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Ambulatory versus inpatient management of severe nausea and vomiting of pregnancy: a randomised control trial with patient preference arm

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ABSTRACT

Objective To determine whether ambulatory (outpatient (OP)) treatment of severe nausea and vomiting of pregnancy (NVP) is as effective as inpatient (IP) care.

Design Non-blinded randomised control trial (RCT) with patient preference arm.

Setting Two multicentre teaching hospitals in London.

Participants Women less than 20 weeks' pregnant with severe NVP and associated ketonuria (>1+).

Methods Women who agreed to the RCT were randomised via web-based application to either ambulatory or IP treatment. Women who declined randomisation underwent the treatment of their choice in the patient preference trial (PPT) arm. Treatment protocols, data collection and follow-up were the same for all participants.

Main outcome measures Primary outcome was reduction in Pregnancy Unique Quantification of Emesis (PUQE) score 48 hours after starting treatment. Secondary outcome measures were duration of treatment, improvement in symptom scores and ketonuria at 48 hours, reattendances within 7 days of discharge and comparison of symptoms at 7 days postdischarge.

Results 152/174 eligible women agreed to participate with 77/152 (51%) recruited to the RCT and 75/152 (49%) to the PPT. Patients were initially compared in four groups (randomised IP, randomised OP, non-randomised IP and non-randomised OP). Comprehensive cohort analysis of participants in the randomised group (RCT) and non-randomised group (PPT) did not demonstrate any differences in patient demographics or baseline clinical characteristics. Pooled analysis of IP versus OP groups showed no difference in reduction in PUQE score at 48 hours (p=0.86). There was no difference in change in eating score (p=0.69), drinking score (p=0.77), well-being rating (p=0.64) or reduction in ketonuria (p=0.47) at 48 hours, with no difference in duration of index treatment episode (p=0.83) or reattendances within 7 days (p=0.52).

Conclusions Ambulatory management is an effective direct alternative to IP management of severe NVP. The trial also demonstrated that many women requiring treatment for severe NVP have strong preferences regarding treatment setting, which may need to be considered by care providers, especially given the psychological impact of severe NVP.

Strengths and limitations of this study

- ► This trial provides an evidence base for offering ambulatory care to women with severe nausea and vomiting of pregnancy as a direct alternative to traditional inpatient care.
- ► A specific and validated scoring system was used as the primary outcome.
- ► Strong patient preference for treatment setting meant that the projected randomised control trial numbers from a previously started trial would be underpowered to detect any difference in efficacy; a patient preference arm was required to make the trial feasible.

Trial registration number http://www.isrctn.com/ISRCTN24659467 (March 2014).

INTRODUCTION

Estimates of prevalence of nausea and vomiting of pregnancy (NVP) range from 35% to 91% with an average 69% reporting symptoms.[1] An estimated one-third of women with NVP require medical intervention,[2] and severe NVP is one of the most common reasons for hospital admission in the first half of pregnancy.[3] The condition often requires repeated and/or prolonged hospital treatment and has physical, social, psychological and economic implications for women and their families.[4–8] For healthcare providers, treatment of NVP has major service provision implications and is associated with considerable economic burden.[9–11]

The term hyperemesis gravidarum (HG) is used for a severe or protracted form of NVP. HG has a variable prevalence of 0.2%–2% depending on the definition used and population studied.[3 12] There are no universally accepted criteria to diagnose HG, and the crossover from NVP to HG is not distinct.[13]

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Commonly used or proposed diagnostic features are intractable vomiting, dehydration, electrolyte imbalance and weight loss.[4 5 14] Treatment of severe NVP and HG is the same with intravenous fluid therapy, antiemetic medication, electrolyte replacement, vitamin supplementation and thromboprophylaxis forming the mainstay of supportive care.[15–17] For the purposes of this paper, we refer therefore to severe NVP and HG interchangeably.

Hospital admission for severe NVP remains standard practice, though some units in the UK (currently 22) have started an ambulatory service involving daily attendance for treatment.[14] However, despite recent Royal College of Obstetrics and Gynaecology (RCOG) guidance recommending ambulatory care, there is limited evidence for this management.[11 18–20] The objective of our trial was to evaluate the efficacy of ambulatory (outpatient (OP)) treatment of severe NVP as an alternative to conventional inpatient (IP) treatment with particular focus on improvement in symptoms.

It is established that conventionally designed randomised trials, where the setting of care is the focus of the trial, are particularly difficult in terms of trial accrual rates and recruiting a population that reflects the study population of interest.[21] This is in part because treatments compared in a randomised trial should have equal value and acceptability, with patients having similar familiarity with each treatment method and being in a position of equipoise.[22] Patients in trials of settings where one arm involves staying at home however have pretrial perceptions of at least one of the intervention settings.[21] Thus, such trials can be over-represented by hospital averse (home inclined) and under-represented by home averse (hospital inclined) patients. This is evident in particular in maternity where 68%–85% of patients decline participation in place of birth trials due to preference for a particular setting.[21]

Randomised control trial (RCT) methodology is widely accepted as the top of the hierarchical level of evidence as it is designed to be unbiased by avoidance of confounding factors that may influence results.[23 24] However, this trial design does not guarantee quality as many RCTs involve small numbers, with significant numbers of patients with the condition not included in the trial because of reluctance to be randomised, thus diminishing the external validity of the study among patients with the disease.[21 25]

Incorporating a patient preference trial (PPT) arm has been used by other women's health researchers in areas where patient preference is a pertinent component.[26–28] Corbett *et al* conducted an exploratory evaluation on the impact of pretrial preferences and concluded that the use of trial designs that incorporate a preference component should be more widely adopted when treatment settings are being trialed.[21] Arditi *et al*[29] looked at the addition of non-randomised data to a Cochrane review and found that this type of data increased directness of evidence and better represented the general setting. Thus, having initially found limited willingness for participation in a previous randomised study of HG management, we opted for the approach suggested by Brewin and Bradley, and more recently Corbett *et al*[21] of a trial design incorporating a preference component.

METHODS

Study design: combined RCT and PPT

The trial was carried out over a 2-year period from March 2014 until February 2016 at two UK inner city centres: Chelsea and Westminster Hospital, London, and St Mary's Hospital, London. These hospitals offered OP management of hyperemesis on a case-by-case basis but in neither was there a developed OP management 'service'. Therefore, service guidelines, protocols and staff training were undertaken prior to the start of recruitment. Patients were approached at the time of presentation, given written information and adequate time to consider their participation. Written consent was taken.

The RCT protocol was designed in accordance with the Consolidated Standards of Reporting Trials guidance and was registered and published via the ISRCTN registry (www.isrctn.com/ISRCTN24659467).[30] Randomisation was performed centrally via a web-based system provided by an independent third party, on a 1:1 ratio. Once participants were randomised, the allocated treatment arm was communicated to the patient prior to starting treatment.

For the initial phase of the trial (February 2014–June 2014), participants were recruited under an RCT design only. The proportion of failed approaches due to women declining randomisation owing to a preference for a specific place of treatment prompted a review of methodology in June 2014. The design was then modified to include a non-randomised arm of women who were willing to participate in a study of treatment effect but declined randomisation.

From June 2014 to March 2016, the trial operated as a partially randomised PPT design.[19] This design combines an RCT design with a patient preference study, where participants can choose either randomisation or a form of treatment based on individual preference. The PPT format used was based on that described by Brewin and Bradley,[31] initially dividing the patients into four groups: randomised IP (group 1), randomised OP (group 2), non-randomised IP (group 3) and non-randomised OP (group 4).

Patients willing to participate in the study but requesting a particular place of treatment (declining randomisation) were enrolled into the PPT arm.[19] We conducted a comprehensive comparison of participants in all four groups prior to pooled analysis of IP versus ambulatory management (groups 1 and 3 vs groups 2 and 4). Separate RCT and PPT analyses were performed. A flow chart of the combined RCT and PPT methodology is found in online supplementary figure 1.

Registration

The trial was initially prospectively registered to be undertaken at St George's Hospital, London

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(ISRCTN47846769) but was subsequently transferred to Chelsea and Westminster as the primary recruitment centre. Prior to starting recruitment at Chelsea and Westminster, we contacted The ISRCTN (February 2014), who recommended issuing a new registration number rather than an alteration to the previous registration. There was no change to the protocol other than location. Due to this process of issuing a new registration, online publication of the trial registration occurred 2 weeks after the start of recruitment.

Participants

Women presenting to secondary care for treatment and fulfilling the following eligibility criteria were screened and approached for participation in the trial at presentation: (1) up to 20 weeks' gestation, (2) persistent severe nausea and vomiting and (3) ketonuria (≥1+ urinary ketones on dipstick).

The exclusion criteria were as follows: (1) gestation greater than 20 weeks, (2) any medical condition that may manifest as nausea and vomiting such as urinary tract infection, pre-existing medical condition requiring higher level monitoring (eg, diabetes mellitus or cardiac disease), (4) serum potassium ≤3.2 mmol/L and/or serum sodium level ≤130 mmol/L, (5) abnormal thyroid function associated with symptoms of hyperthyroidism (goitre, tremor and heat intolerance) and (6) transaminase levels (alkaline phosphatase (ALT) or aspartate aminotransferase (AST)) of ≥250 IU/L. Transient and asymptomatic mild transaminitis and/or biochemical hyperthyroidism are relatively common findings in women with NVP,[32–36] which resolve spontaneously and were not considered contraindications to inclusion in the trial.

Treatment protocols

Strict treatment protocols were used for IP and ambulatory groups, with the same protocol used for women in the randomised and patient arms (trial protocol and 216 treatment protocols available as supplementary information). First-line antiemetics used were cyclizine, prochlorperazine and metoclopramide (as the study was carried out prior to RCOG 2016 guidance recommending metoclopromide as a second-line treatment[14]), initially alone and then in combination according to patient response. The second-line antiemetic was ondansetron. In women with resistant symptoms, third-line treatment with systemic steroid therapy was considered on an individual basis. All women (both IP and ambulatory) received low molecular weight heparin thromboprophylaxis and were given intravenous then oral vitamin supplementation. Women experiencing symptoms of reflux/gastritis received ranitidine. Symptoms (symptom questionnaire), weight, urinary ketones and serum biochemistry were assessed daily. No specific dietary advice was given as there is currently no evidence of efficacy from dietary modifications.[36] According to the hospital guidance on antenatal care, a dietician referral was made if a woman's body mass index (BMI) was 18 or less at the time of booking. Clinicians were also able to make direct referrals to the dietetics teams if there were clinical concerns regarding poor oral intake or ongoing weight loss; this service was available to women in the IP and OP arms.

IP protocol

Women in the IP care groups were admitted to a gynaecology ward for continuous supportive care. Intravenous 0.9% sodium chloride solution with 20 mmol potassium chloride was given in the following regimen: 1 L over 2 hours, 1 L over 4 hours, 1 L over 6 hours then each subsequent 1 L over 8 hours. Antiemetics were given by mouth, intramuscular injection or intravenous injection.

Ambulatory protocol

Women in the OP groups attended for clinical review and treatment in an ambulatory care unit or gynaecology ward area each day. Two litres of 0.9% sodium chloride solution with 20 mmol of potassium chloride were given intravenous over a total of 4 hours. At each attendance, women were given bolus dose(s) of antiemetic(s) either intravenous or intramuscular during treatment and were asked to continue regular oral medication while at home.

Outcome measures

Participant data

The following data were collected on all participants at recruitment: age, ethnicity, employment status, gestational age, gravidity, parity, previous history of NVP/HG requiring hospital treatment, previous hospital attendances, previous hospital treatment for NVP/HG in current pregnancy and current medication (if any) for NVP. Clinical data were collected from patients at presentation, daily during treatment, at 48 hours following the start of treatment (if discharged) and at 7 days postdischarge from the primary treatment episode. The 7-day postdischarge follow-up was performed at ±2 days depending on researcher and patient availability, by face-to-face review or telephone consultation.

Symptoms scores and clinical assessment

The 12 hours Pregnancy Unique Quantification of Emesis (PUQE) score was used as the primary measure of symptoms. This validated pregnancy specific measure of the severity of NVP provides an objective quantification of symptoms in the preceding 12 hours.[37 38] The scale is an assessment of three symptoms: nausea, vomiting and retching, giving an overall score out of 15 (score minimum 1 and maximum 5 in each symptom category).[37] During the trial, the PUQE score was completed as far as possible at the same time of day for IPs. For OPs, the symptom questionnaire was completed prior to daily treatment. Women attended the ambulatory care unit for a morning or afternoon session, depending on time of initial presentation.

In addition, women were asked to complete three other questions relating to their symptoms in the past 24 hours. In the eating and the drinking scoring systems, women

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grade oral intake as normal (score 1), nearly normal (score 2), less than normal (score 3), virtually nothing (score 4) and nothing (score 5). This system was used as an arbitrary assessment of oral intake as no specific validated oral intake scale was available. The measure was used along with the PUQE score and well-being rating to determine if treatment was effective or required alteration, as well as being used as a secondary outcome measure. The well-being rating was previously validated in conjunction with the PUQE score.[38] Women were asked to grade their well-being from 0, 'feeling absolutely awful, the worst I've ever felt', to 10, 'feeling absolutely wonderful, the best I've ever felt', using the well-being rating as an overall subjective assessment to include emotional well-being.[38]

Duration of treatment

In both the IP and ambulatory groups, treatment continued until a woman was able to tolerate food and drink, had no vomiting for at least 12 hours and had absence of ketonuria. Comparison was made between the groups of the number of days of intravenous fluid treatment required during the primary treatment episode.

Reattendance and repeat treatment

Reattendances within 7 days of discharge from treatment were recorded. In addition, repeat treatment episodes up to 20 weeks' gestation were recorded in women who continued with their pregnancy and booked antenatal care at the recruiting hospital.

Primary and secondary study outcomes

The primary study outcome was reduction in PUQE score 48 hours after starting treatment. Secondary outcome measures were duration of treatment, improvement in symptom scores and ketonuria at 48 hours, reattendances within 7 days of discharge and comparison of symptoms at 7 days postdischarge.

Statistical analysis

To test the hypothesis that ambulatory management is as effective as IP admission for the treatment for severe NVP, the initial sample size calculation, accepting an alpha risk of 0.05 and a beta risk of 0.15 in a two-sided test, allowing for 20% loss to follow-up, indicated that two groups of 60 patients were necessary to detect a statistical significant difference in symptom improvement of 0.6 SD of the PUQE score. The RCT and PPT cohorts were compared for: maternal age, ethnicity, gestational age at presentation, gravidity, parity, BMI, employment status, symptoms at presentation, previous attendance to hospital with NVP, previous hospital treatment for NVP and treatment (if any) for NVP prior to recruitment.

Analysis was by intention to treat. Baseline characteristics and clinical measures were summarised using standard descriptive statistics: frequency (percentage) for categorical variables and mean (SD) for continuous variables or median (IQR) if they were positively skewed. Comparisons between all four groups (randomised IP, randomised ambulatory, non-randomised IP and non-randomised ambulatory) were evaluated using the χ^2 of Fisher's exact tests for categorical variables and the one-way analysis of variance or Kruskal-Wallis rank test for continuous variables. Comparisons within RCT (groups 1 vs 2) and PPT populations (groups 3 vs 4), and comparisons within IP and ambulatory (groups 1 and 3 vs 2 and 4) treatment groups were conducted using the χ^2 test for categorical variables and the t-test or Wilcoxon rank-sum test for continuous variables. All calculated p values were two sided, and analyses were carried out using Stata statistical software V.14.

RESULTS

Participant groups

Over a 2-year period, 174 women were screened for participation with 152 recruited to the trial. Enrolment was carried out as detailed in figure 1. Of the six women who withdrew from the RCT following treatment allocation (before start of treatment), five were subsequently recruited to the PPT. In total, 72 women participated in the RCT (47%) and 80 (53%) in the PPT. Three women withdrew during the trial: one from the RCT and two from the PPT. One woman who withdrew from the PPT (on day 2) agreed for data already collected to be used. Among the women declining randomisation but recruited to the PPT common reasons for declining randomisation were: no childcare at home (requested ambulatory), unable to care for children when unwell (requested IP), unable to travel to and from the hospital daily (requested IP), work commitments (requested ambulatory) and felt too unwell to go home (requested IP).

Patient characteristics

Participant characteristics for all women are shown in table 1. Comparison of randomised and non-randomised groups did not identify any statistically or clinically significant differences in population characteristics. There was no difference in age at presentation, gestation at presentation, BMI at presentation, gravidity, parity, ethnicity, employment status, PUQE score at presentation, eating score at presentation, drinking score at presentation, well-being score at presentation, previous hospital attendance for NVP in current pregnancy, previous hospital treatment in current pregnancy and number taking oral antiemetics at the time of recruitment.

In comparison of treatment groups (IP and OP), there was a small difference in PUQE score at presentation between women in the PPT IP group who had a mean score 1.3 points higher than the those in the PPT ambulatory group. Women in the non-randomised group who opted for IP care had the highest presenting PUQE score overall (mean 13.7).

Treatment efficacy

The primary and secondary outcomes are detailed in table 2 (RCT and PPT cohorts separately), and table 3 shows the combined analysis. In both cohorts and in the

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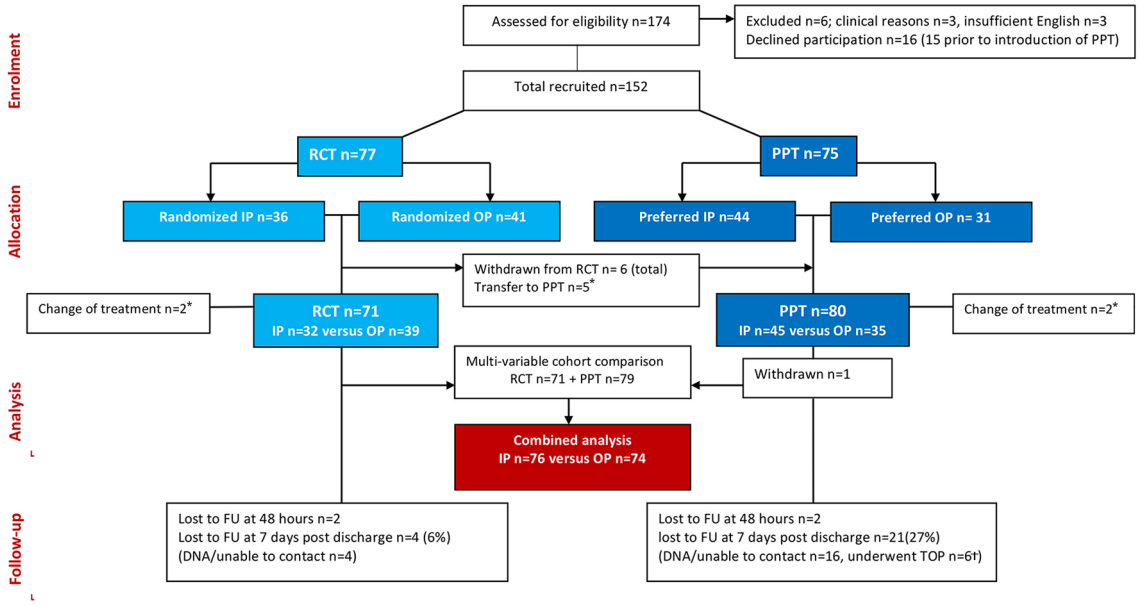


Figure 1 Flow chart of recruitment, treatment allocation, analysis and follow-up. *Analysis by intention to treat except where participants withdrew from RCT prior to the start of treatment (n=5); consented to participate in PPT. †Underwent termination of pregnancy within 7 days of discharge from index treatment episode (via service connected to recruiting centre). RCT, randomised control trial; PPT, patient preference trial; IP, inpatient management; OP, outpatient (ambulatory) management; TOP, termination of pregnancy.

pooled analysis, there was no significant difference in reduction in mean PUQE score at 48 hours following the start of treatment between the IP and ambulatory treatment groups, with a mean reduction in PUQE score of 6.5 (SD 3.5) in the IP group versus 6.6 (SD 3.2) in the ambulatory group (p=0.86). In other symptom scales, both treatment options were effective in improving eating and drinking scores and well-being rating. There was no difference between groups in mean reduction in eating score (p=0.69), mean reduction in drinking score (p=0.77), improvement in well-being rating (p=0.63) and reduction in ketonuria (p=0.47) at 48 hours following the start of treatment.

Duration of treatment

In the IP group, the median duration of primary treatment was 2 days (IQR 2), and in the ambulatory group, it was also 2 days (IQR 1), demonstrating no significant difference between groups (p=0.83).

Protocol adherence

In the ambulatory group, two women were admitted for IP therapy for clinical reasons (one in RCT, one in PPT) as they required intravenous steroid treatment. One participant was admitted on day 3 of ambulatory care and the other on day 5; both required a total of 7 days treatment overall. One further woman in the ambulatory group (RCT) received IP care following ambulatory treatment (she felt too unwell to travel home and requested IP care). In the IP group, one woman in the PPT requested transfer to ambulatory management on day 2 of the trial due to difficulties with childcare and another in the RCT group was transferred to ambulatory care due to hospital capacity issues. One adverse incidence occurred during the trial with a discharged patient (IP non-randomised group) returning to the emergency department with suspected oculogyric crisis following administration of intravenous cyclizine prior to discharge; symptoms were mild, and the patient was discharged following a period of observation.

Missing data were termed 'lost to follow-up', for example, if participants did not attend 7-day follow-up. The data already collected for these women were still used unless women contacted the authors to request otherwise.

Repeat treatment

There was no difference in the number of women reattending within 7 days of discharge from index presentation (20 (30%) vs 18 (25%), p=0.52) or requiring repeat treatment within this timeframe (18 (27%) vs 15 (21%), p=0.40) between IP and ambulatory treatment groups.

For overall reattendances following trial participation (up to 20 weeks' gestation), data were available for 135 women receiving ongoing antenatal care at the recruiting hospital. Seventy-seven (57%) of these women reattended with symptoms of severe NVP following their index treatment episode with 65 of those reattending requiring further hospital treatment. Within this group, 40 patients received ambulatory treatment on at least one occasion. The median number of repeat treatment days (IP nights or ambulatory days) was 2 (range 1–29).

7 days postdischarge

One hundred and twenty-five women completed assessments at 7 days postdischarge from primary treatment

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Table 1 Baseline characteristics by group

Characteristic	Overall (n=150)	Randomised cohort (n=71)			Non-randomised cohort (n=79)			Overall comparison
		Inpatient Group 1 (n=32)	Outpatient Group 2 (n=39)	P value*	Inpatient Group 3 (n=44)	Outpatient Group 4 (n=35)	P value*	P value†
Age (years)‡, mean (SD)	28.8 (5.9)	28.8 (6.7)	28.0 (4.6)	0.566	29.2 (6.5)	29.5 (5.6)	0.827	0.702
BMI (kg/m^2)‡, mean (SD)	23.9 (5.1)	24.1 (6.1)	23.9 (5.1)	0.864	24.0 (5.0)	23.7 (4.3)	0.755	0.988
Ethnicity, n (%)				0.818			0.513	0.596
Caucasian	58 (38.7)	12 (37.5)	14 (35.9)		19 (43.2)	13 (37.1)		
Asian	37 (24.6)	5 (15.5)	9 (23.1)		10 (22.7)	13 (37.1)		
Black	31 (20.7)	7 (21.9)	9 (23.1)		10 (22.7)	5 (14.3)		
Other	24 (16.0)	8 (25.0)	7 (17.9)		5 (11.4)	4 (11.4)		
Employment status, n (%)				0.430			0.649	0.668
Employed	76 (50.7)	15 (46.9)	24 (61.5)		20 (45.5)	17 (48.6)		
Unemployed	36 (24.0)	8 (25.0)	6 (15.4)		14 (31.8)	8 (22.9)		
Primary care of children	38 (25.3)	9 (28.1)	9 (23.1)		10 (22.7)	10 (28.6)		
Gestation (weeks)‡, mean (SD)	9.3 (2.6)	9.6 (2.7)	10.0 (2.7)	0.537	8.8 (2.5)	9.0 (2.3)	0.779	0.127
Gravidity, median (IQR)	2 (2)	2 (2)	2 (1)	0.184	2 (2)	2 (2)	0.853	0.386
Parity, median (IQR)	0 (1)	0 (2)	0 (1)	0.250	0 (1)	1 (1)	0.736	0.638
PUQE score‡, mean (SD)	12.9 (2.3)	12.9 (2.3)	12.5 (2.2)	0.473	13.7 (2.0)	12.4 (2.6)	0.019	0.059
Eating score‡, mean (SD)	4.4 (0.7)	4.4 (0.8)	4.4 (0.6)	0.980	4.5 (0.7)	4.3 (0.7)	0.292	0.744
Drinking score‡, mean (SD)	4.1 (0.8)	4.1 (0.8)	4.2 (0.7)	0.526	4.1 (0.8)	3.9 (0.8)	0.206	0.336
Well-being rating‡, mean (SD)	1.0 (1.2)	0.8 (1.3)	1.2 (1.1)	0.136	0.9 (1.3)	1.2 (1.1)	0.328	0.336
Previous hospital attendance§, n (%)	60 (40.0)	17 (53.1)	12 (30.8)	0.057	14 (31.8)	13 (37.1)	0.620	0.195
Previous hospital treatment¶, n (%)	30 (20.0)	8 (25.0)	7 (17.9)	0.469	8 (18.)	7 (20.0)	0.838	0.875
Antiemetics prior recruitment, n (%)	71 (47.0)	18 (56.2)	15 (38.5)	0.135	21 (47.7)	17 (48.6)	0.941	0.517

Group 1=randomised inpatient, group 2=randomised outpatient (ambulatory), group 3=non-randomised inpatient and group 4=non-randomised outpatient (ambulatory).
*Comparisons between the two groups were evaluated using χ^2 test for categorical variables, two-sample t-test for age, BMI, weeks of gestation and scores/ratings and Wilcoxon rank-sum test for gravidity and parity since distributions were positively skewed.
†Overall group comparisons between groups were evaluated using χ^2 test for categorical variables, one-way analysis of variance for age, BMI, weeks of gestation and scores/ratings and Kruskal-Wallis rank test for gravidity and parity since distributions were positively skewed.
‡Characteristic or measure at presentation.
§Previous emergency attendance with symptoms of nausea and vomiting in current pregnancy.
¶Previous hospital treatment (inpatient or outpatient) for NVP/HG in current pregnancy.
BMI, body mass index; HG, hyperemesis gravidarum; NVP, nausea and vomiting of pregnancy.

episode. This was broken down to 96% in the RCT group and 79% in the PPT group. The follow-up consisted of the symptom questionnaire, review of treatment and weight measurement. Six women were not contacted as they were known to have chosen to undergo termination of pregnancy within this time.

There was no difference between the IP or ambulatory groups in the reduction of PUQE score at 7 days postdischarge compared with PUQE score at admission (p=0.78) or compared with PUQE score at discharge (p=0.22). In both groups, there had been a deterioration in symptoms (increase in PUQE score) at 7 days postdischarge compared with the day of discharge (reduction in PUQE score from start of index presentation −2.3 (SD 3.9) IP vs −1.5 (SD 3.3) ambulatory). Reduction in eating and drinking scores were significantly different between groups at 7 days postdischarge compared with assessment of oral intake at the time of discharge (p=0.03 and p=0.01, respectively); those in the ambulatory group maintained their level of oral intake, whereas those in the IP group had a worsening of symptoms. For well-being rating, there was no difference in well-being at 7 days compared with presentation (p=0.35) or 7 days compared with discharge (p=0.14). Significantly fewer women in the ambulatory treatment group were taking antiemetics: 51/64 (79.7%) versus 57/59 (96.6%), (p=0.004) at the time of follow-up. There was no difference in change in weight between groups comparing weight at presentation to 7-day follow-up (p=0.20) and weight at discharge compared with 7-day follow-up (p=0.30).

DISCUSSION

Principle findings and interpretation

This study has shown that ambulatory (OP) management of women with severe NVP is of equal efficacy to IP treatment. No significant difference was found in the reduction of symptoms, oral intake or maternal well-being at 48 hours following the start of treatment. Duration of index treatment episode and the number of repeat treatment episodes were similar in both groups. Ambulatory treatment was associated with a higher likelihood

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Table 2 Outcome measures, separate RCT and PPT analyses

	Randomised cohort					Non-randomised cohort				
	Inpatient Group 1		Outpatient Group 2			Inpatient Group 3		Outpatient Group 4		
Measure	n		n		P value*	n		n		P value*
Reduction in PUQE score, mean (SD)										
24 hours postpresentation	32	5.2 (3.0)	39	4.7 (2.6)	0.483	44	4.4 (2.9)	35	4.4 (3.5)	0.953
48 hours postpresentation	31	7.0 (3.1)	38	7.3 (2.7)	0.595	44	6.1 (3.7)	33	5.7 (3.6)	0.600
7 days postdischarge (compare discharge)	31	5.7 (3.5)	36	6.2 (4.1)	0.608	30	4.9 (5.0)	28	5.4 (4.1)	0.686
7 days postdischarge (compare discharge)	31	−1.4 (3.7)	36	−1.5 (3.4)	0.981	30	−3.2 (4.1)	28	−1.5 (3.3)	0.101
Reduction in eating score, mean (SD)										
24 hours postpresentation	32	1.3 (1.3)	39	1.1 (1.1)	0.353	44	1.0 (1.1)	35	0.9 (1.1)	0.695
48 hours postpresentation	32	2.1 (1.2)	38	1.9 (1.1)	0.479	44	1.6 (1.4)	33	1.6 (1.1)	0.839
7 days postdischarge (compare presentation)	31	1.8 (1.5)	36	2.1 (1.3)	0.376	30	1.4 (1.3)	28	1.8 (1.3)	0.223
7 days postdischarge (compare discharge)	31	−0.3 (1.3)	36	0.2 (1.2)	0.144	30	−0.7 (1.2)	28	−0.2 (1.2)	0.114
Reduction in drinking score, mean (SD)										
24 hours postpresentation	32	1.4 (1.3)	39	1.3 (1.2)	0.824	44	0.9 (1.2)	35	0.7 (0.3)	*0.451*
48 hours postpresentation	32	2.1 (0.9)	38	2.0 (1.1)	0.969	44	1.4 (1.4)	33	1.3 (1.1)	*0.921*
7 days postdischarge (compare presentation)	31	1.7 (1.3)	36	2.2 (1.2)	0.063	30	1.2 (1.6)	28	1.8 (1.2)	*0.112*
7 days postdischarge (compare discharge)	31	−0.4 (1.2)	36	0.1 (1.2)	0.075	30	−0.6 (1.2)	28	0.1 (1.3)	*0.040*
Reduction in drinking score, mean (SD)										
24 hours postpresentation	32	1.4 (1.3)	39	1.3 (1.2)	0.824	44	0.9 (1.2)	35	0.7 (0.3)	0.451
48 hours postpresentation	32	2.1 (0.9)	38	2.0 (1.1)	0.969	44	1.4 (1.4)	33	1.3 (1.1)	0.921
7 days postdischarge (compare presentation)	31	1.7 (1.3)	36	2.2 (1.2)	0.063	30	1.2 (1.6)	28	1.8 (1.2)	0.112
7 days postdischarge (compare discharge)	31	−0.4 (1.2)	36	0.1 (1.2)	0.075	30	−0.6 (1.2)	28	0.1 (1.3)	*0.040*
Improvement in well-being rating, mean (SD)										
24 hours postpresentation	32	−3.9 (2.3)	39	−3.0 (2.3)	0.120	44	−2.7 (2.2)	35	−2.3 (2.4)	*0.476*
48 hours postpresentation	32	−5.5 (2.9)	38	−4.6 (2.4)	0.174	44	−3.4 (3.2)	33	−4.4 (2.5)	*0.149*
7 days postdischarge (compare presentation)	31	−4.7 (3.0)	36	−4.7 (2.9)	0.983	30	−3.4 (3.2)	28	−4.1 (2.3)	*0.348*
7 days postdischarge (compare discharge)	31	0.9 (2.3)	36	0.2 (2.4)	0.271	31	1.7 (3.0)	28	0.6 (2.4)	*0.138*
Reduction in ketonuria, mean (SD)										
24 hours postpresentation	32	2.4 (1.5)	39	2.2 (1.3)	0.600	44	1.3 (1.2)	35	1.5 (1.3)	*0.616*
48 hours postrecruitment	22	3.1 (1.3)	28	3.1 (1.3)	0.958	40	2.6 (1.6)	28	2.9 (1.4)	*0.487*
Change in weight (kg), mean (SD)										
Presentation to 7 days postdischarge	25	−0.3 (3.0)	29	0.7 (1.5)	0.137	25	0.2 (2.5)	21	−1.1 (4.2)	*0.199*
Discharge to 7 days postdischarge	25	−0.9 (1.2)	28	−0.2 (1.5)	0.101	24	−0.3 (1.9)	20	−0.8 (1.7)	*0.300*
Duration of index presentation (days), median (IQR)	32	2 (1)	39	2 (1)	0.087	43	2 (2)	35	2 (1)	*0.394*
Reattendance within 7 days of discharge†, n (%)	31	8 (25.8)	37	10 (27.0)	0.270	35	12 (34.3)	34	8 (23.5)	*0.325*
Repeat treatment within 7 days of discharge‡, n (%)	31	8 (25.8)	37	9 (24.3)	0.243	35	10 (28.6)	34	6 (17.6)	*0.282*
Still taking antiemetics at 7 days postdischarge, n (%)	30	29 (96.7)	36	31 (86.1)	0.137	29	28 (96.7)	28	20 (71.4)	*0.009*

Group 1=randomised inpatient, group 2=randomised outpatient (ambulatory), group 3=non randomised inpatient and group 4=non randomised outpatient (ambulatory).
*Comparisons between inpatient treatment and outpatient therapy were evaluated using χ^2 test for categorical variables, t-test for scores/ratings, reduction in ketonuria and change in weight and Wilcoxon rank-sum test for duration of index presentation as distribution was positively skewed.
†Reattendance to emergency department within 7 days following discharge.
‡Repeat inpatient/outpatient treatment within 7 days following discharge.
PPT, patient preference trial; PUQE, Pregnancy Unique Quantification of Emesis; RCT, randomised control trial.

of maintaining oral intake and lower requirement for antiemetics 1 week following discharge. The findings were the same in the individual RCT and PPT analyses, although individually these were not adequately powered to detect differences in treatment efficacy. Combined analysis (powered to show a difference of 0.6SD in the

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Table 3 Outcome measures, combined RCT and PPT analysis

	Inpatient Groups 1 and 3		Outpatient Groups 2 and 4		
Measure	**n**		**n**		**P value***
Reduction in PUQE score, mean (SD)					
24 hours postpresentation	76	4.7 (2.9)	74	4.6 (3.0)	*0.769*
48 hours postpresentation	75	6.5 (3.5)	71	6.6 (3.2)	*0.860*
7 days postdischarge (compare presentation)	61	5.3 (4.3)	64	5.8 (4.1)	*0.478*
7 days postdischarge (compare discharge)	61	−2.3 (3.9)	64	−1.5 (3.3)	*0.224*
Reduction in eating score, mean (SD)					
24 hours postpresentation	76	1.1 (1.2)	74	1.0 (1.1)	*0.432*
48 hours postpresentation	76	1.8 (1.3)	71	1.7 (1.1)	*0.687*
7 days postdischarge (compare presentation)	61	1.6 (1.4)	64	2.0 (1.3)	*0.122*
7 days postdischarge (compare discharge)	61	−0.5 (1.3)	64	0.0 (1.2)	*0.025*
Reduction in drinking score, mean (SD)					
24 hours postpresentation	76	1.1 (1.3)	74	1.0 (1.1)	*0.688*
48 hours postpresentation	76	1.7 (1.3)	71	1.7 (1.2)	*0.769*
7 days postdischarge (compare presentation)	61	1.5 (1.4)	64	2.1 (1.2)	*0.013*
7 days postdischarge (compare discharge)	61	−0.5 (1.2)	64	0.1 (1.2)	*0.006*
Improvement in well-being rating, mean (SD)					
24 hours postpresentation	76	−3.2 (2.3)	74	−2.7 (2.3)	*0.196*
48 hours postpresentation	76	−4.3 (3.2)	71	−4.5 (2.4)	*0.627*
7 days postdischarge (compare presentation)	61	−4.1 (3.2)	64	−4.4 (2.6)	*0.475*
7 days postdischarge (compare discharge)	62	1.2 (2.7)	64	0.4 (2.4)	*0.054*
Reduction in ketonuria, mean (SD)					
24 hours postpresentation	76	1.8 (1.4)	74	1.9 (1.3)	*0.695*
48 hours postrecruitment	62	2.8 (1.5)	56	3.0 (1.3)	*0.468*
Change in weight (kg), mean (SD)					
Presentation to 7 days postdischarge	50	0.0 (2.7)	50	−0.1 (3.1)	*0.962*
Discharge to 7 days postdischarge	49	−0.6 (1.6)	48	-0.5 (0.5)	*0.789*
Duration of index presentation (days), median (IQR)	75	2 (2)	74	2 (1)	*0.941*
Reattendance within 7 days of discharge†, n (%)	66	20 (30.3)	71	18 (25.4)	*0.518*
Repeat treatment within 7 days of discharge‡, n (%)	66	18 (27.3)	71	15 (21.1)	*0.401*
Still taking antiemetics at 7 days postdischarge, n (%)	59	57 (96.6)	64	51 (79.7)	*0.004*

*Comparisons between inpatient treatment and outpatient therapy were evaluated using χ^2 test for categorical variables, t-test for scores/ratings, reduction in ketonuria and change in weight and Wilcoxon rank-sum test for duration of index presentation as distribution was positively skewed.
†Reattendance to emergency department within 7 days following discharge.
‡Repeat inpatient/outpatient treatment within 7 days following discharge.
PPT, patient preference trial; PUQE, Pregnancy Unique Quantification of Emesis; RCT, randomised control trial.

PUQE score) however confirmed no difference in efficacy according to treatment setting.

Overall, compliance to follow-up was good (97% at 48 hours and 81% at 7 days postdischarge). Included in the lost to follow-up at 7 days postdischarge group were six women in the PPT who chose to undergo termination of pregnancy and one woman who withdrew from this arm of the study. No information was available on whether this decision was based on the experience of NVP, although previous studies have highlighted the incidence of women opting for termination due to severity of nausea and vomiting.[39] The compliance rate for women eligible for 7-day follow-up (after excluding the six women who undertook TOP within 7 days and the women that decided to withdraw, all in the PPT) was 96% in the RCT and 89% in the PPT. The slightly lower follow-up rates may be a reflection of the motivation to participate in research (specifically to be randomised) that could be for multiple reasons, including uncertainty about continuing with the pregnancy. Women in the PPT IP group had a significantly higher PUQE score at presentation compared with women who opted for ambulatory management (13.7 vs 12.4, p=0.02). Other symptom scale measures were not significantly different within the PPT group. This finding may be attributed to many factors, both clinical and social, but potentially suggests that some women with more severe symptoms prefer to have IP care rather than ambulatory treatment despite it being of equal efficacy.

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There has been limited previous evidence for the use of ambulatory treatment of severe NVP. Murphy *et al* and McParlin *et al* both conducted RCTs to assess the efficacy of ambulatory management of NVP as an initial or intermediate treatment between community and IP care.[11 18] Both of these trials found day case (ambulatory) treatment proved effective in reducing symptoms and reducing the number of women subsequently admitted to hospital. We assessed ambulatory treatment instead of IP admission rather than a limited day case treatment spell to try and avoid admission. Many women in our study population thus had two or more ambulatory treatment spells, which was effective for the management of their symptoms, rather than resorting to admission if they re-presented. Given treatment for severe NVP is essentially supportive, with limited effective treatment until spontaneous resolution[40]; it is expected that many women will have more than one treatment spell. Reattendance is therefore not an indication of treatment failure but rather a reflection of the ongoing nature on the condition.

Recent RCOG guidance on nausea and vomiting in pregnancy suggests that ambulatory daycare treatment should be offered where primary/community treatments have failed to control symptoms and the PUQE score is less than 13.[14] This recommendation was based on a single study in the USA assessing efficacy of home intravenous therapy and systemic administration of antiemetics.[19] In our study, 93 participants (61%) had a PUQE score of 13 or above at the time of presentation yet only two patients in the ambulatory group (n=74) had 'failed' treatment and were admitted on medical advice, both of whom required third-line (steroid) treatment. Accordingly, using a PUQE score cut-off value to base patient selection for ambulatory management is not supported by our study.

Also considered important is the finding of strong patient preference for a specific treatment setting among this patient population. Incorporating women's preferences is recognised as of equal importance to clinical indicators in design of treatment services.[41] Patient choice has intrinsic value to patients,[28] and patient-reported experience measures and patient-reported outcome measures such as used in this study allow researchers to measure the impact of treatment options (in this case place of treatment) on their well-being and their ability to play an active role in society.[41] We aim to evaluate the impact of place of setting on patient satisfaction as part of a questionnaire study commenced in 2015 on a slightly different cohort of the same NVP patient population ('The psychological impact of hyperemesis gravidarum: a two point case control evaluation of psychological symptoms, infant bonding and patient perception of their treatment'). This is a two-point survey study assessing patient experience of care for women with HG (treated as IPs and ambulatory patients), the emotional impact of the condition and the time they took off work prior to planned maternity leave in pregnancy.

Strengths and limitations

While randomisation is the most robust method of preventing selection bias, when patients have strong preferences among treatments, basing treatment allocation on patients' preferences can be appropriate.[42] That this study was not fully randomised is considered both a limitation and a strength. A previous study on women's views on participating in an RCT in pregnancy reported that the most common reason for non-participation was preference for a specific type of treatment.[43] This was evident in our trial with around half of women recruited conferring a strong patient preference for a particular treatment. We consider therefore that the inclusion of the patient preference arm increased recruitment of women in the hyperemesis population and therefore generalisability. For women randomised, as it was not possible to blind patients to their treatment allocation, they may have complied less well if they did not receive their preferred treatment or conversely reported better symptom improvement if they did receive the treatment of their choice.[44] Such bias is difficult to evaluate and should be considered in the interpretation of the findings.[21]

At the time of trial design, the validated PUQE-12 symptom score was used in the protocol, reflecting symptoms over the last 12 hours. The subsequently described PUQE-24 would have captured patient-reported symptom scores encompassing the last 24 hours such that any potential influence from the time of day or sleeping hours would have been mitigated.[45]

This study was not designed to assess the impact of non-pharmaceutical nursing, midwifery and medical support. However, women in the study used the face-to-face and telephone advice available and open access approach to treatment. This may have influenced the outcomes especially in light of known psychological and physical morbidity caused by the condition.[7 18]

Cost analysis

Cost analysis of IP and OP treatment will be undertaken as a separate analysis, comparing costs to the healthcare provider taking into account also the economic burden on women and their families and wider society in terms of working days lost due to time off work for management of NVP/HG. This information will be acquired from our questionnaire study described above ('The psychological impact of hyperemesis gravidarum: a two point case control evaluation of psychological symptoms, infant bonding and patient perception of their treatment') that required women to record the number of days sickness taken during pregnancy prior to planned maternity leave. Murphy *et al* recently conducted a separate analysis of their RCT on day case versus IP management of HG to include economic perspectives from both providers and patients and found that OP (ambulatory) care was cost-effective compared with IP management.[11]

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CONCLUSION

This trial has shown that ambulatory (OP) treatment is as effective as IP care for the management of severe NVP. We would therefore recommend an ambulatory service to manage women with severe NVP as first line. An important secondary finding of this study is that many women requiring treatment for severe NVP have a strong preference regarding the treatment setting, often based on social factors. Given the significant physical and psychological morbidity incurred by severe NVP, it is vital that healthcare providers optimise treatment and support services available to women though this may mean continuing to offer IP therapy for some patients who express a strong preference.

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Contributors The study idea was conceived by CB. CB and NM-J designed the study protocol and obtained ethical approval. JAF set up the trial at the secondary unit (St Mary's Hospital, London, UK). NM-J, JAF and CB recruited patients and collected all data. AT performed statistical analysis. The draft article was written by NM-J. All other authors (CB, TB, JAF and AT) reviewed and revised the final article.

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