A novel approach to hyperemesis gravidarum: evaluation by a visual analogue scale score and treatment with transdermal clonidine

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Summary

Objective: A preliminary report on the symptomatic effect of clonidine in severe hyperemesis gravidarum (HG).

Design: Observational.

Setting: Hospital based: Ospedale Sant'Anna, Torino, Italy.

Population: Twelve pregnant women, 8–16 weeks, affected by severe, refractory HG.

Methods: Assessment by two clinical score indexes: Pregnancy Unique Quantification of Emesis (PUQE) score and a Visual Analogue Scale (VAS) 5-item questionnaire, filled out daily, to detect subjective improvement or worsening of symptoms.

Main outcome measures: PUQE score and VAS score before and after transdermal clonidine treatment.

Results: We found substantial improvement of symptoms and severity score indexes after four and 14 days. The comparison of pretreatment and post-treatment scores shows a significant statistical difference $P < 0.0001$.

Conclusion: Transdermal clonidine may be considered as a treatment for resistant severe HG.

Keywords: hyperemesis gravidarum, treatment, clonidine

INTRODUCTION

Nausea and vomiting are common complaints in the first trimester of pregnancy; 80% of all pregnant women suffer some degree of nausea and/or vomiting, so-called morning sickness. The most severe grade of this condition is known as hyperemesis gravidarum (HG): it leads to dehydration and ketosis and may require hospital admission and intravenous fluid therapy, affecting the quality of life in pregnancy.^{1–3} Given the high prevalence of the condition, 1% of severely compromised patients creates a burden of admissions.⁴ In 2009, in our Institution, a tertiary level obstetric referral centre, 216 patients were admitted because of hyperemesis. In 21 cases, the admission lasted more than seven days, essentially for persistence of symptoms.

HG is a diagnosis of exclusion: other causes of vomiting should be carefully sought before treating the patient: diabetes, hyperthyroidism, Addison's disease, pyelonephritis, cholecystitis, pancreatitis and acute abdomen should be considered in the differential diagnosis.^{5,6}

The duration of symptoms is a crucial determinant for the development of complications, specifically Wernicke's encephalopathy as a result of thiamine deficiency in the mother.^{7,8} It has also been shown that severe HG may lead to a significant

reduction of birth weight and birth weight percentile, mostly in patients requiring repeated hospital admissions: infants of mothers who have lost weight in early pregnancy are more likely to have a birth weight below the 10th percentile at delivery.⁹ *In utero* exposure to HG may lead to increased risks of psychological and behavioural disorders in the offspring.¹⁰

Assessment of severity has been addressed by ranking the symptoms through proper clinical score indexes. One of the most widely used is the Pregnancy Unique Quantification of Emesis (PUQE) score, which is based on three symptoms: nausea, vomiting and retching over the past 12 hours. Its scale of severity ranges from 3 to 15.

A score ≤ 6 indicates mild HG, between 7 and 12 moderate HG, ≥ 13 severe HG^{11,12} (Table 1). PUQE score index has been validated by studying the association with a number of clinical outcomes such as ability to take folic acid supplementation, rates of emergency room visits and hospitalizations and health-care costs.¹¹ The PUQE score index is a very useful instrument for clinical assessment and it is appropriate to evaluate antiemetic drug efficacy; however, it does not take account of hyper-salivation (sialorrhea, ptyalism), a frequent and disturbing symptom of HG. So, we hypothesized that a different score index could fill this gap in the clinical assessment.

Concerning therapy, a wide range of different antiemetic regimens, given either as single agents or in combination, are the mainstay of treatment. These include ginger, antihistamines, phenothiazines, vitamin B6, metoclopramide, steroids and acupuncture.^{13,14} These therapies are somewhat effective at reducing symptoms, though benefits are sometimes equivocal and

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Table 1 Motherisk PUQE scoring system^{10,11} Circle the answer that best describes your situation for the last 12 hours

1. In the last 12 hours, for how long have you felt nauseated or sick to your stomach				
Not at all (n = 1)	1 hour or less (n = 2)	2-3 hours (n = 3)	4-6 hours (n = 4)	More than 6 hours (n = 5)
2. In the last 12 hours, have you vomited or thrown up				
7 or more times (n = 5)	5-6 (n = 4)	3-4 (n = 3)	1-2 (n = 2)	I did not throw up (n = 1)
3. In the last 12 hours, how many times have you had retching or dry heaves without bringing anything up				
No time (n = 1)	1-2 (n = 2)	3-4 (n = 3)	5-6 (n = 4)	7 or more (n = 5)
Total score: mild, <6; moderate, 7-12; severe, >13				

rehydration is the only therapy which always improves the women's condition.¹⁵⁻¹⁷ Rehydration has been reputed to be so important that rapid outpatient management of hyperemesis has been advocated to minimize the social and financial cost of admissions to hospitals.^{18,19}

Here we report a serendipitous observation showing that transdermal (TD) clonidine treatment significantly improved symptoms in a group of women with severe HG.

PATIENTS AND METHODS

Twelve pregnant women of gestational age between eight and 16 weeks were admitted to our hospital because of severe, persistent HG. There were 11 singleton pregnancies and one twin pregnancy; parity 0000 ($n = 5$), 0100 ($n = 1$), 1001 ($n = 4$), 2002 ($n = 2$); mean age 34 years (range 27–43); mean body mass index 22 (range 18–28). Nine were Caucasian, three Latin American. Five out of 12 women had experienced severe HG symptoms during previous pregnancies. Two were affected by chronic hypertension and needed alternative treatment having stopped oral antihypertensive medication because of inability to swallow pills without vomiting: TD clonidine was chosen as a suitable alternative antihypertensive.

In all women, active treatments for correction of dehydration and electrolyte disturbance and antiemetics (promethazine, metoclopramide, ondansetron and domperidone) were continued; five patients received thiamine supplementation, four patients underwent steroid treatment for HG, obtaining only a transitory effect; four patients agreed to have acupuncture therapy without benefit. In all cases, antacid and antireflux medication (ranitidine, omeprazole) was prescribed. All women received psychological support during hospitalization.

Severe HG was defined, before treatment with clonidine, as a PUQE score index ≥ 13 (Table 1)^{10–12} or a lower score associated with one or more of the following conditions: weight loss $> 5\%$ of pregravid weight, electrolyte disturbances, dehydration, duration of symptoms > 10 days, inadequate food and drink intake.

ETHICS

All women were given written information about the treatment with clonidine, concerning feasibility and safety for use in pregnancy and they signed a written form to give consent to off-label treatment.

TREATMENT

TD clonidine patch at a dose of 5 mg was applied and renewed every 5–6 days.

EVALUATION OF TREATMENT EFFICACY

Blood pressure, lying and standing, was monitored twice daily throughout the hospital admission period and daily after discharge. Ketonuria on morning urine sample was checked daily until full recovery.

Serum electrolytes, liver enzymes, creatinine, full blood count were performed at admission and before discharge from the hospital. Decisions regarding discharge were made on an individual basis after substantial improvement of symptoms.

After the first assessment with the PUQE scale administered by an interviewer before starting treatment, a second questionnaire was administered at day 4, when the drug was supposed to be fully active through the TD system before changing the patch, and then at day 14 in order to examine the persistence of the effect after renewing the patch system.

The new score (am-score) index based on a visual analogue scale is described in Table 2. It featured five items (sense of well-being, nausea, vomiting and retching, hypersalivation, and food and drink intake) with a scale of severity from 0 to 10 for every item. Each patient self-administered the questionnaire, filling out the form before the beginning of the treatment and then every day, on the basis of symptoms in the previous 24 hours.

STATISTICAL ANALYSIS

Means and SD of PUQE and am-score index, before and after therapy, at the fourth and 14th day, were compared with the use of paired *t*-tests. The null hypothesis was rejected at $P < 0.05$.

RESULTS

There was a substantial improvement in the symptoms of HG after treatment with TD clonidine. The reported improvement began after 36–48 hours in all cases and became clinically remarkable in the days following.

At day 4, a significant reduction of both severity indexes (PUQE and am-score) was evident. Mean PUQE was 12.9 (SD

Table 2 am-score index

	0	1	2	3	4	5	6	7	8	9	10
Best	Worst										
Fill out the form every day at the same time For each item, score the severity of symptoms in the last 24 hours from 0 (best) to 10 (worst)											
1.	Sense of wellbeing										0-10
2.	Nausea										0-10
3.	Vomiting and retching										0-10
4.	Hypersalivation										0-10
5.	Food and drink intake										0-10
											Sum 0-50

1.73) before therapy and dropped to 5.4 (SD 1.51) after treatment. Mean am-score was 38.1 (SD 6.82) before therapy and decreased to 13.2 (SD 6.23) at day 4. At day 14, the assessment results did not change compared with day 4: mean PUQE was 4.80 (SD 1.79) and mean am-score was 12.1 (SD 7.37) (Figure 1).

Side-effects were negligible: blood pressure remained in the normal ranges for the first trimester, there was some degree of lassitude, but no symptomatic hypotension occurred; two cases of skin patch intolerance were evident after a few weeks of use; a few women complained of dryness or metallic taste in the mouth. Discharge was possible in the majority of cases (7 out of 12) within one week.

Two women continued the therapy throughout the pregnancy, showing a brisk relapse of HG symptoms when trying to stop the treatment; in four patients a stepwise reduction of dosage had to be negotiated on an individual basis well beyond the 14th week.

All women had live births. There were three preterm deliveries: one elective caesarean section in the twin pregnancy and two caused by premature Preterm Rupture Of Membranes (pPROM) at 34–35th weeks. Mean birth weight was 2942 g (range 1700–4160 g). Neither adverse effects nor major malformations have been reported in the newborns.

DISCUSSION

Clonidine is a centrally acting alpha-2 adrenergic agonist drug mainly used as an antihypertensive. In recent years, it has been shown to have other uses mediated by a reduction in central adrenergic output. It has been effectively used in the treatment of postoperative pain,^{20,21} labour and delivery pain,²² abstinence syndromes,²³ nervous tics, dystonias²⁴ and menopausal vasomotor symptoms,²⁵ and to reduce postoperative nausea.^{26–28} In some experimental animal models, clonidine and other alpha-2 adrenergic agonists have been shown to be effective in inhibiting the emetic response to pharmacological stimulation.²⁹ The mechanism for the antiemetic effect is as yet unknown: a reduction of selective brain adrenergic stimulation or an intrinsic structure-related effect on ventral brainstem imidazoline receptors have been hypothesized.^{27,29}

There is no report of its use and effect in HG.

As far as we know, this is the first study to report on the effect of clonidine in HG. TD clonidine seems to be an effective treatment in patients affected by severe, refractory forms of HG. A critical point is the duration of the TD system which is patented to last seven days – according to our study, the effects did not last more than five days. Thus the patch was changed before loss of effect, to avoid symptoms worsening. According to Buchanan *et al.*,³⁰ who studied the kinetics of oral clonidine in pregnancy, reduced duration of action is due to an increase of non-renal clearance. The same mechanism may explain our findings. Moreover, TD drug delivery may be enhanced by cutaneous vasodilation of pregnancy.

Unexpectedly, we did not record any case of substantial drop of blood pressure, even in normotensive patients – the level of systolic and diastolic pressure remained within the normal reference limits for pregnancy and no case of symptomatic hypotension was recorded.

A word of caution: clonidine is reported to be safe for use in pregnancy even in the first trimester,^{30,31} but this is the first report concerning HG therapy and the drug should be tested comparatively with placebo and other effective treatments.

Clonidine does cross the placenta and similar concentrations are measured in maternal and umbilical cord plasma.²⁸ A recent paper from Seattle³² gives some indications of a non-uniform effect of clonidine on the cardiovascular system in pregnancy and eventually, in some cases, on fetal growth.

So, its use at the moment should be considered only for severe, intractable cases of HG.

We are planning to submit for approval to our local Ethical Committee a formal study comparing clonidine with placebo in severe HG, named CLONEMESI: if approved, it should be completed within one year.

We devised the new self-administered score system because we thought it could better describe the patients' condition. In five patients, a PUQE score of <13 underestimated the severity of HG because it did not consider the long duration of symptoms and consequent physical prostration. However, we were not able to demonstrate any substantial advantage of the am-score over PUQE scoring index, which remains the gold standard of reference.

CONCLUSION

TD clonidine may be another treatment option for severe forms of HG. Further studies comparing the treatment with placebo and with other well-established therapies are needed.

Figure 1 HG severity score indexes after treatment with transdermal clonidine (☆ $P < 0.0001$)

Long-term safety for the mother and fetus has not been established.

DECLARATIONS

Disclosure of interests: No conflict of interest declared.

Funding: No funding required.

Ethical approval: Safety details of use in pregnancy and off label use of clonidine was explained to patients. Every patient gave informed consent to treatment.

Author contributions. AM contributed to conceptualizing the study, recruitment, clinical evaluation and preparation of manuscript; TT helped with patient advice and consent and assisted with the recruitment of patients and the revision of the manuscript.

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