapy in 14 women and i.v. hydrocortisone (50 mg t.i.d.; two women required 100 mg t.i.d.) was used initially for 24–48 h. Nineteen women commenced prednisolone 10 mg t.i.d. and this achieved suppression of vomiting within 48 h in all but two women who required 15 mg t.i.d. Two distinct subtypes of hyperemesis gravidarum were identified. Remitting hyperemesis spontaneously ceases between 14 and 22 weeks gestation and accounts for approximately 80% of cases. In contrast, full-term hyperemesis persists until minutes after delivery. These separate sub-types have not previously been described. Steroid treatment of hyperemesis should be considered in women who fulfil the criteria of severe disease.

Keywords: hyperemesis, prednisolone, steroid therapy, vomiting, termination of pregnancy

INTRODUCTION

Hyperemesis gravidarum occurs with a range of severity, and when vomiting is unremitting and unresponsive to standard antiemetics, therapeutic termination is sometimes considered. Two small series describing successful therapy using high-dose steroids were reported over a decade ago.^{1,2} A multicentre double-blind placebo-controlled one-week trial of prednisolone therapy in hyperemesis demonstrated significant benefits of steroids with respect to wellbeing, food intake and weight gain at one week, but did not have the power to demonstrate effect on readmission.³ Two prospective randomized studies have confirmed that steroid treatment is superior to standard antiemetic therapies.^{4,5} We have previously reported that steroid therapy is uniformly effective in a consecutive series of women with severe hyperemesis as defined by the criterion of weight loss of >5% of pre-pregnant weight.⁶ However, knowledge about steroid dosage regimens to achieve control of hyperemesis is not widespread. In this report, we describe successful management of a woman who had undergone two previous terminations for hyperemesis, and document the route and dosage of steroid therapy used in a consecutive five-year case series of 33 women.

CASE REPORT

A 28-year-old woman was referred for pre-pregnancy advice about hyperemesis. She had suffered severe hyperemesis during her first pregnancy in 2001 with weight loss from 72 kg to approximately 58 kg and admission to hospital for i.v. fluids every one to two weeks throughout the pregnancy. Therapeutic termination at eight weeks gestation was advised because of severe hyperemesis in both 2003 and 2004. She and her husband were extremely concerned about the prospect of frequent hospital admissions and debilitating illness during the planned pregnancy that they very much wanted. She had been offered admission during the first 12 weeks of pregnancy by her local maternity unit. Apart from asthma she was healthy. Her mother had suffered severe vomiting during pregnancy.

She was advised of the high likelihood of occurrence of severe hyperemesis in a fourth pregnancy. The effectiveness of high-dose prednisolone in controlling hyperemesis was described. The potential maternal side-effects of steroids were explained. The lack of clear evidence of side-effects on the baby was discussed. The possibility of requirement for prednisolone throughout pregnancy was explained. She wished to proceed with conception on the basis that prednisolone therapy would be commenced at the onset of severe nausea. Prednisolone tablets were provided together with written instructions to take 10 mg t.i.d. from the time of onset of severe vomiting and to telephone for further advice.

She became pregnant within three months and experienced the onset of nausea and vomiting many times each day at six

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weeks gestation. Prednisolone was commenced as instructed. The vomiting continued and the dose was increased to 45 mg, then 55 mg daily over a three-day period. The vomiting then stopped although nausea continued. By 10 weeks gestation, vomiting remained controlled on prednisolone 10 mg t.i.d. Severe nausea persisted and breakthrough vomiting at 12 weeks necessitated short-term increase of prednisolone to a total of 35 mg per day. By 18 weeks gestation she was well enough to return to work on prednisolone 20 mg daily. Several trials of decreasing the dosage below 15 mg per day were all followed by return of vomiting and she remained on this dose for the rest of the pregnancy.

Weight increased from 78.1 kg pre-pregnancy to 82.0 kg at 36 weeks gestation. She did not require hospital admission during the pregnancy. There were no obstetric complications and a healthy baby was delivered at term. Bone densitometry six months post-partum showed a z score in the normal range.

CASE SERIES

A consecutive series of 33 pregnancies complicated by severe hyperemesis were identified in the preceding five years and case-notes were available for the entire group. Each had been referred by her obstetrician to the obstetric medical service and was judged to meet the criteria for commencement of steroid therapy. The index case is part of the case series. All women had received antiemetics without benefit. The severity of the hyperemesis is reflected by the clinical characteristics. The group had a median weight loss in pregnancy of 5.5 kg (range 2.0–12.5 kg) and had been admitted on a median of 3.0 (range 0–9) occasions. The mean duration of i.v. fluid requirement was 7.5 (range 0–25) days. At the time of referral, 27 of 31 women had marked wasting of leg muscles as shown by inability to stand up from a squatting position without use of arms. There were 28 Caucasian, four Asian and one African woman. Other clinical features are shown in Table 1.

All women received thiamine prior to use of steroid. Prednisolone or hydrocortisone therapy was administered as shown in Figure 1. Continuing vomiting prevented oral steroid therapy in 14 women, and for these women intravenous hydrocortisone at a dose of 50 mg t.i.d. was used initially to control vomiting and this was required for 24–48 hours. Two women required hydrocortisone 100 mg t.i.d. to induce remission of vomiting sufficient to commence oral prednisolone. Nineteen women commenced prednisolone 10 mg t.i.d. and this achieved suppression of vomiting within 48 hours in all but two women who required 15 mg t.i.d. After control of vomiting, the dose was continued unchanged for seven to 10

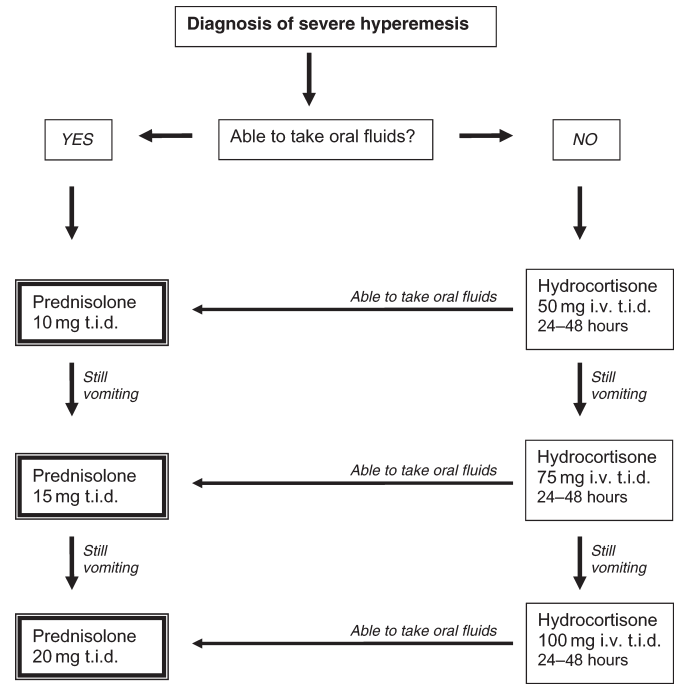


Figure 1 Newcastle guideline for management of hyperemesis. Notes: (1) Initial i.v. fluid should be normal saline with 20 mmol potassium. Change to 10% Dextrose with potassium 24 hours after thiamine first given (note that lactate administration using Hartmanns is not optimal and also contraindicated before thiamine replacement). (2) Vomiting may temporarily settle with bed rest and i.v. fluids, allowing oral prednisolone to be commenced. (3) Use ranitidine orally or i.v. if heartburn is present. (4) Once vomiting is controlled and food intake has resumed, continue the required dose of prednisolone for 10 days, then advise decrease every week thereafter by 5–10 mg depending on the degree of wellbeing. If vomiting recurs, go back to immediately previous dose. (5) Prednisolone 1 mg is approximately equivalent to hydrocortisone 5 mg

days. Discharge from hospital was usually possible within 48 hours of oral steroid therapy. Nausea usually persisted to a variable degree and ptyalism, if present, persisted for several weeks. In one woman ptyalism lasted throughout the pregnancy despite control of vomiting.

After discharge, the dose of prednisolone was decreased at a rate of approximately 5 mg per week. Written instructions were provided so that if severe vomiting recurred, a return to the previous dosage level was undertaken immediately. It was observed that most women reached a stable dose around 15 mg per day and attempts to reduce below this level typically led to recurrence of vomiting until the natural history of hyperemesis had run its course. The nausea remitted with characteristic suddenness between 14 weeks and 22 weeks in most women and, thus, steroid dose could rapidly be decreased without return of symptoms. This did not occur in six women who experienced hyperemesis requiring suppression with prednisolone until term. In the latter women, nausea remitted within minutes of delivery. There was no difference in any of the presenting clinical features between those women whose condition remitted and those with full term hyperemesis. The dose requirement of prednisolone for each of these groups of women in relation to gestation is shown in Figure 2. The median duration of steroid use was eight (4–20) weeks in the spontaneously remitting group and 25 (22–28) weeks in the full-term hyperemesis group.

Table 1 Clinical characteristics of the group

	Median	Minimum	Maximum
Age (years)	28	16	43
Gestation at onset (weeks)	6	4	8
Gestation at referral (weeks)	11	6	21
Pre-pregnancy weight (kg)	72.0	49.5	91.0
Weight at 8-12 weeks (kg)	66.0	45.5	87.0
Weight at 12-16 weeks (kg)	69.0	48.5	93.0
Weight 16-20 weeks (kg)	72.0	50.5	95.0
Gestation at delivery (weeks)	38	34	41
Birth weight (kg)	3.44	1.71	4.15

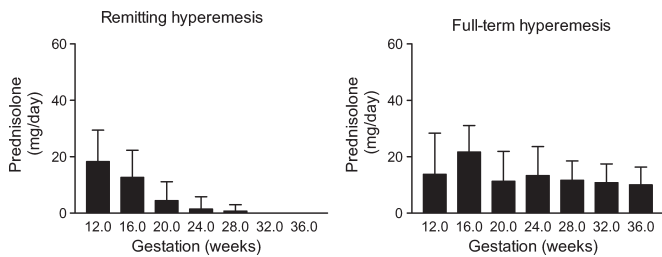


Figure 2 Change in daily prednisolone dosage (mean \pm SD) for the remitting hyperemesis group ($n=27$) and for the full-term hyperemesis group ($n=6$). One woman in the remitting group required steroids for an unrelated condition in late pregnancy

DISCUSSION

Steroid therapy for hyperemesis has been used in Newcastle since 1994 and cases prior to the present series have previously been reported.^{2,6} The main purpose of this report is to describe the expected pattern of prednisolone usage to achieve control of symptoms in addition to drawing attention to the possibility of avoiding termination. The case described involving therapeutic terminations for hyperemesis is far from unique and more widespread recognition of available medical treatment would be of benefit to women.

Central to the discussion of management of hyperemesis is the matter of defining severity. The condition manifests a wide range of intensity, from frequent vomiting but intake of some food on most days to life-threatening prostration. We have previously suggested that severe hyperemesis is best defined by weight loss of $>5\%$ of pre-pregnant body weight.⁶ The present series is based upon this definition, with the exception of women who have previously had severe hyperemesis and present in a subsequent pregnancy with classical symptoms. The definition was chosen as a guide to define a group for whom steroid treatment was clearly justified, but should be interpreted as part of the overall clinical assessment. Symptoms are affected by physical movement and the apparent remission during hospital bed-rest, but recurrence on discharge has reinforced the view quoted in obstetric textbooks that the condition has a psychological basis.⁷⁻¹⁰ Professionals dealing with hyperemesis are sometimes less than sympathetic as reflected by patient websites (see www.hyperemesis.org.uk; www.hyperemesis.org).

The characteristic time-course of severe hyperemesis is not well-recognized. It universally manifests before eight weeks gestation (usually 4–6 weeks), is at its worst early in pregnancy and spontaneously remits in over 80% of women between 14 and 22 weeks (remitting hyperemesis). In the remaining group with full-term hyperemesis, symptoms continue until delivery and although symptoms may fluctuate in intensity, there appear to be no intermediate phenotypes. Remitting hyperemesis does not relapse in the rest of pregnancy. However, full-term hyperemesis requires treatment throughout pregnancy to avoid the return of severe vomiting, dehydration and weight loss. The two groups were similar in age (median 28.9 versus 26.7 years) and gestational age at onset (median 5.8 versus 5.2 weeks) for remitting and full-term hyperemesis, respectively; 22/27 and 6/6 women were Caucasian. Previous detailed description of the natural history of severe hyperemesis is lacking and the present observations allow correction of the textbook definition of hyperemesis as 'severe vomiting of onset before 20 weeks gestation'.¹¹

Steroid therapy has been used for severe asthma and inflammatory bowel disease for many years, and many studies have not identified evidence of any harmful effect on the fetus.¹²⁻¹⁷ The transplacental passage of prednisolone is limited to around 10%.¹⁸ Some animals are susceptible to orofacial clefts after high-dose cortisone.¹⁹ Although the study of Rodriguez-Pinilla and Martinez-Frias is often quoted as demonstrating a significant effect of first trimester steroid use and cleft lip and palate, three of the five identified cases appear unlikely to be relevant.²⁰ One of the three received only two doses of prednisolone after eight weeks gestation when lip fusion would have already occurred, another was associated with multiple abnormalities and a third was receiving replacement doses of hydrocortisone. One of the largest studies (20,820 malformed infants) found oral cleft rates to be similar between controls and those taking steroids in the first trimester.²¹ A recent study of 1141 babies with cleft lip and/or cleft palate identified 33 cases in which the mother reported use of inhaled, topical or systemic steroids. Only one case related to use of steroids solely around the time of lip fusion (5–7 weeks), although if steroids were reported to have been taken from week one to week eight, six cases were identified and this was greater than the risk of orofacial clefts in controls. For women reporting steroid use only in the four weeks prior to pregnancy there was also an association. In this study no association was found with isolated cleft palate. The data about use of steroids solely after five weeks duration do not allow clear conclusion about safety, but any absolute risk of orofacial clefts associated with steroid use must be close to background rates. Using the same methodology, Carmichael *et al.*²² have demonstrated that stressful events are associated with increased risk of cleft lip and palate, and it has to be considered that the stress of the underlying illness for which steroids are used may contribute to any excess risk. This clearly indicates that illness itself is a potential confounder of any association. Taking all of the published information together, commencing steroid therapy after five weeks gestation appears safe. There were no serious maternal side-effects of steroid therapy. In particular, no glucose intolerance was observed despite regular postprandial testing and no effect on blood pressure was observed. In the present series no women had type 1 diabetes, but we have previously reported how this may be managed in the context of steroid treatment for hyperemesis.²³ One woman became acutely depressed on the initial dose of steroids, but this resolved and maintenance dosage of prednisolone was well tolerated. A degree of steroid acne was evident in approximately 20% of women and this resolved rapidly on dose reduction.

Some exceptions to the general pattern of prednisolone dose response outside the period of the present case series require mention. Three of approximately 70 women have required prednisolone 60 mg to achieve remission. Very recently, during the preparation of this report, a single case of hyperemesis failed to respond to high-dose steroid therapy. This is the sole non-responder in our cumulative experience of approximately 100 cases. Subsequently, this woman had a pregnancy with remitting severe hyperemesis, which did respond to steroid therapy. Hence, although the dose of steroid required to induce remission of vomiting does vary, non-response is rare.

The general good care of women with severe hyperemesis extends beyond the use of steroid therapy. Thiamine replacement, possibly with other water-soluble vitamins is required if vomiting has been prolonged in order to avoid Wernicke's encephalopathy.^{24,25} Deficiency can arise after lack of food

intake for several weeks. Thiamine is an essential cofactor for critical enzymes of carbohydrate metabolism and it is important that it is replaced before carbohydrate is given. However, once thiamine has been replaced, provision of calories as i.v. 10% Dextrose (which provides 400 kcal/L) hastens recovery. Significant heartburn is frequently caused by the regurgitated gastric acid and this requires treatment with ranitidine. Finally, mobilization must be gradual as physical movement exacerbates the underlying nausea. Discharge is not wise as soon as i.v. fluids are no longer necessary, as this may be associated with loss of control precipitated by the journey home. Full and sympathetic explanation of the condition and likely prognosis is also part of routine management.

It has been suggested that total parenteral nutrition or enteral tube feeding can be used in the management of severe hyperemesis.^{26,27} While these approaches may minimize weight loss and prevent adverse nutritional consequences for the fetus, there are substantial drawbacks. Total parenteral nutrition is associated with potentially serious hazards including septicaemia.²⁸ A naso-gastric tube is uncomfortable and is also associated with hazards.²⁹ Both modalities leave the woman in hospital or at least attached to tubes and are inferior to steroid therapy in restoring wellbeing.

Steroid therapy achieves remission of vomiting in women with hyperemesis severe enough to cause marked muscle wasting and loss of weight. This severity of hyperemesis is rare, and occurred at a rate of 1.2 per 1000 live-births in our series. The decision to use steroids requires careful discussion with the individual woman. It is a choice which should be considered before therapeutic termination of pregnancy.

DECLARATION

None of the authors have any competing interests. This paper was presented to the MacDonald Obstetric Medicine Society in April 2008.

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