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Usability of Pregnancy-Unique Quantification of Emesis Questionnaire in Women Hospitalized for Hyperemesis Gravidarum: A Prospective Cohort Study

| Journal:       | BMJ Open                     |
|----------------|------------------------------|
| Manuscript ID  | bmjopen-2021-058364          |
| Article Type:  | Original research            |
| Date Submitted by the Author: | 13-Oct-2021                |

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Keywords: OBSTETRICS, GYNAECOLOGY, PUBLIC HEALTH
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Usability of Pregnancy-Unique Quantification of Emesis Questionnaire in Women Hospitalized for Hyperemesis Gravidarum: A Prospective Cohort Study

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word count: 3642
ABSTRACT

Objectives: Pregnancy-unique quantification of emesis (PUQE) questionnaire is mainly used in outpatient care to assess the severity of nausea and vomiting of pregnancy (NVP). Our aim was to evaluate the usability of PUQE in hospitalized women with hyperemesis gravidarum (HG).

Design: Prospective cohort study.

Setting: University Hospital in Finland.

Participants: Ninety-five women admitted due to HG for at least overnight.

Primary and secondary outcome measures: Categorized and continuous PUQE scores, physical and mental quality of life (QoL) and urine ketones on admission and discharge days.

Results: The most common PUQE categories on admission day were ‘moderate’ and ‘severe’, whereas on discharge day they were ‘mild’ and ‘moderate’. Likewise, continuous PUQE scores decreased (on admission day mean PUQE 11.9±2.5, on discharge day mean 6.3±2.6, P<0.0001). On admission day, women rating worse physical QoL (first admission AOR 1.09; 95% CI 1.03–1.16; all admissions AOR 1.10; 95% CI 1.05–1.15) and women with ketonuria of +++ (first admission AOR 16.00; 95% CI 1.44–177.82; all admissions AOR 14.97; 95% CI 1.67–134.00) fell into higher PUQE score category. On discharge day, women with better physical QoL had lower PUQE score category (first admission AOR 0.94; 95% CI 0.91–0.98; all admissions AOR 0.94; 95% CI 0.92–0.97). The results between physical QoL and continuous PUQE scores were similar. As for mental QoL, better mental QoL was associated with lower PUQE score category only at discharge when including all admissions (AOR 0.96; 95% CI 0.93–0.98), and worse mental QoL was associated with higher continuous PUQE score only at admission (all admissions, ß 0.03, P=0.011).

Conclusions: PUQE scores reflected alleviation of NVP severity in hospitalized HG women. Further, the decrease in PUQE score was associated with improved physical QoL. We therefore suggest PUQE as a complementary instrument for inpatient setting.
Keywords: 1 PUQE, 2 hyperemesis gravidarum, 3 quality of life, 4 urine ketones

Abbreviations
AOR Adjusted odds ratio; BMI Body mass index; HG Hyperemesis gravidarum; NVP Nausea and vomiting of pregnancy; OR odds ratio; PUQE Pregnancy-Unique Quantification of Emesis Questionnaire; QoL Quality of life; VAS Visual analog scale

Article summary

Strengths and limitations of this study

- This study applied PUQE questionnaire in HG patients in inpatient setting comparing PUQE scores at admission and at discharge and distinguishing the first admission period and readmissions.

- Both categorized PUQE scores according to the original validation studies of the questionnaire as well as continuous PUQE scores were analyzed, and the scores were compared with the estimations of physical and mental QoL and urine ketones.

- Admission and discharge criteria were not strictly defined, and the treatment protocol was not standardized.

- Selection bias was possible since the women were enrolled from a single unit and information of women who refused to participate was lacking.
INTRODUCTION

Hyperemesis gravidarum (HG) represents the extremity of symptoms of nausea and vomiting of pregnancy (NVP).[1,2] Most pregnant women have some degree of NVP.[2] Hence, NVP is often considered as a normal part of pregnancy,[3] whereas HG is rare, with an estimated prevalence of only 0.3–3.6 %.[1] However, the distinction between severe NVP and HG is often overlapping. In addition, even mild NVP may decrease women’s quality of life (QoL).[3,4] Consequently, it is evident that HG causes not only extreme physical impairment but also substantial mental distress.[5–7]

Usually in clinical practice, HG is diagnosed when severe NVP symptoms lead to weight loss, dehydration and electrolyte imbalances.[2] No useable biomarker has been established,[8] although urine ketones are often used despite controversial evidence.[8–11] All in all, need of hospitalization is assessed individually and due to the lack of standardized diagnostic criteria of HG or generally applied questionnaire to evaluate the severity of HG symptoms, admittance to hospital and length of admission easily varies according to the physician’s assessment.

Pregnancy-Unique Quantification of Emesis (PUQE) questionnaire[12] is a simple tool to measure the severity of NVP. PUQE score, ranging from 3 to 15 points, is the sum of the replies to three questions concerning duration of nausea in hours and the quantity of both vomiting and retching episodes. According to the total PUQE points, NVP is categorized into ‘no’, ‘mild’, ‘moderate’ and ‘severe’. PUQE has been validated to cover symptoms from previous 12 hours[13] and 24 hours[14] (PUQE-24) as well as from the entire first trimester.[15] PUQE is mostly used in outpatient setting to screen patients with NVP and accordingly the need of hospitalization.[2,9]
hospital settings of HG patients, PUQE has been used in few studies mainly comparing the
effectiveness of different therapeutic interventions.[16–18]

To best of our knowledge, only two previous studies, a Norwegian PUQE validation study[19] and
another study from Nepal,[20] applied the PUQE questionnaire during hospitalization due to HG,
both showing an improvement in PUQE score after treatment. In the Norwegian study, also a
connection between higher PUQE score and both lower general wellbeing and insufficient
nutritional intake was shown. While in the Norwegian study both categorized PUQE scores as
validated in the original studies[12,13] and continuous PUQE scores were analyzed, the Nepalese
study considered PUQE scores only as continuous scores. Given the sparsity of previous research,
further studies regarding usability of the PUQE questionnaire in clinical settings, including
evaluation of the tool in both the first admission period and in readmissions, were needed. Thus, our
aim was to evaluate these topics in the context of usability of the PUQE questionnaire in women
hospitalized for HG.

MATERIAL AND METHODS

Women hospitalized for HG in antenatal ward of Turku University Hospital, Turku, Finland during
2011–2019 were enrolled after oral and written information about the study. Volunteers were
eligible to participate and gave written informed consent. Capability to read and understand Finnish
language was required, and thus most of the participants were Finnish. The study was approved by
the Joint Ethics Committees of University of Turku and Turku University Central Hospital, Turku,
Finland (60/180/2011).
HG was diagnosed according to the International Statistical Classification of Diseases and Related Health Problems (ICD–10; O21.0, O21.1, O21.9). Decision of admission for HG was based on current practice and clinician’s assessment concerning general sickness of the women, as well as clinical signs or laboratory findings of dehydration or presence of urine ketones. HG treatment consisted of intravenous fluids and antiemetic medication (metoclopramide and/or ondansetron). Decision to discharge was made according to cessation or alleviation of vomitus and nausea, signs of improved hydration and self-judgement of the woman of her own well-being.

Altogether 106 women participated. Only data of women with singleton pregnancies and admissions lasting at least overnight were included, resulting in a total of 95 women for analysis (figure 1). The women filled in the study questionnaire daily during hospitalization. However, only questionnaires from admission and discharge days were included in the analyses.

NVP was assessed with PUQE score concerning the previous 12 hours.[12] In accordance with the original version,[12] four NVP categories of ‘no’ (3 points), ‘mild’ (4–6 points), ‘moderate’ (7–12 points) and ‘severe’ (13–15 points) were formed. In addition, PUQE score was used as a continuous variable. PUQE questionnaire has previously been translated into Finnish by a professional translator with the permission of the PUQE owners and back translated by another professional translator.[21] PUQE scores were recorded only for study purposes, and thus the scores did not guide the decisions of treatment, admittance, discharge or readmission of the women.

The PUQE score was considered both as a categorized and a continuous value and compared to both physical and mental QoL scores and to urine ketones, measures which in clinical practice are typically used as markers of hospital admittance and discharge of the HG patients. Physical and mental QoL were estimated with two visual analog scales (VAS). QoL VAS scores ranged from 0
to 100 with higher points indicating better QoL, but in statistical analysis the scores were reversed, and thus higher points indicated worse QoL. Urine ketones were measured by urinalysis reagent strips (Mission®, Acon Laboratories, Inc, San Diego, USA), with detection levels of – (no detectable ketones), + (15 mg/dL=1.5 mmol/L), ++ (40 mg/dL=4.0 mmol/L) and +++ (80 mg/dL=8.0 mmol/L).

Basic demographic data of the women were obtained from hospital medical records including gestational weeks (gwk) at admission, parity (nulliparous/multiparous), body mass index (BMI, kg/m², calculated from pre-pregnancy weight and height), smoking (no/yes), marital status (cohabited/single), the total length of all admissions (days), the number of readmissions and urine ketones results. Age was calculated by comparing the date of reply to the date of birth.

**Statistical analyses**

For power calculation, the difference of at least three PUQE points between admission and discharge days was considered as clinically relevant. Minimum sample size was 58 with difference from 12 to 9 points and standard deviation (SD) of 8 and aiming for alpha=5% and power of 80% (nQuery Advisor 4.0: paired t-test). Recruitment was continued up to 106 participants because some number of incomplete questionnaires and missing data were anticipated.

Continuous variables were characterized using means, standard deviations (SD) and ranges and categorical variables using frequencies and percent. The severity of NVP was categorized according to PUQE total score (‘no’/‘mild’/‘moderate’/‘severe’) on both admission and discharge days. Because of low number of values in category ‘mild NVP’ (n=2) on admission day and ‘severe NVP’ (n=1) on discharge day, these values were excluded from the analyses on admission and
discharge days. In addition, when analyzing the change of PUQE categories (delta, Δ) between admission and discharge, due to the low number of values in the change of three PUQE categories (n=3), the change of three PUQE categories and the change of two PUQE categories were combined.

Concerning physical or mental QoL measured by VAS, the probability to belong to a higher (admission day) PUQE category or lower (discharge day) PUQE category was calculated with multinominal logistic regression on both admission and discharge days. Two separate analyses were performed: 1) analysis of the first admission period, and 2) analysis of all admission periods. GEE estimation was used when all admissions were included in analyses. The same analyses were performed for urine ketones categories (−/+/+/++/++++). In analysis of urine ketones, p-values were adjusted using Tukey-Kramer method because of multiple comparisons. Further, similar analyses on admission and discharge days using PUQE score as a continuous score were also performed. Comparisons both with physical and mental QoL VAS, urine ketones and continuous PUQE total points were calculated with linear mixed model for the first admission and linear mixed model with random intercept for patient when all admissions were included in analyses. All these results were adjusted for age, BMI and parity. In addition, continuous PUQE scores and VAS scores on admission and discharge days were compared using ANOVA. The results are presented with odds ratios (OR) and beta (β) with 95% confidence intervals (CI). Statistical significance was set at p-values <0.05. Analyses were carried out using a 9.4 version of SAS Institute Inc. (Cary, NC, USA) for Windows.

**Patient and public involvement statement**

Patients and the public were not involved in the design or reporting of this study.
RESULTS

Basic characteristics

Basic characteristics of the women and the questionnaire data are presented in table 1 and table 2.

On admission day, according to categorized PUQE scores, most of the women suffered from ‘moderate’ or ‘severe NVP’. On the contrary, on discharge day, most of the women had ‘mild’ or ‘moderate NVP’ (figure 2). Likewise, the mean continuous PUQE scores were higher on admission day compared to discharge day (table 2). Further, on admission day, physical and mental QoL scores were higher indicating worse QoL than on discharge day (table 2). On admission day, over half of the women had urine ketones, whereas most of the women had no urine ketones on discharge day (figure 3).

Table 1. Basic characteristics of the women. Total n=95.

|                                | n   | Mean ± SD or n (%) | Range     |
|--------------------------------|-----|-------------------|-----------|
| Age (years)                    | 95  | 29.5 ± 5.0        | 18.9–42.7 |
| Gwk                            | 95  | 9.8 ± 2.5         | 6.3–20.3  |
| Parity                         |     |                   |           |
| Nulliparous                    | 35  | (37.6)            |           |
| Multiparous                    | 58  | (62.4)            |           |
| BMI (kg/m²)                    | 91  | 25.2 ± 5.4        | 18.0–40.6 |
| Smoking                        |     |                   |           |
| Non-smokers                    | 87  | (96.7)            |           |
| Smokers                        | 3   | (3.3)             |           |
| Marital status                 |     |                   |           |
| Cohabited                      | 85  | (92.4)            |           |
| Single                         | 7   | (7.6)             |           |
| Number of admissions           | 95  |                   |           |
| 1                              | 60  | (63.2)            |           |
| ≥ 2                            | 35  | (36.8)            |           |
| Length of admissions (days)    | 160*| 3.1 ± 2.2         | 1–12      |

BMI = Body mass index
GWK = Gestational week
*Total number of all admission periods with available data
Table 2. PUQE total points and VAS scores.

|                  | First admission | All admissions |
|------------------|-----------------|----------------|
|                  | n*  | mean ± SD | range     | n*  | mean ± SD | range     | P     | P     |
| PUQE total points|     |            |            |     |            |            |       |       |
| Admission day    | 68  | 11.6 ± 2.3 | 5–15      | 122 | 11.9 ± 2.5 | 4–15      | <0.0001|       |
| Discharge day    | 65  | 6.5 ± 2.4  | 3–12      | 122 | 6.3 ± 2.6  | 3–13      |       | <0.0001|
| Physical QoL VAS |     |            |            |     |            |            | <0.0001| <0.0001|
| Admission day    | 68  | 84.2±11.7  | 50–100    | 122 | 83.8 ± 12.6 | 30–100    |       |       |
| Discharge day    | 65  | 45.4±19.3  | 4–90      | 122 | 46.3 ± 20.3 | 0–90      |       |       |
| Mental QoL VAS   |     |            |            |     |            |            | <0.0001| <0.0001|
| Admission day    | 68  | 65.4±17.9  | 15–100    | 122 | 69.7 ± 19.2 | 12–100    |       |       |
| Discharge day    | 65  | 38.2±20.3  | 0–90      | 122 | 42.8 ± 23.5 | 0–90      |       |       |

ANOVA
PUQE = Pregnancy-Unique Quantification of Emesis Questionnaire
QoL = Quality of life
VAS = Visual analog scale 0–100, higher number indicates worse QoL
*Total number of the women = 95. Total number of available data for the first admission period = 93 and for all admission periods = 162.
PUQE score category and the first admission period

When evaluating only the first admission period, on admission day women with worse physical QoL fell into a higher PUQE score category, both in unadjusted and in adjusted (age, BMI, parity) analysis. Instead, worse mental QoL was not associated with PUQE score category. In addition, women with severe ketonuria (+++) vs no urine ketones) fell into higher PUQE score category both in unadjusted and in adjusted analysis. On discharge day of the first admission period, the women with better physical QoL fell into lower PUQE score category in both unadjusted and in adjusted analysis. Instead, mental QoL and the presence of urine ketones were not associated with PUQE score categories. (Table 3 and Table 4.)

PUQE score category and all admission periods

When including all admission periods, the results between physical QoL and PUQE score categories on admission day and on discharge day were similar to those including only the first admission period: worse physical QoL was associated with higher PUQE category on admission day and better physical QoL with lower PUQE category on discharge day. The same held true with severe ketonuria on admission day which was associated with higher PUQE category. As for mental QoL, on admission day of all admission periods, women with worse mental QoL fell into higher PUQE score category in unadjusted analysis but in adjusted analysis the results showed only a tendency. On discharge day of all admission periods, women with better mental QoL fell into lower PUQE score category in adjusted analysis. On discharge day, there were no associations between urine ketones categories and PUQE score categories. (Table 3 and Table 4.)

Change in PUQE score categories, QoL and in urine ketones categories

During the first admission period, compared to PUQE score category on the admission day, the PUQE score category decreased on discharge day two categories in 11 women, one category in 22
Table 3. Physical and mental QoL in VAS on admission and discharge days and the probability to fall into a higher or lower PUQE score category*.

|                | PUQE admission day |                  | PUQE discharge day |                  | Δ                  |
|----------------|--------------------|------------------|--------------------|------------------|--------------------|
|                | OR                 | 95%CI            | P                  | AOR              | 95%CI             | P                  | AOR              | 95%CI             | P                  | OR                 | 95%CI             | P                  | AOR              | 95%CI             | P                  |
| Physical QoL VAS | 1.10               | 1.04–1.16        | 0.001              | 1.09              | 1.03–1.16        | 0.003              | 0.95              | 0.92–0.98        | 0.001              | 0.94              | 0.91–0.98        | 0.003              | 0.95              | 0.93–0.98        | 0.0008             | 0.93              | 0.90–0.97        | 0.0002             |
| Mental QoL VAS  | 1.00               | 0.97–1.03        | 0.983              | 1.01              | 0.97–1.04        | 0.765              | 0.98              | 0.95–1.00        | 0.071              | 0.97              | 0.94–1.00        | 0.062              | 0.97              | 0.95–1.00        | 0.045              | 0.97              | 0.94–0.99        | 0.011              |

All admissions

|                | PUQE admission day |                  | PUQE discharge day |                  | Δ                  |
|----------------|--------------------|------------------|--------------------|------------------|--------------------|
|                | OR                 | 95%CI            | P                  | AOR              | 95%CI             | P                  | AOR              | 95%CI             | P                  | OR                 | 95%CI             | P                  | AOR              | 95%CI             | P                  |
| Physical QoL VAS | 1.10               | 1.05–1.15        | <0.0001            | 1.10              | 1.05–1.15        | <0.0001            | 0.95              | 0.93–0.97        | <0.0001            | 0.94              | 0.92–0.97        | <0.0001            | 0.95              | 0.93–0.98        | 0.0008             | 0.93              | 0.93–0.98        | 0.0002             |
| Mental QoL VAS  | 1.03               | 1.00–1.06        | 0.037              | 1.03              | 1.00–1.06        | 0.063              | 0.97              | 0.95–1.00        | 0.062              | 0.96              | 0.93–0.98        | 0.0007             | 0.97              | 0.95–1.00        | 0.018              | 0.96              | 0.94–0.98        | <0.0001             |

Multinominal logistic regression
AOR = Adjusted odds ratio: adjusted for age, body mass index and parity
PUQE = Pregnancy-Unique Quantification of Emesis Questionnaire
QoL = Quality of life
VAS = Visual analog scale
*Higher PUQE category on admission day and lower PUQE category on discharge day
Table 4. Urine ketones categories on admission and discharge days and the probability to fall into higher or lower PUQE score category*.

| First admission | PUQE admission day | PUQE discharge day | Δ | Change category | OR | 95%CI | P | AOR | 95%CI | P | OR | 95%CI | P | AOR | 95%CI | P |
|-----------------|--------------------|--------------------|---|----------------|----|--------|---|-----|--------|---|----|--------|---|-----|--------|---|
| Urine ketones   | OR 95%CI P | AOR 95%CI P | OR 95%CI P | AOR 95%CI P | OR 95%CI P | AOR 95%CI P | OR 95%CI P | AOR 95%CI P | OR 95%CI P | AOR 95%CI P | OR 95%CI P | AOR 95%CI P | OR 95%CI P | AOR 95%CI P |
| + vs -          | 0.68 0.23 1.00 1.99 | 0.676 0.207 0.740 8.21 | 0.016 | -3 vs -2 | 1.16 0.13 1.00 1.99 | 0.098 0.14 0.740 2.55 | 0.016 | -3 vs -1 | 14.83 1.00 220.01 12.07 | 0.050 12.07 0.982 21.60 | 0.013 | -3 vs 0 | 1.63 0.21 12.80 | 0.928 2.55 0.709 25.58 | 0.019 | -2 vs -1 | 12.78 0.76 215.95 | 0.095 8.38 0.722 184.74 | 0.020 | -2 vs 0 | 1.41 0.15 13.28 | 0.980 1.77 0.933 20.78 | 0.020 | -1 vs 0 | 0.11 0.01 1.44 0.14 17.80 | 0.21 0.21 3.71 | 0.504 |
| ++ vs -         | 0.38 0.02 1.00 1.99 | 0.740 8.21 | 0.016 | -3 vs 0 | 1.63 0.21 12.80 | 0.928 2.55 0.709 25.58 | 0.019 | -2 vs -1 | 12.78 0.76 215.95 | 0.095 8.38 0.722 184.74 | 0.020 | -2 vs 0 | 1.41 0.15 13.28 | 0.980 1.77 0.933 20.78 | 0.020 | -1 vs 0 | 0.11 0.01 1.44 0.14 17.80 | 0.21 0.21 3.71 | 0.504 |
| +++ vs -        | 7.00 1.00 16.00 14.4 | 0.049 0.016 | 177.82 | -3 vs 0 | 1.63 0.21 12.80 | 0.928 2.55 0.709 25.58 | 0.019 | -2 vs -1 | 12.78 0.76 215.95 | 0.095 8.38 0.722 184.74 | 0.020 | -2 vs 0 | 1.41 0.15 13.28 | 0.980 1.77 0.933 20.78 | 0.020 | -1 vs 0 | 0.11 0.01 1.44 0.14 17.80 | 0.21 0.21 3.71 | 0.504 |

Urine ketones categories: -/+/++/++++
Change in urine ketones categories: presented as the number and the direction of changed categories between admission and discharge days

1 Higher PUQE category on admission day and lower PUQE category on discharge day
women and remained unchanged in 14 women. Concerning all admission periods, compared to PUQE score category on admission day, the PUQE score category decreased on discharge day three PUQE categories in three women, two PUQE categories in 26 women, one PUQE category in 38 women and remained unchanged in 24 women. In three women, the PUQE category got worse.

During both the first and all admission periods, the decrease (indicating better QoL) in both physical and mental QoL VAS score was associated with a decrease in the PUQE category in both unadjusted and adjusted analysis (Table 3). During the first admission period, there was a decrease between admission and discharge days in urine ketones categories (from -3 to -1), which was associated with a decrease in the PUQE category in unadjusted analysis, but this finding was lost in adjusted analysis (Table 4). However, when including all admission periods, a similar decrease (from -3 to -1) was associated with a decrease in PUQE category both in unadjusted and adjusted analysis. In unadjusted analysis, the decrease from -2 to -1 was statistically significant as well, but this finding was lost in adjusted analysis. (Table 4).

**Continuous PUQE score, QoL scores and urine ketones**

When PUQE points were considered as continuous value, on admission day, worse physical QoL was associated with high PUQE points both during the first admission period and when all admission periods were included. Worse mental QoL was associated with high PUQE points only when including all admissions. The results were similar in adjusted analysis. On admission day, there was a tendency between high urine ketones categories and high PUQE points ($P=0.067$ first admission, $P=0.046$ all admissions). Further, in adjusted analysis, severe ketonuria (+++ vs no urine ketones) was associated with high PUQE points at first admission ($P=0.026$ first admission, $P=0.056$ all admissions). On discharge day, both better physical QoL and better mental QoL were associated with low PUQE points during the first admission period and when including all
admissions. Instead, urine ketones showed no association ($P=0.224$ first admission, $P=0.545$ all admissions). In adjusted analysis, the results remained the same. (Figure 4 and Figure 5).

The improvement (the mean difference in VAS values between admission and discharge days) in both physical QoL and mental QoL was associated with the change in continuous PUQE scores during the first admission period and when including all admissions. The results remained the same in adjusted analysis. Instead, no association emerged between the change in continuous PUQE score and urine ketones ($P=0.294$ first admission, $P=0.355$ all admissions). (Figure 4 and Figure 5).

**DISCUSSION**

We were the first to use PUQE questionnaire in hospitalized HG women in Finland. PUQE showed to be a feasible clinical tool for assessing recovery; a marked improvement in PUQE score was found when comparing scores between admission and discharge using PUQE both as categorized and as continuous scores. In addition, high PUQE scores were associated with worse physical QoL at admission and low PUQE scores with better physical QoL at discharge, both in the first admission and in readmissions, indicating that PUQE scores were well concurrent with the measurement of physical QoL. As for the associations between mental QoL and PUQE scores, the association was found at both admission and discharge when PUQE scores were taken as continuous scores in readmissions. Concerning mental QoL and categorized PUQE scores, the association was found only in the adjusted results at discharge. These findings could be explained by that even though PUQE questionnaire is measuring physical events of NVP, it may also reflect mental QoL, especially in prolonged NVP: the overall misery of illness at admission and on readmissions, and, on the other hand, the relief of improved condition at discharge. As for
ketonuria, instead, only severe ketonuria at admission was associated with higher PUQE score category, but otherwise ketonuria showed no connection with PUQE.

Our study has limitations. First, admission and discharge criteria were not strictly and uniformly defined, being based on common current practice concerning the well-being of the women and clinical signs or laboratory findings of dehydration. In Finland, the primary health care system is based on national health coverage and practically all pregnant women visit free-of-cost public maternity health care clinics. From there, women with HG are referred to hospitals to specialized obstetrics clinics which are part of public services provided to all citizens by several hospital districts. These clinics in hospitals are led by specialists in obstetrics and women can be admitted to hospital or the treatment can continue in outpatient care. Therefore, hospital admittance and discharge decisions were not dependent for instance on women having a health care insurance or adequate wealth. Secondly, management between the patients was not totally similar, but standardized clinical practice and the treatment protocols were followed. In addition, all women were enrolled in the same unit, which further ensured that the treatment was uniform. Third, the number and reasons of refusal to participate were not recorded and thus drop-out analyses were not possible to perform. Therefore, we cannot rule out selection bias that only women who felt better participated and those too sick did not, or vice versa. In addition, we lack the information of previous HG, albeit almost half of the participants were nulliparas. Further, we used the original 12-hour PUQE, but PUQE-24 could have recorded the previous day more accurately. The merits of our study include a large sample of women based on power calculations. In addition, the prospective setting can be considered as a merit. Also, PUQE and exact VAS scores were available and analyzed only by the researchers, not by clinicians treating the women, and thus the discharge or readmittance were not dependent on the research data.
Similar to our study, only two previous studies, one Scandinavian three-center study from Norway[19] and another study from Nepal[20] applied PUQE questionnaire to evaluate the severity of NVP in hospitalized HG patients. In the Norwegian PUQE validation study, Birkeland et al[19] compared 38 hospitalized HG patients to 31 healthy pregnant outpatient controls. PUQE-24 scores of HG patients were recorded at admission (median 13) and discharge (median 6). In addition to the significant improvement in the continuous PUQE scores, also shifting to the lower PUQE categories was found between admission and discharge days. Furthermore, the PUQE scores correlated with the general wellbeing score. Although using PUQE-12, which evaluates NVP in the past 12 hours as originally validated by Koren et al.[13] we ended up with similar results as Birkeland et al’s study. Comparative results were obtained also in the Nepalese study;[20] all HG patients (n=81) admitted in B.P. Koirala Institute of Health Sciences during one year were selected and studied for different maternal characteristics. NVP symptoms were evaluated with modified PUQE daily, but information of whether they used PUQE-12 or PUQE-24 was not available in the publication. The mean PUQE score at admission was 12.4, whereas after two days it had decreased to mean 5.5 (mean hospital stay 3.2 days), however, no analyses of categorized PUQE scores were performed. In addition, the authors in the Nepalese study did not analyze the usability of the PUQE score, mainly concentrating on describing the basic characteristics of the HG women.

As the diagnostic criteria of HG are currently not firmly established despite of very recent consensus definition,[22] and no reliable biomarker has been found,[8] the use of validated questionnaires would bring an important addition for diagnosis and treatment follow-up care. Owing to its shortness and simplicity, PUQE is practical, including both quality (vomitus and retching), quantity (frequency) and duration of NVP.[12] However, HG may manifest with other discomforts as well, and therefore, not all women hospitalized for HG fulfill the criteria of severe NVP rated by the highest PUQE scores, as was seen in our study, too. In addition to physical
symptoms, other reasons such as emotional needs or social challenges can contribute to the need of hospitalization. To cover even better most of the HG symptoms, MacGibbon et al[23] have invented and validated a new HELP Score, which, besides including the severity of nausea, vomiting and retching, encompasses estimations of intake, psychosocial functioning, hydration, treatment effectiveness and overall progress. The superiority of a longer and detailed questionnaire which certainly gives a more comprehensive estimation of the illness than the considerably shorter PUQE questionnaire may be, however, lost by being too time-consuming in daily use in hospital setting.

PUQE questionnaire concentrates on physical symptoms. When validating the original PUQE questionnaire, Koren et al[13] added a single rating scale of overall well-being (0–10) where lower value indicating lower QoL correlated with higher PUQE score. We used separate VAS questions for both physical and mental QoL. Predictably, the physical QoL associated better with PUQE than the mental QoL. However, women suffering especially from prolonged and severe NVP report marked negative psychosocial effects to everyday life and even psychiatric symptoms continuing to postpartum.[5–7] In our study, the mean mental QoL VAS score in readmissions was higher indicating worse mental QoL, than the mean score in the first admission. To estimate QoL in women with NVP in more detail, Lacasse et al[24] have validated a NVPQOL-questionnaire. It evaluates QoL during the past week and consists of questions of four different domains: physical symptoms/aggravating factors, fatigue, emotions, and limitations. All in all, as mental well-being consists of wide spectrum of traits, comprehensive estimation with a single question is a challenge.

Ketones are produced when the body lacks carbohydrates, for example in fasting and in prolonged starvation.[25] Ketones can be easily measured from urine, and they are often detected in patients with HG. Thus, the existence of urine ketones has been used in guidelines as a sign of HG.[9,10]
However, recent studies have questioned the importance of urine ketones in diagnosing HG since urine ketones are not present in all HG women.\cite{8,11} In our study, the women had different categories of urine ketones both at admission and at discharge, although in most of the women they resolved during treatment and at discharge severe ketonuria (+++) was not detected. Thus, the clinical value of urine ketones in HG should be interpreted with caution, although severe ketonuria (+++) at admission was associated with higher PUQE score in our study, reflecting more severe NVP.

**Conclusion**

In our study, the PUQE questionnaire showed to be a usable tool to measure the severity of NVP symptoms in a hospital setting. Distinct alleviation of the scores were found between admission and discharge when using the PUQE score both as categorized according to the original version and as continuous PUQE scores. Utilization of PUQE could thus bring feasible complement to the evaluation of the women hospitalized for HG, in addition to the simple question of physical well-being and measurement of urine ketones typically assessed in clinical care. Further challenge would be to develop a tool for estimating the optimal length of hospital admission for sufficient recovery and to avoid rapid readmission.

**Figure legends**

**Figure 1.** Flowchart of the study.

**Figure 2.** PUQE categories on admission and discharge days including a) the first admission and b) all admission periods. PUQE = Pregnancy unique quantification of emesis questionnaire.

**Figure 3.** Urine ketones categories on admission and discharge days including a) the first admission and b) all admission periods.
Figure 4. Associations between continuous PUQE points, physical QoL and mental QoL including the first admission. PUQE = Pregnancy unique quantification of emesis questionnaire; QoL = Quality of life.

Figure 5. Associations between continuous PUQE points, physical QoL and mental QoL including all admission periods. PUQE = Pregnancy unique quantification of emesis questionnaire; QoL = Quality of life.

Author statement

Contributions

MN, PR and PP-K initialized and planned the study. LL collected the data with NK, LL planned the statistical analyses with MK and PP-K and LL wrote the first version of the manuscript. MK performed the statistical analyses. EO participated in data collection and practical arrangements at the hospital antenatal ward. All authors critically reviewed the manuscript and accepted the final submitted version.

Data sharing statement

The dataset of this study is available from the corresponding author on reasonable request.

Funding statement

This work was supported by Turku University Foundation (LL), Finnish Government (Research funds from specified government transfers, LL) and Finnish Cultural Foundation, Southwest Finland Regional Fund (LL). The funders were not involved in the study design, data collection, analysis or interpretation of the data or submitting the manuscript.

Competing interests
None declared.

**Ethics statements**

**Patient consent for publication**

Not applicable.

**Ethics approval**

The study was approved by the Joint Ethics Committees of University of Turku and Turku University Central Hospital, Turku, Finland (60/180/2011). All participants gave written informed consent.
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106 women recruited

5 twin pregnancies: excluded

6 admissions less than overnight: excluded

95 women final sample
STROBE Statement—checklist of items that should be included in reports of observational studies

| Item No | Recommendation |
|---------|----------------|
| **Title and abstract** | |
| 1 | (a) Indicate the study’s design with a commonly used term in the title or the abstract |
| 2 | (b) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | |
| 2 | Explain the scientific background and rationale for the investigation being reported |
| **Objectives** | |
| 3 | State specific objectives, including any prespecified hypotheses |
| **Methods** | |
| 4 | Present key elements of study design early in the paper |
| 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| 6 | (a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up |
| 5-6 | Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls |
| 5-6 | Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants |
| NA | (b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed |
| 5-6 | Case-control study—For matched studies, give matching criteria and the number of controls per case |
| 6,7 | Variables |
| 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| 6,7 | Data sources/measurement |
| 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| 8 | Bias |
| 9 | Describe any efforts to address potential sources of bias |
| 7 | Study size |
| 10 | Explain how the study size was arrived at |
| 7 | Quantitative variables |
| 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| 7 | Statistical methods |
| 12 | (a) Describe all statistical methods, including those used to control for confounding |
| 7-8 | (b) Describe any methods used to examine subgroups and interactions |
| 8 | (c) Explain how missing data were addressed |
| 16 | (d) Cohort study—If applicable, explain how loss to follow-up was addressed |
| NA | Case-control study—If applicable, explain how matching of cases and controls was addressed |
| 16 | Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy |
| 16 | (e) Describe any sensitivity analyses |
## Results

| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed  | 6 |
|--------------|-----|---------------------------------------------------------------------------------|----|
| (b) Give reasons for non-participation at each stage | 16 |
| (c) Consider use of a flow diagram | Fig1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 9 |
| (b) Indicate number of participants with missing data for each variable of interest | Tables |
| (c) Cohort study—Summarise follow-up time (eg, average and total amount) | 6 |
| Outcome data | 15* | Cohort study—Report numbers of outcome events or summary measures over time | NA |
| Case-control study—Report numbers in each exposure category, or summary measures of exposure | |
| Cross-sectional study—Report numbers of outcome events or summary measures | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Table 3-4 |
| (b) Report category boundaries when continuous variables were categorized | 6 |
| (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | NA |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | NA |

## Discussion

| Key results | 18 | Summarise key results with reference to study objectives | 15-16 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 16 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 15-19 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 19 |

## Other information

| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 20 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.
Usability of Pregnancy-Unique Quantification of Emesis Questionnaire in Women Hospitalized for Hyperemesis Gravidarum: A Prospective Cohort Study

Journal: BMJ Open

Manuscript ID: bmjopen-2021-058364.R1

Article Type: Original research

Date Submitted by the Author: 14-Mar-2022

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Primary Subject Heading: Obstetrics and gynaecology

Secondary Subject Heading: Obstetrics and gynaecology, Global health, Public health

Keywords: OBSTETRICS, GYNAECOLOGY, PUBLIC HEALTH, Maternal medicine < OBSTETRICS, MENTAL HEALTH
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Usability of Pregnancy-Unique Quantification of Emesis Questionnaire in Women Hospitalized for Hyperemesis Gravidarum: A Prospective Cohort Study

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word count: 3672
ABSTRACT

Objectives: Pregnancy-unique quantification of emesis (PUQE) questionnaire is mainly used in outpatient care to assess the severity of nausea and vomiting of pregnancy (NVP). Our aim was to evaluate the usability of PUQE in hospitalized women with hyperemesis gravidarum (HG).

Design: Prospective cohort study.

Setting: University Hospital in Finland.

Participants: Ninety-five women admitted due to HG for at least overnight.

Primary and secondary outcome measures: Categorized and continuous PUQE scores, physical and mental quality of life (QoL) and urine ketones on admission and discharge days.

Results: The most common PUQE categories on admission day were ‘moderate’ and ‘severe’, whereas on discharge day they were ‘mild’ and ‘moderate’. Likewise, continuous PUQE scores decreased (on admission day mean PUQE 11.9±2.5, on discharge day mean 6.3±2.6, P<0.0001). On admission day, women rating worse physical QoL (first admission AOR 1.09; 95% CI 1.03–1.16; all admissions AOR 1.10; 95% CI 1.05–1.15) and women with ketonuria of +++ (first admission AOR 16.00; 95% CI 1.44–177.82; all admissions AOR 14.97; 95% CI 1.67–134.00) fell into higher PUQE score category. On discharge day, women with better physical QoL had lower PUQE score category (first admission AOR 0.94; 95% CI 0.91–0.98; all admissions AOR 0.94; 95% CI 0.92–0.97). The results between physical QoL and continuous PUQE scores were similar. As for mental QoL, better mental QoL was associated with lower PUQE score category only at discharge when including all admissions (AOR 0.96; 95% CI 0.93–0.98), and worse mental QoL was associated with higher continuous PUQE score only at admission (all admissions, ß 0.03, P=0.011).

Conclusions: PUQE scores reflected alleviation of NVP severity in women hospitalized due to HG. Further, the decrease in PUQE score was associated with improved physical QoL. We therefore suggest PUQE as a complementary instrument for inpatient setting.
Keywords: 1 PUQE, 2 hyperemesis gravidarum, 3 quality of life, 4 urine ketones

Abbreviations

ANOVA Analysis of variance; AOR Adjusted odds ratio; BMI Body mass index; CI Confidence interval; GEE Generalized estimating equation; HG Hyperemesis gravidarum; NVP Nausea and vomiting of pregnancy; OR odds ratio; PUQE Pregnancy-Unique Quantification of Emesis Questionnaire; QoL Quality of life; VAS Visual analog scale

Article summary

Strengths and limitations of this study

- This study applied PUQE questionnaire in HG patients in inpatient setting comparing PUQE scores at admission and at discharge and distinguishing the first admission period and readmissions.

- Both categorized PUQE scores according to the original validation studies of the questionnaire as well as continuous PUQE scores were analyzed, and the scores were compared with the estimations of physical and mental QoL and urine ketones.

- Admission and discharge criteria were not strictly defined, and the treatment protocol was not standardized.

- Selection bias was possible since the women were enrolled from a single unit and information of women who refused to participate was lacking.
INTRODUCTION

Hyperemesis gravidarum (HG) represents the extremity of symptoms of nausea and vomiting of pregnancy (NVP).[1,2] Most pregnant women have some degree of NVP.[2] Hence, NVP is often considered as a normal part of pregnancy,[3] whereas HG is rare, with an estimated prevalence of only 0.3–3.6%.[1] However, the distinction between severe NVP and HG is often overlapping. In addition, even mild NVP may decrease women’s quality of life (QoL).[3,4] Consequently, it is evident that HG causes not only extreme physical impairment but also substantial mental distress, leading even to suicidal ideation, depressive symptoms continuing postpartum and affecting future family planning.[5–8]

Usually in clinical practice, HG is diagnosed when severe NVP symptoms lead to weight loss, dehydration and electrolyte imbalances.[2] No usable biomarker has been established,[9] although urine ketones are often used despite controversial evidence.[9–12] All in all, need of hospitalization is assessed individually and due to the lack of standardized diagnostic criteria of HG or generally applied questionnaire to evaluate the severity of HG symptoms, admittance to hospital and length of admission easily varies according to the physician’s assessment. Repeated hospital admissions are often needed.[13,14]

Pregnancy-Unique Quantification of Emesis (PUQE) questionnaire[15] is a simple tool for measuring the severity of NVP. PUQE score, ranging from 3 to 15 points, is the sum of the replies to three questions concerning duration of nausea in hours and the quantity of both vomiting and retching episodes. According to the total PUQE points, NVP is categorized into ‘no’, ‘mild’, ‘moderate’ and ‘severe’. PUQE has been validated to cover symptoms from previous 12 hours[16] and 24 hours[17] (PUQE-24) as well as from the entire first trimester.[18] PUQE is mostly used in
outpatient setting to screen patients with NVP and accordingly the need of hospitalization.[2,10] In hospital settings of HG patients, PUQE has been used in few studies mainly comparing the effectiveness of different therapeutic interventions.[19–21]

To best of our knowledge, only two previous studies, a Norwegian PUQE validation study[22] and another study from Nepal,[23] applied the PUQE questionnaire during hospitalization due to HG, both showing an improvement in PUQE score after treatment. In the Norwegian study, also a connection between higher PUQE score and both lower general wellbeing and insufficient nutritional intake was shown. While in the Norwegian study both categorized PUQE scores as validated in the original studies[15,16] and continuous PUQE scores were analyzed, the Nepalese study considered PUQE scores only as continuous scores.

Given the sparsity of previous research, further studies were needed regarding the usability of the PUQE questionnaire in clinical settings, including evaluation of the tool in both the first admission period and in readmissions, reflecting milder HG (first admission) and prolonged HG (readmissions). Thus, our aim was to evaluate the clinical usability of the PUQE questionnaire in terms of the improvement of the PUQE scores between admission and discharge among women hospitalized for HG. The PUQE scores were considered both as categorized and continuous values and compared to both physical and mental QoL scores and to urine ketones, measures which in clinical practice are typically used as markers of hospital admittance and discharge of HG patients.

MATERIAL AND METHODS

Women hospitalized for HG in antenatal ward of Turku University Hospital, Turku, Finland during 2011–2019 were enrolled after oral and written information about the study. Volunteers were
eligible to participate and gave written informed consent. Capability to read and understand Finnish language was required, and thus most of the participants were Finnish. The study was approved by the Joint Ethics Committees of University of Turku and Turku University Central Hospital, Turku, Finland (60/180/2011).

HG was diagnosed according to the International Statistical Classification of Diseases and Related Health Problems (ICD–10; O21.0, O21.1, O21.9). Decision of admission for HG was based on current practice[24] and clinician’s assessment concerning general sickness of the women, as well as clinical signs or laboratory findings of dehydration or presence of urine ketones. HG treatment for all women consisted of intravenous fluids and most women received antiemetic medication (metoclopramide and/or ondansetron). Only a minority of women needed parenteral nutrition. (Table 1). Decision to discharge was made according to cessation or alleviation of vomitus and nausea, signs of improved hydration and self-judgement of the woman of her own well-being.

Altogether 106 women participated. Only data of women with singleton pregnancies and admissions lasting at least overnight were included, and thus data of 95 women was eligible for analysis (figure 1). In Turku University Hospital, during the recruitment period, there were annually 32–68 admissions for HG (including readmissions of the same women), resulting in 433 admission periods, which gave estimation of the participation rate of 37% (162 periods/433 periods). Furthermore, the number of deliveries varied from 3708 to 4214 annually,[25] giving the admission rate due to HG of 0.8–1.7 %.

NVP was assessed with PUQE score concerning the previous 12 hours.[15] In accordance with the original version,[15] four NVP categories of ‘no’ (3 points), ‘mild’ (4–6 points), ‘moderate’ (7–12 points) and ‘severe’ (13–15 points) were formed. In addition, PUQE score was used as a continuous
variable. PUQE questionnaire has previously been translated into Finnish by a professional
translator with the permission of the PUQE owners and back translated by another professional
translator [26] PUQE scores were recorded only for study purposes, and thus the scores did not
guide the decisions of treatment, admittance, discharge or readmission of the women.

Physical and mental QoL were estimated with two visual analog scales (VAS). Urine ketones were
measured by urinalysis reagent strips (Mission®, Acon Laboratories, Inc, San Diego, USA), with
detection levels of – (no detectable ketones), + (15 mg/dL=1.5 mmol/L), ++ (40 mg/dL=4.0
mmol/L) and +++ (80 mg/dL=8.0 mmol/L).

Basic demographic data of the women were obtained from hospital medical records including
gestational weeks (gwk) at admission, parity (nulliparous/multiparous), body mass index (BMI,
kg/m², calculated from pre-pregnancy weight and height), smoking (no/yes), marital status
(cohabited/single), the total length of all admissions (days), the number of readmissions and urine
ketones results. Age was calculated by comparing the date of reply to the date of birth.

**Statistical analyses**

Power calculation estimated minimum sample size of 58 (difference of three PUQE points between
admission and discharge, alpha=5% and power of 80%, nQuery Advisor 4.0: paired t-test). The
distribution of values was evaluated before statistical analyses both visually and statistically and the
variables followed approximately normal distribution, enabling the use of parametric tests.
Continuous variables were characterized using means standard deviations (SD) and ranges and
categorical variables using frequencies and percent. The severity of NVP was categorized according
to PUQE total score (‘no’/‘mild’/‘moderate’/‘severe’) on both admission and discharge days.
Because of low number of values in category ‘mild NVP’ (n=2) on admission day and ‘severe
NVP’ (n=1) on discharge day, these values were excluded from the analyses on admission and discharge days, respectively. In addition, when analyzing the change of PUQE categories (delta, Δ) between admission and discharge, due to the low number of values in the change of three PUQE categories (n=3), the change of three PUQE categories and the change of two PUQE categories were combined.

Concerning physical or mental QoL measured by VAS, the probability to belong to a higher (admission day) PUQE category or lower (discharge day) PUQE category was calculated with multinominal logistic regression on both admission and discharge days. Two separate analyses were performed: 1) analysis of the first admission period, and 2) analysis of all admission periods. Generalized estimating equation (GEE) estimation was used when all admissions were included in analyses. The same analyses were performed for urine ketones categories (–/+/+//++/+++). In analysis of urine ketones, p-values were adjusted using Tukey-Kramer method because of multiple comparisons. Further, similar analyses on admission and discharge days using PUQE score as a continuous score were also performed. Comparisons both with physical and mental QoL VAS, urine ketones and continuous PUQE total points were calculated with linear mixed model for the first admission and linear mixed model with random intercept for patient for all admissions. All these results were adjusted for age, BMI and parity. In addition, continuous PUQE scores and VAS scores on admission and discharge days were compared using ANOVA. The results are presented with odds ratios (OR) and beta (β) with 95% confidence intervals (CI). Both unadjusted and adjusted results are shown in the tables, but only adjusted results are presented in the Results main text. Statistical significance was set at p-values <0.05. Analyses were carried out using a 9.4 version of SAS Institute Inc. (Cary, NC, USA) for Windows.

Patient and public involvement statement
Patients and the public were not involved in the design or reporting of this study.

RESULTS

Basic characteristics

Basic characteristics of the women and the questionnaire data are presented in table 1 and table 2. On admission day, according to categorized PUQE scores, most of the women suffered from ‘moderate’ or ‘severe NVP’. On the contrary, on discharge day, most of the women had ‘mild’ or ‘moderate NVP’ (figure 2). Likewise, the mean continuous PUQE scores were higher on admission day compared to discharge day (table 2). Further, on admission day, physical and mental QoL scores were higher indicating worse QoL than on discharge day (table 2). On admission day, over half of the women had urine ketones, whereas most of the women had no urine ketones on discharge day (figure 3).

PUQE score category and the first admission period

When evaluating only the first admission period, on admission day women with worse physical QoL fell into a higher PUQE score category. Instead, worse mental QoL was not associated with PUQE score category. In addition, women with severe ketonuria (+++) vs no urine ketones) fell into higher PUQE score category ($P=0.016$). On discharge day of the first admission period, the women with better physical QoL fell into lower PUQE score category. Instead, mental QoL and the presence of urine ketones were not associated with PUQE score categories. (Table 3 and supplementary Table 1.)
Table 1. Basic characteristics of the women. Total n=95.

|                                | n   | Mean ± SD or n (%) | Range       |
|--------------------------------|-----|--------------------|-------------|
| Age (years)                    | 95  | 29.5 ± 5.0         | 18.9–42.7   |
| Gwk                            | 95  | 9.8 ± 2.5          | 6.3–20.3    |
| Parity                         | 93  |                    |             |
| Nulliparous                    | 35  | (37.6)             |             |
| Multiparous                    | 58  | (62.4)             |             |
| BMI (kg/m²)                    | 91  | 25.2 ± 5.4         | 18.0–40.6   |
| Smoking                        | 90  |                    |             |
| Non-smokers                    | 87  | (96.7)             |             |
| Smokers                        | 3   | (3.3)              |             |
| Marital status                 | 92  |                    |             |
| Cohabited                      | 85  | (92.4)             |             |
| Single                         | 7   | (7.6)              |             |
| Number of admissions           | 95  |                    |             |
| 1                              | 60  | (63.2)             |             |
| ≥ 2                            | 35  | (36.8)             |             |
| Length of admissions (days)    | 160 * |                | 1–12        |
| HG treatment                   | 93  |                    |             |
| Intravenous fluids             | 93  | (100.0)            |             |
| Antiemetic medication          | 75  | (80.6)             |             |
| Metoclopramide                 | 32  | (42.7)             |             |
| Ondansetron                    | 12  | (16.0)             |             |
| Both                           | 31  | (41.3)             |             |
| Parenteral nutrition           | 5   | (5.4)              |             |

BMI = Body mass index
GWK = Gestational week

*Total number of all admission periods with available data.
Table 2. PUQE total points and VAS scores.

|                      | First admission |                      | All admissions |                      |
|----------------------|----------------|----------------------|----------------|----------------------|
|                      | n*  mean ± SD  | range               | P             | n*  mean ± SD  | range               | P             |
| PUQE total points    |                | <0.0001              | <0.0001       |                |                      |               |
| Admission day        | 68  11.6 ± 2.3 | 5–15                | <0.0001       | 122  11.9 ± 2.5 | 4–15                | <0.0001       |
| Discharge day        | 65  6.5 ± 2.4  | 3–12                | <0.0001       | 122  6.3 ± 2.6  | 3–13                | <0.0001       |
| Physical QoL VAS     |                | <0.0001              | <0.0001       |                |                      |               |
| Admission day        | 68  84.2±11.7  | 50–100               | <0.0001       | 122  83.8 ± 12.6 | 30–100              | <0.0001       |
| Discharge day        | 65  45.4±19.3  | 4–90                 | <0.0001       | 122  46.3 ± 20.3 | 0–90                | <0.0001       |
| Mental QoL VAS       |                | <0.0001              | <0.0001       |                |                      |               |
| Admission day        | 68  65.4±17.9  | 15–100               | <0.0001       | 122  69.7 ± 19.2 | 12–100              | <0.0001       |
| Discharge day        | 65  38.2±20.3  | 0–90                 | <0.0001       | 122  42.8 ± 23.5 | 0–90                | <0.0001       |

ANOVA
PUQE = Pregnancy-Unique Quantification of Emesis Questionnaire
QoL = Quality of life
VAS = Visual analog scale 0–100, higher number indicates worse QoL
*Total number of the women = 95. Total number of available data for the first admission period = 93 and for all admission periods = 162.
Table 3. Physical and mental QoL in VAS on admission and discharge days and the probability to fall into a higher or lower PUQE score category*.

| First admission | PUQE admission day | PUQE discharge day | Δ |
|-----------------|-------------------|-------------------|---|
|                  | OR 95%CI P        | OR 95%CI P        | OR 95%CI P |
| Physical QoL VAS| 1.10 1.04–1.16 0.001 1.09 1.03–1.16 0.003 | 0.95 0.92–0.98 0.001 0.94 0.91–0.98 0.003 | 0.95 0.93–0.98 0.0008 0.93 0.90–0.97 0.0002 |
| Mental QoL VAS  | 1.00 0.97–1.03 0.983 1.01 0.97–1.04 0.765 | 0.98 0.95–1.00 0.071 0.97 0.94–1.00 0.062 | 0.97 0.95–1.00 0.045 0.97 0.94–0.99 0.011 |

All admissions

| PUQE admission day | PUQE discharge day | Δ |
|-------------------|-------------------|---|
|                  | OR 95%CI P        | OR 95%CI P        | OR 95%CI P |
| Physical QoL VAS  | 1.10 1.05–1.15 <0.0001 1.10 1.05–1.15 <0.0001 | 0.95 0.93–0.97 <0.0001 0.94 0.92–0.97 <0.0001 | 0.95 0.93–0.98 0.0008 0.95 0.93–0.98 0.0002 |
| Mental QoL VAS    | 1.03 1.00–1.06 0.037 1.03 1.00–1.06 0.063 | 0.97 0.95–1.00 0.062 0.96 0.93–0.98 0.0007 | 0.97 0.95–1.00 0.018 0.96 0.94–0.98 <0.0001 |

Multinominal logistic regression
AOR = Adjusted odds ratio: adjusted for age, body mass index and parity
PUQE = Pregnancy-Unique Quantification of Emesis Questionnaire
QoL = Quality of life
VAS = Visual analog scale
*Higher PUQE category on admission day and lower PUQE category on discharge day
**PUQE score category and all admission periods**

When including all admission periods, the results between physical QoL and PUQE score categories on admission day and on discharge day were similar to those including only the first admission period: worse physical QoL was associated with higher PUQE category on admission day and better physical QoL with lower PUQE category on discharge day. The same held true with severe ketonuria on admission day which was associated with higher PUQE category ($P=0.008$). As for mental QoL, on admission day of all admission periods, women with worse mental QoL fell into higher PUQE score category in unadjusted analysis but in adjusted analysis the results showed only a tendency. On discharge day of all admission periods, women with better mental QoL fell into lower PUQE score category. On discharge day, there were no associations between urine ketones categories and PUQE score categories. (Table 3 and supplementary Table 1.)

During both the first and all admission periods, the decrease (indicating better QoL) in both physical and mental QoL VAS score was associated with a decrease in the PUQE category (Table 3).

**Continuous PUQE score, QoL scores and urine ketones**

When PUQE points were considered as continuous value, on admission day, worse physical QoL was associated with high PUQE points both during the first admission period and when all admission periods were included. Worse mental QoL was associated with high PUQE points only when including all admissions. On admission day, severe ketonuria (+++ vs no urine ketones) was associated with high PUQE points at first admission ($P=0.026$ first admission, $P=0.056$ all admissions). On discharge day, both better physical QoL and better mental QoL were associated with low PUQE points during the first admission period and when including all admissions. On the
contrary, urine ketones showed no association ($P=0.224$ first admission, $P=0.545$ all admissions). (Figure 4 and Figure 5).

The improvement (the mean difference in VAS values between admission and discharge days) in both physical QoL and mental QoL was associated with the change in continuous PUQE scores during the first admission period and when including all admissions. Instead, no association emerged between the change in continuous PUQE score and urine ketones ($P=0.294$ first admission, $P=0.355$ all admissions). (Figure 4 and Figure 5).

**DISCUSSION**

We were the first to use PUQE questionnaire in hospitalized HG women in Finland. PUQE showed to be a feasible clinical tool for assessing recovery; a marked improvement in PUQE score was found when comparing scores between admission and discharge using PUQE both as categorized and as continuous scores. In addition, high PUQE scores were associated with worse physical QoL at admission and low PUQE scores with better physical QoL at discharge, both in the first admission and in readmissions, indicating that PUQE scores were well concurrent with the measurement of physical QoL. As for the associations between mental QoL and PUQE scores, the association was found at both admission and discharge when PUQE scores were taken as continuous scores in readmissions. Concerning mental QoL and categorized PUQE scores, the association was found only in the adjusted results at discharge. These findings could be explained by that even though PUQE questionnaire is measuring physical events of NVP, it may also reflect mental QoL, especially in prolonged NVP: the overall misery of illness at admission and on readmissions, and, on the other hand, the relief of improved condition at discharge. As for
ketonuria, only severe ketonuria at admission was associated with higher PUQE score category, but otherwise ketonuria showed no connection with PUQE.

Our study has limitations. First, admission and discharge criteria were not strictly and uniformly defined, being based on common current practice concerning the well-being of the women and clinical signs or laboratory findings of dehydration. In Finland, the primary health care system is based on national health coverage and practically all pregnant women visit free-of-cost public maternity health care clinics. From there, women with HG are referred to hospitals to specialized obstetrics clinics which are part of public services provided to all citizens by several hospital districts. These clinics in hospitals are led by specialists in obstetrics and women can be admitted to hospital or the treatment can continue in outpatient care. Therefore, hospital admittance and discharge decisions were not dependent for instance on women having a health care insurance or adequate wealth. Secondly, management between the patients was not totally similar, but standardized clinical practice and the treatment protocols were followed. However, since there were no strict admission or discharge criteria, no reliable biomarker to assess or predict the disease severity of HG or the probability of readmission, the treatment decisions were clinically individually assessed and possibly additionally affected by other determinants than physical parameters, for instance factors related to women’s housing situation or to family responsibilities. Hence, these factors may have influenced our results. In addition, all women were enrolled in the same unit, which further ensured that the treatment was uniform. Third, the number and reasons of refusal to participate were not recorded and thus drop-out analyses were not possible to perform. Therefore, we cannot rule out selection bias that only women who felt better participated and those too sick did not, or vice versa. Moreover, the recruitment process took several years and was dependent on the activity of the nurses in the ward who recruited the women according to researchers’ instructions on the top of their other duties without any extra compensation. In
addition, we lack the information of previous HG, albeit almost half of the participants were nulliparas. The weight change during admission periods was not recorded although it could have reflected the nutritional status of the women better than urine ketones. Further, we used the original 12-hour PUQE, but PUQE-24 could have recorded the previous day more accurately.

The merits of our study included a prospective study design with a large sample size based on power calculations. As the study questionnaire was available only in Finnish it practically ruled out foreign participants and thus our sample was quite homogenous and representative of the Finnish population. Compared to existing literature, we were the first to analyze the first admission period and readmissions separately, which roughly reflected milder HG (first admission) and prolonged HG (readmissions). This procedure also considered the possibility of learning effect since the women who were repeatedly hospitalized filled in the PUQE several times. Also, PUQE and exact VAS scores were available and analyzed only by the researchers, not by clinicians treating the women, and thus the discharge or readmittance were not dependent on the research data.

Similar to our study, only two previous studies, one Scandinavian three-center study from Norway[22] and another study from Nepal[23] applied PUQE questionnaire to evaluate the severity of NVP in hospitalized HG patients. In the Norwegian PUQE validation study, Birkeland et al[22] compared 38 hospitalized HG patients to 31 healthy pregnant outpatient controls. PUQE-24 scores of HG patients were recorded at admission (median 13) and discharge (median 6). In addition to the significant improvement in the continuous PUQE scores, also shifting to the lower PUQE categories was found between admission and discharge days. Furthermore, the PUQE scores correlated with the general wellbeing score. Although using PUQE-12, which evaluates NVP in the past 12 hours as originally validated by Koren et al.[16] we ended up with similar results as Birkeland et al’s study. Comparative results were obtained also in the Nepalese study;[23] all HG
patients (n=81) admitted in B.P. Koirala Institute of Health Sciences during one year were selected and studied for different maternal characteristics. NVP symptoms were evaluated with modified PUQE daily, but information of whether they used PUQE-12 or PUQE-24 was not available in the publication. The mean PUQE score at admission was 12.4, whereas after two days it had decreased to mean 5.5 (mean hospital stay 3.2 days), however, no analyses of categorized PUQE scores were performed. In addition, the authors in the Nepalese study did not analyze the usability of the PUQE score, mainly concentrating on describing the basic characteristics of the HG women.

As the diagnostic criteria of HG are currently not firmly established despite of very recent consensus definition,[27] and no reliable biomarker has been found,[9] the use of validated questionnaires would bring an important addition for diagnosis and treatment follow-up care. Owing to its shortness and simplicity, PUQE is practical, including both quality (vomitus and retching), quantity (frequency) and duration of NVP.[15] However, HG may manifest with other discomforts as well, and therefore, not all women hospitalized for HG fulfill the criteria of severe NVP rated by the highest PUQE scores, as was seen in our study, too. In addition to physical symptoms, other reasons such as emotional needs or social challenges can contribute to the need of hospitalization. To cover even better most of the HG symptoms, MacGibbon et al[28] have invented and validated a new HELP Score, which, besides including the severity of nausea, vomiting and retching, encompasses estimations of intake, psychosocial functioning, hydration, treatment effectiveness and overall progress. The superiority of a longer and detailed questionnaire which certainly gives a more comprehensive estimation of the illness than the considerably shorter PUQE questionnaire may be, however, lost by being too time-consuming in daily use in hospital setting.
PUQE questionnaire concentrates on physical symptoms. Adjacent to the original PUQE, Koren et al.[15] used a single rating scale (0–10) of overall well-being. In their PUQE validation study,[16] lower value in the well-being score indicating lower QoL correlated with higher PUQE score. We used two VAS questions separately for both physical and mental QoL to assess QoL comprehensively. Predictably, the physical QoL was associated rather with PUQE than the mental QoL. However, women suffering especially from prolonged and severe NVP report marked negative psychosocial effects to everyday life and even psychiatric symptoms continuing into postpartum.[5–7] Accordingly in our study, not only the mean mental QoL VAS score in readmissions was higher indicating worse mental QoL than the mean score in the first admission but also the associations between mental QoL and PUQE score emerged in women with readmissions, thus emphasizing the mental consequences of prolonged HG. To estimate QoL in women with NVP in more detail, Lacasse et al.[29] have validated a NVPQOL-questionnaire. It evaluates QoL during the past week and consists of questions of four different domains: physical symptoms/aggravating factors, fatigue, emotions, and limitations. All in all, as mental well-being consists of wide spectrum of traits, comprehensive estimation with a single question is a challenge.

Ketones are produced when the body lacks carbohydrates, for example in fasting and in prolonged starvation.[30] Ketones can be easily measured from urine, and they are often detected in patients with HG. Thus, the existence of urine ketones has been used in guidelines as a sign of HG.[10,11] However, recent studies have questioned the importance of urine ketones in diagnosing HG since urine ketones are not present in all HG women.[9,12] In our study, the women had different categories of urine ketones both at admission and at discharge, although in most of the women they resolved during treatment and at discharge severe ketonuria (+++ was not detected. Thus, the clinical value of urine ketones in HG should be interpreted with caution, although severe ketonuria
(+++) at admission was associated with higher PUQE score in our study, reflecting more severe NVP.

**Conclusion**

In our study, the PUQE questionnaire showed to be a usable tool to measure the severity of NVP symptoms in a hospital setting. Distinct alleviation of the scores were found between admission and discharge when using the PUQE score both as categorized according to the original version and as continuous PUQE scores which supports the assessment of individual PUQE points instead of focusing only on the change of PUQE categories. Utilization of PUQE could thus bring feasible complement to the evaluation of the women hospitalized for HG, in addition to the simple question of physical well-being and measurement of urine ketones typically assessed in clinical care. Further challenge would be to develop a tool for estimating the optimal length of hospital admission for sufficient recovery and to avoid rapid readmission.

**Figure legends**

**Figure 1.** Flowchart of the study.

**Figure 2.** PUQE categories on admission and discharge days including a) the first admission and b) all admission periods. PUQE = Pregnancy unique quantification of emesis questionnaire.

**Figure 3.** Urine ketones categories on admission and discharge days including a) the first admission and b) all admission periods.

**Figure 4.** Associations between continuous PUQE points, physical QoL and mental QoL including the first admission. PUQE = Pregnancy unique quantification of emesis questionnaire; QoL = Quality of life.
**Figure 5.** Associations between continuous PUQE points, physical QoL and mental QoL including all admission periods. PUQE = Pregnancy unique quantification of emesis questionnaire; QoL = Quality of life.

**Author statement**

**Contributions**

MN, PR and PP-K initialized and planned the study. LL collected the data with NK, LL planned the statistical analyses with MK and PP-K and LL wrote the first version of the manuscript. MK performed the statistical analyses. EO participated in data collection and practical arrangements at the hospital antenatal ward. All authors critically reviewed the manuscript and accepted the final submitted version.

**Data sharing statement**

The dataset of this study is available from the corresponding author on reasonable request.

**Funding statement**

This work was supported by Turku University Foundation (LL), Finnish Government (Research funds from specified government transfers, LL) and Finnish Cultural Foundation, Southwest Finland Regional Fund (LL). The funders were not involved in the study design, data collection, analysis or interpretation of the data or submitting the manuscript.

**Competing interests**

None declared.

**Ethics statements**
Patient consent for publication

Not applicable.

Ethics approval

The study was approved by the Joint Ethics Committees of University of Turku and Turku University Central Hospital, Turku, Finland (60/180/2011). All participants gave written informed consent.
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106 women recruited

5 twin pregnancies: excluded

6 admissions less than overnight: excluded

95 women final sample
Supplementary table 1. Urine ketones categories on admission and discharge days and the probability to fall into higher or lower PUQE score category*.

| First admission | PUQE admission day | PUQE discharge day |
|-----------------|--------------------|--------------------|
| Urine ketones   | OR     95%CI P | AOR 95%CI P | OR 95%CI P | AOR 95%CI P |
| + vs -          | 1.56 0.11–22.22 | 0.974 5.11 0.22–0.542 | 0.68 0.23–118.15 | 0.97 2.07 0.24–0.709 |
| ++ vs -         | 1.33 0.10–18.49 | 0.992 1.69 0.10–0.965 | 0.38 0.02–29.43 | 0.96 0.74–17.80 |
| +++ vs -        | 7.00 1.00–48.81 | 0.049 16.00 1.44–0.016 | NA NA NA |

| All admissions  | PUQE admission day | PUQE discharge day |
|-----------------|--------------------|--------------------|
| Urine ketones   | OR     95%CI P | AOR 95%CI P | OR 95%CI P | AOR 95%CI P |
| + vs -          | 1.13 0.09–13.41 | 0.993 2.65 0.16–0.814 | 1.47 0.50–4.34 | 0.67 0.75–0.874 |
| ++ vs -         | 3.38 0.46–24.58 | 0.394 3.26 0.32–0.556 | 2.64 0.12–57.32 | 0.74 5.85–316.49 |
| +++ vs -        | 7.43 1.52–36.38 | 0.007 14.97 1.67–0.008 | NA NA NA |

Urine ketones categories: -/+/+/+ +++
Multinominal logistic regression
AOR = Adjusted odds ratio: adjusted for age, body mass index and parity
PUQE = Pregnancy-Unique Quantification of Emesis Questionnaire
NA = Not applicable
*Higher PUQE category on admission day and lower PUQE category on discharge day
STROBE Statement—checklist of items that should be included in reports of observational studies

| Item No | Recommendation                                                                                                                                   | Page No |
|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Title and abstract | (a) Indicate the study’s design with a commonly used term in the title or the abstract<br>(b) Provide in the abstract an informative and balanced summary of what was done and what was found | 1, 2    |
| Introduction | Explain the scientific background and rationale for the investigation being reported                                                        | 4, 5    |
| Objectives | State specific objectives, including any prespecified hypotheses                                                                             | 5       |
| Methods | Present key elements of study design early in the paper                                                                                       | 5-6     |
| Setting | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection                  | 5       |
| Participants | (a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants<br>(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed<br>Case-control study—For matched studies, give matching criteria and the number of controls per case | 5-6, NA |
| Variables | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 6, 7    |
| Data sources/measurement | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 6, 7    |
| Bias | Describe any efforts to address potential sources of bias                                                                                       | 8       |
| Study size | Explain how the study size was arrived at                                                                                                       | 7       |
| Quantitative variables | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 7       |
| Statistical methods | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) Cohort study—If applicable, explain how loss to follow-up was addressed<br>Case-control study—If applicable, explain how matching of cases and controls was addressed<br>Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses | 7-8, 16, NA |

Continued on next page
## Results

### Participants

| Number | Description |
|--------|-------------|
| 13*    | (a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
|        | (b) Give reasons for non-participation at each stage |
|        | (c) Consider use of a flow diagram |

### Descriptive data

| Number | Description |
|--------|-------------|
| 14*    | (a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders |
|        | (b) Indicate number of participants with missing data for each variable of interest |
|        | (c) **Cohort study**—Summarise follow-up time (e.g., average and total amount) |

### Outcome data

| Number | Description |
|--------|-------------|
| 15*    | **Cohort study**—Report numbers of outcome events or summary measures over time |
|        | **Case-control study**—Report numbers in each exposure category, or summary measures of exposure |
|        | **Cross-sectional study**—Report numbers of outcome events or summary measures |

### Main results

| Number | Description |
|--------|-------------|
| 16     | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
|        | (b) Report category boundaries when continuous variables were categorized |
|        | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |

### Other analyses

| Number | Description |
|--------|-------------|
| 17     | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses |

## Discussion

### Key results

| Number | Description |
|--------|-------------|
| 18     | Summarise key results with reference to study objectives |

### Limitations

| Number | Description |
|--------|-------------|
| 19     | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |

### Interpretation

| Number | Description |
|--------|-------------|
| 20     | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |

### Generalisability

| Number | Description |
|--------|-------------|
| 21     | Discuss the generalisability (external validity) of the study results |

## Other information

| Number | Description |
|--------|-------------|
| 22     | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of *PLoS Medicine* at http://www.plosmedicine.org/, *Annals of Internal Medicine* at http://www.annals.org/, and *Epidemiology* at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.
## Usability of Pregnancy-Unique Quantification of Emesis Questionnaire in Women Hospitalized for Hyperemesis Gravidarum: A Prospective Cohort Study

| Journal:        | BMJ Open                  |
|-----------------|---------------------------|
| Manuscript ID   | bmjopen-2021-058364.R2    |
| Article Type:   | Original research         |
| Date Submitted by the Author: | 01-May-2022 |

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**Secondary Subject Heading:** Obstetrics and gynaecology, Global health, Public health

**Keywords:** OBSTETRICS, GYNAECOLOGY, PUBLIC HEALTH, Maternal medicine < OBSTETRICS, MENTAL HEALTH
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Usability of Pregnancy-Unique Quantification of Emesis Questionnaire in Women Hospitalized for Hyperemesis Gravidarum: A Prospective Cohort Study

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word count: 3677
ABSTRACT

Objectives: Pregnancy-unique quantification of emesis (PUQE) questionnaire is mainly used in outpatient care to assess the severity of nausea and vomiting of pregnancy (NVP). Our aim was to evaluate the usability of the Finnish translated PUQE in hospitalized women with hyperemesis gravidarum (HG).

Design: Prospective cohort study.

Setting: University Hospital in Finland.

Participants: Ninety-five women admitted due to HG for at least overnight.

Primary and secondary outcome measures: Categorized and continuous PUQE scores, physical and mental quality of life (QoL) and urine ketones at admission and at discharge, analyzing the first admission and readmissions separately.

Results: The most common PUQE categories at admission were ‘moderate’ and ‘severe’, whereas at discharge they were ‘mild’ and ‘moderate’. Likewise, continuous PUQE scores decreased improved between admission and discharge (P<0.0001). At admission, women rating worse physical QoL (first admission AOR 1.09; 95% CI 1.03–1.16; readmissions AOR 1.13; 95% CI 1.02–1.25) and women with ketonuria of +++ (first admission AOR 16.00; 95% CI 1.44–177.82) fell into higher PUQE score category. On discharge day, women with better physical QoL had lower PUQE score category (first admission AOR 0.94; 95% CI 0.91–0.98; readmissions AOR 0.93; 95% CI 0.90–0.97). The results between physical QoL and continuous PUQE scores were similar. Concerning readmissions, better mental QoL was associated with lower PUQE score category at discharge (AOR 0.93; 95% CI 0.89–0.97). As for continuous PUQE score, worse mental QoL was associated with higher score at admission (readmissions, P=0.007) and better mental QoL with lower score at discharge (readmissions, P=0.007).

Conclusions: PUQE scores reflected alleviation of NVP severity in women hospitalized due to HG. Further, the decrease in PUQE score was associated with improved physical QoL and partly also
with improved mental QoL. We therefore suggest PUQE as a complementary instrument for inpatient setting.

**Keywords:** 1 PUQE, 2 hyperemesis gravidarum, 3 quality of life, 4 urine ketones

**Abbreviations**

ANOVA Analysis of variance; AOR Adjusted odds ratio; BMI Body mass index; CI Confidence interval; GEE Generalized estimating equation; HG Hyperemesis gravidarum; NVP Nausea and vomiting of pregnancy; OR odds ratio; PUQE Pregnancy-Unique Quantification of Emesis Questionnaire; QoL Quality of life; VAS Visual analog scale

**Article summary**

**Strengths and limitations of this study**

- This study applied PUQE questionnaire in HG patients in inpatient setting comparing PUQE scores at admission and at discharge and distinguishing the first admission period and readmissions.

- Both categorized PUQE scores according to the original validation studies of the questionnaire as well as continuous PUQE scores were analyzed, and the scores were compared with the estimations of physical and mental QoL and urine ketones.

- Admission and discharge criteria were not strictly defined, and the treatment protocol was not standardized.
• Selection bias was possible since the women were enrolled from a single unit and information of women who refused to participate was lacking.
INTRODUCTION

Hyperemesis gravidarum (HG) represents the extremity of symptoms of nausea and vomiting of pregnancy (NVP).[1,2] Most pregnant women have some degree of NVP.[2] Hence, NVP is often considered as a normal part of pregnancy,[3] whereas HG is rare, with an estimated prevalence of only 0.3–3.6 %.[1] However, the distinction between severe NVP and HG is often overlapping. In addition, even mild NVP may decrease women’s quality of life (QoL).[3,4] Consequently, it is evident that HG causes not only extreme physical impairment but also substantial mental distress, leading even to suicidal ideation, depressive symptoms continuing postpartum and affecting future family planning.[5–8]

Usually in clinical practice, HG is diagnosed when severe NVP symptoms lead to weight loss, dehydration and electrolyte imbalances.[2] No usable biomarker has been established,[9] although urine ketones are often used despite controversial evidence.[9–12] All in all, need of hospitalization is assessed individually and due to the lack of standardized diagnostic criteria of HG or generally applied questionnaire to evaluate the severity of HG symptoms, admittance to hospital and length of admission easily varies according to the physician’s assessment. Repeated hospital admissions are often needed.[13,14]

Pregnancy-Unique Quantification of Emesis (PUQE) questionnaire[15] is a simple tool for measuring the severity of NVP. PUQE score, ranging from 3 to 15 points, is the sum of the replies to three questions concerning duration of nausea in hours and the quantity of both vomiting and retching episodes. According to the total PUQE points, NVP is categorized into ‘no’, ‘mild’, ‘moderate’ and ‘severe’. PUQE has been validated to cover symptoms from previous 12 hours[16] and 24 hours[17] (PUQE-24) as well as from the entire first trimester.[18] PUQE is mostly used in
outpatient setting to screen patients with NVP and accordingly the need of hospitalization.[2,10]

The PUQE questionnaire has previously been translated into Finnish by a professional translator with the permission of the PUQE owners and back translated by another professional translator and used in general Finnish pregnant outpatient population.[19] In hospital settings of HG patients, PUQE has been used in few studies mainly comparing the effectiveness of different therapeutic interventions.[20–22]

To best of our knowledge, only two previous studies, a Norwegian PUQE validation study[23] and another study from Nepal,[24] applied the PUQE questionnaire during hospitalization due to HG, both showing an improvement in PUQE score after treatment. In the Norwegian study, also a connection between higher PUQE score and both lower general wellbeing and insufficient nutritional intake was shown. While in the Norwegian study both categorized PUQE scores as validated in the original studies[15,16] and continuous PUQE scores were analyzed, the Nepalese study considered PUQE scores only as continuous scores.

Given the sparsity of previous research, further studies were needed regarding the usability of the PUQE questionnaire in clinical settings, including evaluation of the tool in both the first admission period and in readmissions, reflecting milder HG (first admission) and prolonged HG (readmissions). Thus, our aim was to evaluate the clinical usability of the Finnish PUQE questionnaire in terms of the improvement of the PUQE scores between admission and discharge among women hospitalized for HG. The PUQE scores were considered both as categorized and continuous values and compared to both physical and mental QoL scores and to urine ketones, measures which in clinical practice are typically used as markers of hospital admittance and discharge of HG patients.
MATERIAL AND METHODS

Women hospitalized for HG in antenatal ward of Turku University Hospital, Turku, Finland during 2011–2019 were enrolled after oral and written information about the study. Volunteers were eligible to participate and gave written informed consent. Capability to read and understand Finnish language was required, and thus most of the participants were Finnish. The study was approved by the Joint Ethics Committees of University of Turku and Turku University Central Hospital, Turku, Finland (60/180/2011).

HG was diagnosed according to the International Statistical Classification of Diseases and Related Health Problems (ICD–10; O21.0, O21.1, O21.9). Decision of admission for HG was based on current practice[25] and clinician’s assessment concerning general sickness of the women, as well as clinical signs or laboratory findings of dehydration or presence of urine ketones. HG treatment for all women consisted of intravenous fluids and most women received antiemetic medication (metoclopramide and/or ondansetron). Only a minority of women needed parenteral nutrition. (Table 1). Decision to discharge was made according to cessation or alleviation of vomitus and nausea, signs of improved hydration and self-judgement of the woman of her own well-being.

Altogether 106 women participated. Only data of women with singleton pregnancies and admissions lasting at least overnight were included, and thus data of 95 women was eligible for analysis (figure 1). In Turku University Hospital, during the recruitment period, there were annually 32–68 admissions for HG (including readmissions of the same women), resulting in 433 admission periods, which gave estimation of the participation rate of 37% (162 periods/433 periods). Furthermore, the number of deliveries varied from 3708 to 4214 annually,[26] giving the admission rate due to HG of 0.8–1.7 %.
NVP was assessed with PUQE score concerning the previous 12 hours.[15] In accordance with the original version,[15] four NVP categories of ‘no’ (3 points), ‘mild’ (4–6 points), ‘moderate’ (7–12 points) and ‘severe’ (13–15 points) were formed. In addition, PUQE score was used as a continuous variable. PUQE scores were recorded only for study purposes, and thus the scores did not guide the decisions of treatment, admittance, discharge or readmission of the women.

Physical and mental QoL were estimated with two visual analog scales (VAS). Urine ketones were measured by urinalysis reagent strips (Mission®, Acon Laboratories, Inc, San Diego, USA), with detection levels of – (no detectable ketones), + (15 mg/dL=1.5 mmol/L), ++ (40 mg/dL=4.0 mmol/L) and +++ (80 mg/dL=8.0 mmol/L).

Basic demographic data of the women were obtained from hospital medical records including gestational weeks (gwk) at admission, parity (nulliparous/multiparous), body mass index (BMI, kg/m², calculated from pre-pregnancy weight and height), smoking (no/yes), marital status (cohabited/single), the total length of all admissions (days), the number of readmissions and urine ketones results. Age was calculated by comparing the date of reply to the date of birth.

Statistical analyses

Power calculation estimated minimum sample size of 58 (difference of three PUQE points between admission and discharge, alpha=5% and power of 80%, nQuery Advisor 4.0: paired t-test). The distribution of values was evaluated before statistical analyses both visually and statistically and the variables followed approximately normal distribution, enabling the use of parametric tests. Continuous variables were characterized using means, standard deviations (SD) and ranges and categorical variables using frequencies and percent. The severity of NVP was categorized according
to PUQE total score ('no'/'mild'/'moderate'/'severe') on both admission and discharge days.

Because of low number of values in category ‘mild NVP’ (n=2) on admission day and ‘severe NVP’ (n=1) on discharge day, these values were excluded from the analyses on admission and discharge days, respectively. In addition, when analyzing the change of PUQE categories (delta, Δ) between admission and discharge, due to the low number of values in the change of three PUQE categories (n=3), the change of three PUQE categories and the change of two PUQE categories were combined.

Concerning physical or mental QoL measured by VAS, the probability to belong to a higher (admission day) PUQE category or lower (discharge day) PUQE category was calculated with multinominal logistic regression on both admission and discharge days. Two separate analyses were performed: 1) analysis of the first admission period, and 2) analysis of readmission periods.

Generalized estimating equation (GEE) estimation was used when readmissions were included in analyses. The same analyses were performed for urine ketones categories (−/+/++/+++), but concerning the analyses of readmissions, the number of variables in different categories were too low for calculating the estimates and confidence intervals (CI) and thus only the first admission was eligible for analysis. In analysis of urine ketones, p-values were adjusted using Tukey-Kramer method because of multiple comparisons. Further, similar analyses on admission and discharge days using PUQE score as a continuous score were also performed. Comparisons both with physical and mental QoL VAS, urine ketones and continuous PUQE scores were calculated with linear mixed model for the first admission and linear mixed model with random intercept for patient for readmissions. All these results were adjusted for age, BMI and parity. In addition, continuous PUQE scores and VAS scores on admission and discharge days were compared using ANOVA.

The results are presented with odds ratios (OR) and beta (β) with 95% CI. Both unadjusted and adjusted results are shown in the tables, but only adjusted results are presented in the Results main
text. Statistical significance was set at $p$-values <0.05. Analyses were carried out using a 9.4 version of SAS Institute Inc. (Cary, NC, USA) for Windows.

Patient and public involvement statement

Patients and the public were not involved in the design or reporting of this study.

RESULTS

Basic characteristics

Basic characteristics of the women and the questionnaire data are presented in table 1 and table 2. On admission day, according to categorized PUQE scores, most of the women suffered from ‘moderate’ or ‘severe NVP’. On the contrary, on discharge day, most of the women had ‘mild’ or ‘moderate NVP’ (figure 2). Likewise, the mean continuous PUQE scores were higher on admission day compared to discharge day (table 2). Further, on admission day, physical and mental QoL scores were higher indicating worse QoL than on discharge day (table 2). On admission day, over half of the women had urine ketones, whereas most of the women had no urine ketones on discharge day (figure 3).

PUQE score category and the first admission period

When evaluating only the first admission period, on admission day women with worse physical QoL fell into a higher PUQE score category. Instead, worse mental QoL was not associated with PUQE score category. In addition, women with severe ketonuria (+++ vs no urine ketones) fell into higher PUQE score category ($P=0.016$). On discharge day of the first admission period, the women with better physical QoL fell into lower PUQE score category. Instead, mental QoL and the
presence of urine ketones were not associated with PUQE score categories. (Table 3 and supplementary Table 1.)

Table 1. Basic characteristics of the women. Total n=95.

|                          | n    | Mean ± SD or n (%) | Range       |
|--------------------------|------|--------------------|-------------|
| Age (years)              | 95   | 29.5 ± 5.0         | 18.9–42.7   |
| Gwk                      | 95   | 9.8 ± 2.5          | 6.3–20.3    |
| Parity                   | 93   |                    |             |
| Nulliparous              | 35 (37.6) |                 |             |
| Multiparous              | 58 (62.4) |                 |             |
| Pre-pregnancy BMI (kg/m²)| 91   | 25.2 ± 5.4         | 18.0–40.6   |
| Smoking                  | 90   |                    |             |
| Non-smokers              | 87 (96.7) |                |             |
| Smokers                  | 3 (3.3)    |                    |             |
| Marital status           | 92   |                    |             |
| Cohabited                | 85 (92.4) |                |             |
| Single                   | 7 (7.6)    |                    |             |
| Number of admissions     | 95   | 60 (63.2)          |             |
| ≥ 2                      | 35 (36.8) |                | 2–14        |
| Length of admissions (days) | 160* | 3.1 ± 2.2         | 1–12        |
| HG treatment             | 93   |                    |             |
| Intravenous fluids       | 93 (100.0) |               |             |
| Antiemetic medication    | 75 (80.6) |                |             |
| Metoclopramide           | 32 (42.7) |                |             |
| Ondansetron              | 12 (16.0) |                |             |
| Both                     | 31 (41.3) |                |             |
| Parenteral nutrition     | 5 (5.4)    |                    |             |

BMI = Body mass index  
GWK = Gestational week  
*Total number of all admission periods with available data
Table 2. Continuous PUQE scores and VAS scores.

|                     | First admission               | Readmissions                |
|---------------------|-------------------------------|-----------------------------|
|                     | n*   | mean ± SD | range | P     | n*   | mean ± SD | range | P     |
| PUQE score          |      |           |       |       |      |           |       |       |
| total points        | <0.0001 |         |       |       | <0.0001 |         |       |       |
| Admission day       | 68   | 11.6 ± 2.3 | 5–15 | <0.0001 | 54   | 12.3 ± 2.7 | 4–15 |
| Discharge day       | 65   | 6.5 ± 2.4  | 3–12 |         | 57   | 6.1 ± 2.8  | 3–13 |         |
| Physical QoL VAS    |      |           |       |       |      |           |       |       |
| Admission day       | 68   | 84.2±11.7 | 50–100 | <0.0001 | 54   | 83.4 ± 13.7 | 30–100 |
| Discharge day       | 65   | 45.4±19.3 | 4–90  |         | 57   | 47.4 ± 21.4 | 0–88 |         |
| Mental QoL VAS      |      |           |       |       |      |           |       |       |
| Admission day       | 68   | 65.4±17.9 | 15–100 | <0.0001 | 54   | 75.1 ± 19.7 | 12–100 |
| Discharge day       | 65   | 38.2±20.3 | 0–90  |         | 57   | 48.0 ± 26.0 | 0–90 |         |

ANOVA

PUQE = Pregnancy-Unique Quantification of Emesis Questionnaire
QoL = Quality of life
VAS = Visual analog scale 0–100, higher number indicates worse QoL

*Total number of the women = 95. Total number of available data for the first admission period = 93
and for readmission periods = 69.
Table 3. Physical and mental QoL in VAS on admission and discharge days and the probability to fall into a higher or lower PUQE score category*.

|                      | PUQE admission day |                      |                      |                      |                  |
|----------------------|--------------------|----------------------|----------------------|----------------------|------------------|
|                      | OR 95%CI P         | AOR 95%CI P          | OR 95%CI P           | AOR 95%CI P          | Δ                |
|                      |                    |                      |                      |                      |                  |
| Physical QoL VAS     | 1.10 1.04–1.16     | 0.001 1.09 1.03–1.16 | 0.95 0.92–0.98       | 0.001 0.94 0.91–0.98 | 0.95 0.93–0.98   |
| Mental QoL VAS       | 1.00 0.97–1.03     | 0.983 1.01 0.97–1.04 | 0.98 0.95–1.00       | 0.071 0.97 0.94–1.00 | 0.97 0.95–1.00   |

|                      |                     |                      |                      |                      |                  |
|                      |                    |                      |                      |                      |                  |
| Readmissions         | PUQE admission day |                      |                      |                      |                  |
|                      | OR 95%CI P         | AOR 95%CI P          | OR 95%CI P           | AOR 95%CI P          | Δ                |
|                      |                    |                      |                      |                      |                  |
| Physical QoL VAS     | 1.12 1.05–1.21     | 0.001 1.13 1.02–1.25 | 0.95 0.92–0.98       | 0.0007 0.93 0.90–0.97 | 0.96 0.93–1.00   |
| Mental QoL VAS       | 1.06 0.99–1.14     | 0.113 1.04 0.99–1.09 | 0.96 0.93–0.99       | 0.018 0.93 0.89–0.97 | 0.97 0.94–1.00   |

Multinominal logistic regression
AOR = Adjusted odds ratio: adjusted for age, body mass index and parity
PUQE = Pregnancy-Unique Quantification of Emesis Questionnaire
QoL = Quality of life
VAS = Visual analog scale
*Higher PUQE category on admission day and lower PUQE category on discharge day
PUQE score category and readmission periods

When including readmission periods, the results between physical QoL and PUQE score categories on admission day and on discharge day were similar to those including only the first admission period: worse physical QoL was associated with higher PUQE category on admission day and better physical QoL with lower PUQE category on discharge day. As for mental QoL, on admission day of readmission periods, mental QoL was not associated with categorized PUQE score. On discharge day of readmission periods, women with better mental QoL fell into lower PUQE score category. (Table 3.)

During both the first and readmission periods, the decrease (indicating better QoL) in both physical and mental QoL VAS score was associated with a decrease in the PUQE category (Table 3).

Continuous PUQE score, QoL scores and urine ketones

When PUQE scores were considered as continuous value, on admission day, worse physical QoL was associated with high continuous PUQE score both during the first admission period and when readmission periods were included. Worse mental QoL was associated with high continuous PUQE score only when including readmissions. On admission day, severe ketonuria (+++ vs no urine ketones) was associated with high continuous PUQE score at first admission ($P=0.026$ first admission, $P=0.270$ readmissions). On discharge day, both better physical QoL and better mental QoL were associated with low continuous PUQE scores during the first admission period and when including readmissions. On the contrary, urine ketones showed no association ($P=0.224$ first admission, $P=0.990$ readmissions). (Figure 4 and Figure 5).

The improvement (the mean difference in VAS values between admission and discharge days) in both physical QoL and mental QoL was associated with the change in continuous PUQE scores
during the first admission period and when including readmissions. Instead, no association emerged
between the change in continuous PUQE score and urine ketones ($P=0.620$ first admission,
$P=0.746$ readmissions). (Figure 4 and Figure 5).

**DISCUSSION**

We were the first to use PUQE questionnaire in hospitalized HG women in Finland. PUQE showed
to be a feasible clinical tool for assessing recovery; a marked improvement in PUQE score was
found when comparing scores between admission and discharge using PUQE both as categorized
and as continuous scores. In addition, high PUQE scores were associated with worse physical QoL
at admission and low PUQE scores with better physical QoL at discharge, both in the first
admission and in readmissions, indicating that PUQE scores were well concurrent with the
measurement of physical QoL. As for the associations between mental QoL and PUQE scores, the
association was found at both admission and discharge when PUQE scores were taken as
continuous scores in readmissions. Concerning mental QoL and categorized PUQE scores, the
association was found only in the adjusted results at discharge. These findings could be explained
by that even though PUQE questionnaire is measuring physical events of NVP, it may also reflect
mental QoL, especially in prolonged NVP: the overall misery of illness at admission and on
readmissions, and, on the other hand, the relief of improved condition at discharge. As for
ketonuria, only severe ketonuria at admission was associated with higher PUQE score category, but
otherwise ketonuria showed no connection with PUQE.

Our study has limitations. First, admission and discharge criteria were not strictly and uniformly
defined, being based on common current practice concerning the well-being of the women and
clinical signs or laboratory findings of dehydration. In Finland, the primary health care system is
based on national health coverage and practically all pregnant women visit free-of-cost public
maternity health care clinics. From there, women with HG are referred to hospitals to specialized
obstetrics clinics which are part of public services provided to all citizens by several hospital
districts. These clinics in hospitals are led by specialists in obstetrics and women can be admitted to
hospital or the treatment can continue in outpatient care. Therefore, hospital admittance and
discharge decisions were not dependent for instance on women having a health care insurance or
adequate wealth. Secondly, management between the patients was not totally similar, but
standardized clinical practice and the treatment protocols were followed. However, since there were
no strict admission or discharge criteria, no reliable biomarker to assess or predict the disease
severity of HG or the probability of readmission, the treatment decisions were clinically
individually assessed and possibly additionally affected by other determinants than physical
parameters, for instance factors related to women's housing situation or to family responsibilities.
Hence, these factors may have influenced our results. In addition, all women were enrolled in the
same unit, which further ensured that the treatment was uniform. Third, the number and reasons of
refusal to participate were not recorded and thus drop-out analyses were not possible to perform.
Therefore, we cannot rule out selection bias that only women who felt better participated and those
too sick did not, or vice versa. Moreover, the recruitment process took several years and was
dependent on the activity of the nurses in the ward who recruited the women according to
researchers' instructions on the top of their other duties without any extra compensation. In
addition, we lack the information of previous HG, albeit almost half of the participants were
nulliparas. The weight change during admission periods was not recorded although it could have
reflected the nutritional status of the women better than urine ketones. Due to low number of values
in urine ketones categories in readmissions, only analyses concerning the first admission period
with categorized PUQE scores were possible. Further, we used the original 12-hour PUQE, but
PUQE-24 could have recorded the previous day more accurately.
The merits of our study included a prospective study design with a large sample size based on power calculations. As the study questionnaire was available only in Finnish it practically ruled out foreign participants and thus our sample was quite homogenous and representative of the Finnish population. Compared to existing literature, we were the first to analyze the first admission period and readmissions separately, which roughly reflected milder HG (first admission) and prolonged HG (readmissions). This procedure also considered the possibility of learning effect since the women who were repeatedly hospitalized filled in the PUQE several times. Also, PUQE and exact VAS scores were available and analyzed only by the researchers, not by clinicians treating the women, and thus the discharge or readmittance were not dependent on the research data.

Similar to our study, only two previous studies, one Scandinavian three-center study from Norway[23] and another study from Nepal[24] applied PUQE questionnaire to evaluate the severity of NVP in hospitalized HG patients. In the Norwegian PUQE validation study, Birkeland et al[23] compared 38 hospitalized HG patients to 31 healthy pregnant outpatient controls. PUQE-24 scores of HG patients were recorded at admission (median 13) and discharge (median 6). In addition to the significant improvement in the continuous PUQE scores, also shifting to the lower PUQE categories was found between admission and discharge days. Furthermore, the PUQE scores correlated with the general wellbeing score. Although using PUQE-12, which evaluates NVP in the past 12 hours as originally validated by Koren et al.[16] we ended up with similar results as Birkeland et al’s study. Comparative results were obtained also in the Nepalese study;[24] all HG patients (n=81) admitted in B.P. Koirala Institute of Health Sciences during one year were selected and studied for different maternal characteristics. NVP symptoms were evaluated with modified PUQE daily, but information of whether they used PUQE-12 or PUQE-24 was not available in the publication. The mean PUQE score at admission was 12.4, whereas after two days it had decreased
to mean 5.5 (mean hospital stay 3.2 days), however, no analyses of categorized PUQE scores were performed. In addition, the authors in the Nepalese study did not analyze the usability of the PUQE score, mainly concentrating on describing the basic characteristics of the HG women.

As the diagnostic criteria of HG are currently not firmly established despite of very recent consensus definition,[27] and no reliable biomarker has been found,[9] the use of validated questionnaires would bring an important addition for diagnosis and treatment follow-up care. Owing to its shortness and simplicity, PUQE is practical, including both quality (vomitus and retching), quantity (frequency) and duration of NVP.[15] However, HG may manifest with other discomforts as well, and therefore, not all women hospitalized for HG fulfill the criteria of severe NVP rated by the highest PUQE scores, as was seen in our study, too. In addition to physical symptoms, other reasons such as emotional needs or social challenges can contribute to the need of hospitalization. To cover even better most of the HG symptoms, MacGibbon et al[28] have invented and validated a new HELP Score, which, besides including the severity of nausea, vomiting and retching, encompasses estimations of intake, psychosocial functioning, hydration, treatment effectiveness and overall progress. The superiority of a longer and detailed questionnaire which certainly gives a more comprehensive estimation of the illness than the considerably shorter PUQE questionnaire may be, however, lost by being too time-consuming in daily use in hospital setting.

PUQE questionnaire concentrates on physical symptoms. Adjacent to the original PUQE, Koren et al[15] used a single rating scale (0–10) of overall well-being. In their PUQE validation study,[16] lower value in the well-being score indicating lower QoL correlated with higher PUQE score. We used two VAS questions separately for both physical and mental QoL to assess QoL comprehensively. Predictably, the physical QoL was associated rather with PUQE than the mental
QoL. However, women suffering especially from prolonged and severe NVP report marked negative psychosocial effects to everyday life and even psychiatric symptoms continuing to postpartum.[5–7] Accordingly in our study, not only the mean mental QoL VAS score in readmissions was higher indicating worse mental QoL than the mean score in the first admission but also the associations between mental QoL and PUQE score emerged in women with readmissions, thus emphasizing the mental consequences of prolonged HG. To estimate QoL in women with NVP in more detail, Lacasse et al[29] have validated a NVPQOL-questionnaire. It evaluates QoL during the past week and consists of questions of four different domains: physical symptoms/aggravating factors, fatigue, emotions, and limitations. All in all, as mental well-being consists of wide spectrum of traits, comprehensive estimation with a single question is a challenge.

Ketones are produced when the body lacks carbohydrates, for example in fasting and in prolonged starvation.[30] Ketones can be easily measured from urine, and they are often detected in patients with HG. Thus, the existence of urine ketones has been used in guidelines as a sign of HG.[10,11] However, recent studies have questioned the importance of urine ketones in diagnosing HG since urine ketones are not present in all HG women.[9,12] In our study, the women had different categories of urine ketones both at admission and at discharge, although in most of the women they resolved during treatment and at discharge severe ketonuria (+++ was not detected. Thus, the clinical value of urine ketones in HG should be interpreted with caution, although severe ketonuria (+++ at admission was associated with higher PUQE score in our study, reflecting more severe NVP.

Conclusion

In our study, the PUQE questionnaire showed to be a usable tool to measure the severity of NVP symptoms in a hospital setting. Distinct alleviation of the scores were found between admission and
discharge when using the PUQE score both as categorized according to the original version and as continuous PUQE scores which supports the assessment of individual PUQE points instead of focusing only on the change of PUQE categories. Utilization of PUQE could thus bring feasible complement to the evaluation of the women hospitalized for HG, in addition to the simple question of physical well-being and measurement of urine ketones typically assessed in clinical care. Further challenge would be to develop a tool for estimating the optimal length of hospital admission for sufficient recovery and to avoid rapid readmission.

Figure legends

Figure 1. Flowchart of the study.

Figure 2. PUQE categories on admission and discharge days including a) the first admission and b) readmissions. PUQE = Pregnancy unique quantification of emesis questionnaire.

Figure 3. Urine ketones categories on admission and discharge days including a) the first admission and b) readmissions.

Figure 4. Associations between continuous PUQE score, physical QoL and mental QoL including the first admission. PUQE = Pregnancy unique quantification of emesis questionnaire; QoL = Quality of life.

Figure 5. Associations between continuous PUQE score, physical QoL and mental QoL including readmissions. PUQE = Pregnancy unique quantification of emesis questionnaire; QoL = Quality of life.

Author statement

Contributions
MN, PR and PP-K initialized and planned the study. LL collected the data with NK, LL planned the statistical analyses with MK and PP-K and LL wrote the first version of the manuscript. MK performed the statistical analyses. EO participated in data collection and practical arrangements at the hospital antenatal ward. All authors critically reviewed the manuscript and accepted the final submitted version.

Data sharing statement

The dataset of this study is available from the corresponding author on reasonable request.

Funding statement

This work was supported by Turku University Foundation (LL), Finnish Government (Research funds from specified government transfers, LL) and Finnish Cultural Foundation, Southwest Finland Regional Fund (LL). The funders were not involved in the study design, data collection, analysis or interpretation of the data or submitting the manuscript.

Competing interests

None declared.

Ethics statements

Patient consent for publication

Not applicable.

Ethics approval
The study was approved by the Joint Ethics Committees of University of Turku and Turku University Central Hospital, Turku, Finland (60/180/2011). All participants gave written informed consent.
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106 women recruited

5 twin pregnancies: excluded

6 admissions less than overnight: excluded

95 women final sample
Supplementary table 1. Urine ketones categories on admission and discharge days and the probability to fall into higher or lower PUQE score category*.

| First admission | PUQE admission day | PUQE discharge day |
|-----------------|--------------------|--------------------|
| Urine ketones   | OR     95%CI  P    | AOR   95%CI  P    | OR     95%CI  P    | AOR   95%CI  P    |
| + vs -          | 1.56   0.11–22.22 0.974 5.11 0.22–118.15 0.542 | 0.68   0.23–1.99 0.676 2.07 0.24–17.80 0.709 |
| ++ vs -         | 1.33   0.10–18.49 0.992 1.69 0.10–29.43 0.965 | 0.38   0.02–8.21 0.740 NA  NA |
| +++ vs -        | 7.00   1.00–48.81 0.049 16.00 1.44–177.82 0.016 | NA     NA      NA  NA |

Urine ketones categories: -/+/++/++++
Multinominal logistic regression
AOR = Adjusted odds ratio: adjusted for age, body mass index and parity
PUQE = Pregnancy-Unique Quantification of Emesis Questionnaire
NA = Not applicable
*Higher PUQE category on admission day and lower PUQE category on discharge day
### STROBE Statement—checklist of items that should be included in reports of observational studies

| Item No | Recommendation |
|---------|----------------|
| **Title and abstract** | |
| 1 | (a) Indicate the study’s design with a commonly used term in the title or the abstract |
| 1 | (b) Provide in the abstract an informative and balanced summary of what was done and what was found |

| **Introduction** | |
|----------------|----------------|
| 2 | Explain the scientific background and rationale for the investigation being reported |

| **Objectives** | |
| 3 | State specific objectives, including any prespecified hypotheses |

| **Methods** | |
|-------------|----------------|
| 4 | Present key elements of study design early in the paper |
| 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| 6 | (a) **Cohort study**—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up |
| 5,6 | (b) **Case-control study**—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls |
| 5,6 | (c) **Cross-sectional study**—Give the eligibility criteria, and the sources and methods of selection of participants |
| 7 | (b) **Cohort study**—For matched studies, give matching criteria and number of exposed and unexposed |
| NA | (c) **Case-control study**—For matched studies, give matching criteria and the number of controls per case |
| 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| 9 | Describe any efforts to address potential sources of bias |
| 10 | Explain how the study size was arrived at |
| 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| 12 | (a) Describe all statistical methods, including those used to control for confounding |
| 7-8 | (b) Describe any methods used to examine subgroups and interactions |
| 8 | (c) Explain how missing data were addressed |
| 16 | (d) **Cohort study**—If applicable, explain how loss to follow-up was addressed |
| NA | (e) **Case-control study**—If applicable, explain how matching of cases and controls was addressed |
| 16 | (f) **Cross-sectional study**—If applicable, describe analytical methods taking account of sampling strategy |
| 16 | (g) Describe any sensitivity analyses |

Continued on next page
## Results

**Participants** 13*

(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed

(b) Give reasons for non-participation at each stage

(c) Consider use of a flow diagram

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**Descriptive data** 14*

(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders

(b) Indicate number of participants with missing data for each variable of interest

(c) **Cohort study**—Summarise follow-up time (eg, average and total amount)

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**Outcome data** 15*

(a) *Cohort study*—Report numbers of outcome events or summary measures over time

*b Case-control study*—Report numbers in each exposure category, or summary measures of exposure

*b Cross-sectional study*—Report numbers of outcome events or summary measures

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**Main results** 16

(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

(b) Report category boundaries when continuous variables were categorized

(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

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**Other analyses** 17

Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

---

## Discussion

**Key results** 18

Summarise key results with reference to study objectives

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**Limitations** 19

Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

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**Interpretation** 20

Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence

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**Generalisability** 21

Discuss the generalisability (external validity) of the study results

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## Other information

**Funding** 22

Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

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*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.