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Hyperemesis in Pregnancy Study: a pilot randomised controlled trial of midwife-led outpatient care

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Running title: Hyperemesis in pregnancy study

Condensation

This pilot RCT suggests day-case management of severe nausea and vomiting in pregnancy is an effective alternative to in-patient management for some women.

Abstract

Objective: To assess the feasibility of implementing a complex intervention involving rapid intravenous rehydration and ongoing midwifery support as compared to routine in-patient care for women suffering from severe nausea and vomiting in pregnancy, (NVP)/hyperemesis gravidarum (HG).

Study Design: 53 pregnant women attending the Maternity Assessment Unit (MAU), Newcastle upon Tyne NHS Foundation Trust, Newcastle, UK with moderate-severe NVP, (as determined by a Pregnancy Unique Quantification of Emesis and Vomiting [PUQE] score ≥nine), consented to participate in this pilot randomised controlled trial (RCT). Subsequently 27 were randomised to the intervention group, 26 to the control group.

Women in the intervention group received rapid rehydration (three litres Hartman's solution over six hours) and symptom relief on the MAU followed by ongoing midwifery telephone support. The control group were admitted to the antenatal ward for routine in-patient care.

Quality of life (QoL) determined by SF36.V2 score and PUQE score were measured 7 days following randomisation. Completion rates, readmission rate, length of hospital stay and pregnancy outcomes data were collected.

Results: Groups were comparable at baseline. Questionnaire two return rate was disappointing, only 18 womenin the control group (69%) and 13 women in the intervention groups (44%). Nonetheless there were no differences between groups on Day 7 in terms of QoL, mean PUQE score, satisfaction with care, obstetric and

neonatal outcomes or readmission rates. However, total combined admission time was higher in the control group (94 hours versus 27 hours, p=0.001).

Conclusions: This study suggests that day-case management plus ongoing midwifery support may be an effective alternative for treating women with severe NVP/HG. A larger trial is needed to determine if this intervention affects women's QoL.

Key words: Nausea and vomiting in pregnancy, Hyperemesis gravidarum, outpatient management, quality of life, PUQE score

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Introduction

Nausea and vomiting in pregnancy, (NVP), is a frequently occurring but often debilitating condition, which affects 50-85% of pregnant women (1). In most cases symptoms are mild to moderate and self-limiting. However 0.3-1% of pregnancies are affected by hyperemesis gravidarum, (HG), defined as severe intractable vomiting, ketosis, fluid and electrolyte disturbances, nutritional deficiencies and weight loss, (usually more than 5% of the pre-pregnancy weight) (1). There is no clearly defined point at which NVP becomes HG and women are usually categorised according to the severity of their symptoms.

Severe NVP/HG has implications for the health and wellbeing of the mother and baby. A recent systematic review reported that women with HG were more likely to deliver preterm and to have a baby that was small-for-gestational age, although the associations are inconsistent, however there was no evidence of an association with congenital anomalies or perinatal death (2, 3).

Severe NVP also causes emotional and psychological distress and can have a profound effect on women's quality of life (QoL) (4, 5). Recent observational studies have reported higher incidences of depression, anxiety and stress in women diagnosed with HG which can last throughout pregnancy and into the post-natal period (6, 7). As a result women with HG make greater use of health care resources; HG accounts for 30% of admissions before 20 weeks gestation (8).

Management of NVP/HG tends to focus on the alleviation of symptoms and prevention of serious morbidity. Historically women have been admitted to hospital for intravenous (IV) fluid therapy and antiemetics while less time is spent dealing with their psychological, social and emotional needs or providing information and guidance about the condition. The result is that women can feel unsupported,

dissatisfied with care and experience negative interpersonal interactions with health care providers (9).

The aim of this pilot randomised trial was, therefore, to investigate the feasibility of a midwifery led out-patient intervention, consisting of rapid intravenous hydration and ongoing support versus standard in-patient management. Secondary outcomes included differences in QoL, satisfaction with care, readmission rate and pregnancy outcomes.

Methods

All pregnant women less than 20 weeks gestation attending the Maternity Assessment Unit, (MAU), at Newcastle upon Tyne Hospitals NHS Foundation Trust for the first time with moderate-severe NVP, over a twenty month period commencing in January 2004, were considered for inclusion in the study. A formal sample size calculation was not performed as this was a pilot feasibility study and recruitment continued for as long as was practicable and funds were available.

To assess the severity of their symptoms, women were asked to complete a 'Pregnancy Unique Quantification of Emesis and Vomiting Score' (PUQE score) (10-12). The scale quantifies the amount of nausea, vomiting and retching over the preceding 12 hours, each on a scale of one to five (i.e. maximum score 15). Women scoring nine or higher, (the mid-range point for the moderate category), were deemed suitable for inclusion in the study.

Women were excluded if they had an underlying medical condition such as type 1 diabetes mellitus, renal or cardiac disease, were aged less than16 years, required an interpreter or were planning to have a termination of pregnancy. Ethical approval

was granted by the Newcastle and North Tyneside Local Research Ethics Committee (reference number: 2003/207, approval date 25th February 2004).

After gaining written informed consent women were randomly allocated to receive either standard care (control group) or midwifery-led management on the MAU, (intervention group), using a web based system. The computer generated sequence was produced by a statistician independent of the study team using a fixed block size of six and 1:1 allocation.

Women allocated to the intervention group remained on the MAU. After routine clinical observations (temperature, pulse, blood pressure, weight and urinalysis) an intravenous (IV) cannula was sited and bloods taken for urea and electrolytes, liver function and full blood count. Cyclizine, 50mg IV, was given followed by three litres of compound sodium lactate, (Hartman's), solution over six hours; the first litre over one hour, the second over two hours and the third over three hours. Women were then given 50mg of oral thiamine and discharged home with a prescription for oral cyclizine, 50mg to be taken three times daily for seven days. They were advised to see their General Practitioner, (GP) if they needed additional antiemetics. Arrangements were made for the study research midwife to contact all women by telephone on day three and day seven after randomisation to offer ongoing support, reassurance, advice, identify any problems and encourage compliance with anti-emetics following a standard proforma.

Women allocated to the control group were admitted to the antenatal ward, an IV cannula sited and bloods taken. Intravenous cyclizine was given (50mg IV), IV fluids, (one litre of Hartman's solution eight hourly until rehydrated), and a daily dose of oral thiamine (50mg). Temperature, pulse, blood pressure, urinalysis, fluid balance and

frequency of vomiting were recorded daily. Oral fluids were gradually introduced, followed by a bland light diet. Women were discharged home when they were tolerating diet with a prescription for oral cyclizine (as in the intervention group). All participants were given an information sheet about NVP which included simple self-help measures and advice that could be followed at home.

Immediately after randomisation women completed Questionnaire One, which consisted of basic demographic questions, the SF-36v.2, [www.sf36.org, (13)], (a quality of life scale which looks at eight dimensions of physical, emotional and mental wellbeing). Women were then given Questionnaire Two which asked them to complete a PUQE score at the same time every day for the following six days, a further SF-36v.2 score seven days after randomisation together with a short satisfaction survey (14). Participants were reminded to complete this questionnaire when they received their follow up telephone calls, (intervention group), or whilst they were inpatients (control group). A freepost envelope was provided to facilitate return of this questionnaire.

Women re-attending the MAU because of persistent or increasing NVP within seven days of randomisation were offered a second cycle of the treatment to which they had been allocated. If women re-attended a second time within seven days of randomisation they were admitted and received standard care on the antenatal ward.

Data analysis

Analysis was by intention-to-treat using SPSS for Windows, (Statistical Package for Social Sciences Version 21). Serial PUQE scores were analysed by calculating the area under the curve to generate a single summary statistic for each participant (15);

groups were then compared using an independent sample t-test, cross tabulations and chi-squared analysis were used to detect differences between groups. Analysis of co-variance was used to detect differences between the SF36 mean summary scores and the PUQE scores on days one and seven. Customised growth centile charts were used to calculate birth centiles (16). Small for gestational age (SGA) was defined as a birthweight less than the 10th centile for gestational age, maternal parity and sex.

Results

A total of 184 women presented at the MAU during the 20-month recruitment period, 126 of which were eligible to participate. Of these 50 women were not approached by the clinical staff, (either because the women presented at hospital overnight or the MAU was exceptionally busy), 23 declined participation and 53 were randomised. A Consort diagram is presented in Figure 1.

The baseline characteristics of the women in the trial are shown in Table 1. There were no differences between the groups in any of the variables, serum urea and electrolyte concentrations were within normal ranges for all women. Of the 27 women randomised to the intervention, 20 (74%) received the first telephone call on day three and 16 (59%) received the second call on day seven; 14 (52%) received both telephone calls, with each call lasting between two and 10 minutes.

Only 69% of participants in the control group and 44% of participants in the intervention group completed Questionnaire Two, (p=0.06). There was no statistically significant association between completion of questionnaire two and subsequently re-attendance with a resumption of symptoms.

Clinical outcomes are shown in Table 2. All women in the trial received IV cyclizine. As expected more women in the intervention group received at least three litres of IV fluid during the first 24 hours after randomisation and the length of time in hospital for the initial attendance was less. Twenty five (93%) of the women in the intervention group were discharged within 12 hours of attendance compared to one (4%) in the control group.

Re-attendance rate and mean PUQE scores on re-attendance were comparable in both groups, (12.7 in the control group versus 11.7 in the intervention group, p=0.69). Including re-attendances the total time in hospital (related to NVP) was greater in the control group, p<0.001. Delivery and neonatal outcomes were similar in the two groups.

Results from the second questionnaire are shown in Table 3. There were no differences between the groups in any of the eight health domains of the SF36 score (data not shown), the physical and mental health summary scores or satisfaction with care.

In both groups the PUQE score improved significantly by day two with no change thereafter and there was no differences in mean area under the curve between groups over the seven days, mean difference -5.9 (95% confidence intervals -17.7, 5.9).

Discussion

The inpatient experiences of women who present at hospital with severe NVP are often negative (17-19). The findings from this pilot RCT suggest that midwifery-led

day-case management of severe NVP provides an alternative management strategy to admission. Women randomised to day-case management had similar improvements in objectively assessed NVP with no decrement in QoL scores or satisfaction with care measured seven days after randomisation.
Overall time in hospital was reduced substantially in the intervention group suggesting that day-case management is likely to be cost-effective. The results also suggest that a larger trial is feasible; 70% of eligible women approached agreed to be randomised.

The intervention was developed in response to a perceived local and national need (20, 21) to try and improve the experience of care and reduce hospital stay for women with severe NVP. Anecdotally many women report symptomatic improvement after IV hydration. This was apparently confirmed in a subsequent observational study of day-case management of HG involving rehydration with two litres normal saline over four hours and intramuscular / intravenous anti-emetics (22). All women were discharged within 24 hours and 49% within 12 hours (compared to 93% in the intervention group of the current study) and none of the 27 cases were re-admitted. McCarthy et al. (2014), in an RCT comparing day-care and inpatient management, reported that day-care management reduced inpatient stay with no detrimental impact on satisfaction (23). However NVP was not objectively assessed in either study and women allocated to day-care management in the RCT were required to re-present at hospital on a daily basis to have symptoms assessed.

The second part of the intervention was telephone support after discharge. This was included as many women returning to MAU with an apparent exacerbation of

symptoms within seven days of discharge from hospital complained of limited support in the community. The study research midwife attempted to telephone women on two occasions during the first seven days following discharge with the aim of providing ongoing reassurance, encouragement, advice, identify problems, offer possible solutions and refer to the appropriate health care provider as necessary. This approach, along with a listening, sympathetic attitude, is valued by women and has been shown to encourage health promoting behaviours, continuance and adherence to advice and improve compliance with medication. (24-26). Unfortunately, despite pre-arranging the time, only 52% of women received both calls although some telephone contact was made with 81% of women.

The PUQE score (10) was developed from the Rhodes score, (27). This simple three item scoring system was highly correlated with the Rhodes score, (r=0.904), and has been subsequently validated (11) and used as a tool to measure severity of symptoms in other studies (28-32). Women scoring nine or more, the mid-point of the moderate category, were considered eligible to participate. It is noteworthy that none of the women scoring eight or less appeared clinically dehydrated which is similar to the finding of Lombardi and colleagues(33). They investigated the effectiveness of subcutaneous metoclopramide infusions in which it was found that women with an initial mean (SD) PUQE score of 10 (3.0) were more likely to require hospital admission and IV rehydration compared to women with an initial mean (SD) PUQE of 7.6 (2.8).

The Medical Outcome Survey, Short Form 36, (13), was chosen as a screening tool to assess QoL within the study population. It is a generic measure of health status which has been used in a wide variety of clinical and research settings including

pregnancy (5, 8, 34). Results from studies involving healthy pregnant women have shown reduced SF36 scores in some domains, (physical function, bodily pain and physical limitation, (34)). These deviations can be expected when the psychobiological changes that occur normally during pregnancy are taken into consideration (35). However, results from women suffering from NVP have been reported to be lower than those of patients suffering from depression (8) and comparable with patients with chronic illness (5). The results from the current study are consistent with previous findings highlighting the detrimental impact of NVP not only on physical health but also on mental health, emotional well-being and social function. Whilst the eight domains of the SF36 have been validated for use in pregnancy it is possible that the summary scores need further testing (35). A disease specific QoL tool has been developed for use in women with NVP (36). It is possible that a more disease specific tool such as this may be more appropriate to use in future studies.

The short satisfaction questionnaire included six questions scored using ratings of agreement/disagreement on a seven point scale and was developed and validated to address issues theorised to affect perceptions of satisfaction with antenatal care (14). Satisfaction scores did not differ between groups and were comparable with those reported using the same questionnaire in an RCT comparing a telephone support intervention with routine antenatal care in low risk nulliparous women in which values ranged from 28-35.5 (37).

The study has several important limitations. The small number of participants and the low rate of completion of follow up questionnaires mean that conclusions are limited. Almost 40% of eligible women who presented at the MAU were either missed

or not approached about involvement in the trial by clinical staff. The main reason given for this was that staff were too busy. Further, because funding was not available for interpreters, non-English speaking ethnic minorities (comprising 13% of eligible population) were not approached, further limiting the generalisability of the results. Recruitment to any future trial may, therefore, benefit from greater engagement and involvement of the clinical staff in the design and implementation of the study, conducting the trial at multiple sites and employing interpretaors. The use of different formats for questionnaire completion and text messaging reminders may also help to improve questionnaire return rates. Finally, despite the likely cost benefits of the intervention, a formal economic evaluation was not performed.

Conclusion

The results of this pilot RCT suggest that midwife-led outpatient care for severe NVP is achievable with symptomatic improvement comparable to that seen in a women managed as in-patients and that women are satisfied with day-case care. Further it provides evidence that a larger trial, with economic evaluation, is feasible and worthwhile in order to adequately assess whether day-case management of HG is cost-effective. We would recommend that such a trial focused on improvements in the quality of life of sufferers which gives an overall impression of wellbeing and is valued by women. For example, assuming a type one error rate of five percent we would need a sample size of 170 participants (85 in each arm) to detect an effect size of 0.5 standard deviations with 90% power.

Clinical Trial Registration:

ISRCTN Register, http://www.isrctn.org

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Contribution to authorship

All authors contributed to the design of the study, interpretation of the results, and critical revision of the manuscript. CM recruited participants, collected the data and drafted the manuscript. DCS and SCR conceived the study. INS and CM performed the statistical analysis.

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Table 1: Baseline characteristics of participants

	Control (n=26)	Intervention (n=27)	*p*-value
Age/years	27.3 (4.8)	24.5 (7.25)	0.11*
Nulliparous	13 (50%)	17 (63%)	0.85**
White British	18 (69%)	22 (81%)	0.57**
Gestation at recruitment /weeks	10.3 (2.9)	9.3 (2.8)	0.35*
PUQE[a] score (max 15)	11.5 (2.2)	12.6 (2.2)	0.08*
Packed Cell Volume	0.38 (0.03)	0.38 (0.03)	0.72*
Urea (mg/dl)	3.2 (1.2)	3.4 (1.4)	0.55*
Ketones 3 or 4 +	13 (50%)	8 (30%)	0.13**
Weight/kg.	68.2 (14.1)	70.2 (16.9)	0.66*
SF36.v2 PCS[b]	41.4 (10.1)	40.9 (7.8)	0.84*
SF36.v2 MCS[c]	30.7 (12.5)	27.5 (13.0)	0.37*

Figures are mean (SD) or number (%)
* obtained via 2-tailed t-test
** obtained via chi-squared analysis
[a] Pregnancy Unique Quantification of Emesis and nausea
[b] Short Form36 version2 Physical component score
[c] Short Form 36 version2 Mental component score

Table 2: NVP related admission and pregnancy clinical outcome measures

	Control n=26	Intervention n=27	*p*- value
Number of women receiving 3 litres IV fluid on Day 1	12 (46%)	26 (96%)	0.04**
Duration of initial attendance / admission (hrs)	46.5 (24.1)	13.3 (26.8)	<0.001*
Total number of **all** hospital attendances with NVP/number of women (% of group)			
1	13 (50)	20 (74.1)	
2	6 (23.1)	4 (14.8)	
3	2 (7.7)	3 (11.1)	
4	2 (7.7)	0	
5	2 (7.7)	0	
6	1 (3.8)	0	0.08**
Mean (SD) total admission time/hrs for **all** NVP attendances	94.1 (80.2)	27.2 (50.7)	0.001*
Median (IQR) total admission time/hrs for all NVP attendances	65.0 (48.0 – 122.8)	7.0 (6.5 – 14.0)	<0.001***
Spontaneous abortions	2 (8%)	2 (7%)	1.00**
Termination of pregnancy	0	1 (4%)	1.00**
Vaginal delivery	18 (78%)	19 (79%)	1.00**
Gestation at delivery (weeks)	38.7 (6.2)	37.4 (8.7)	0.59*
Birthweight (g).	2918 (1040)	2847 (1230)	0.83*
SGA[a] infant	3 (14%)	3 (13%)	1.00**
SCBU[b] admissions	1 (5%)	2 (8%)	1.00**

Figures are mean (SD), number (%) or median (IQR)
* obtained via 2-tailed t-test,
** obtained via Fishers exact test
*** obtained via Mann-Whitney U test
[a] Small for gestational age
[b] Special care baby unit

Table 3: Questionnaire outcome measures day 7 following randomisation

	Control n=18	Intervention n=13	95% Confidence Intervals
SF36.v2 PCS[a]	39.1 (8.6)	42.8 (6.9)	-9.71, 2.48
SF36.v2 MCS[b]	35.1 (12.5)	34.0 (9.8)	-7.62, 9.91
PUQE[c]	6.2 (2.3)	6.9 (4.1)	-3.07, 1.67
PUQE day 1-7 Area under curve**	49.8 (13.8)	55.7 (18.4)	-17.74, 5.91
Satisfaction Score***	29.8 (4.7)	29.2 (3.3)	-2.63, 3.89

Figures are mean (SD)
* obtained via 2-tailed t-test]
** Based on 18 responses in the control group and 13 responses in the intervention group
*** Based on 17 responses in the control group and 12 in the intervention group.
[a]Short Form36 version2 Physical component score
[b]Short Form 36 version2 Mental component score
[c]Pregnancy Unique Quantification of Emesis and Nausea score

Figure 1 CONSORT diagram