OBSTETRICS

Mirtazapine or ondansetron for hyperemesis gravidarum: a randomized placebo-controlled trial

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BACKGROUND: Hyperemesis gravidarum is a severe pregnancy complication, and ondansetron is recommended as a second-line treatment despite lack of placebo-controlled trials. Case reports suggest that mirtazapine may be more effective, yet it has not been tested in a controlled trial.

OBJECTIVE: The aim of this trial was to examine the effect of mirtazapine and ondansetron in hyperemesis gravidarum.

STUDY DESIGN: The VOMIT (Validating the effect of Ondansetron and Mirtazapine In Treating hyperemesis gravidarum) trial was a randomized double-blind placebo-controlled multicenter trial conducted in 7 hospitals in Denmark 2019 through 2022. Fifty nine pregnant people with hyperemesis gravidarum defined by Pregnancy Unique Quantification of Emesis 24 score ≥13 or Pregnancy Unique Quantification of Emesis 24 score ≥7 if accompanied by weight loss ≥5% or need for hospitalization were included in the trial.

Participants were randomly assigned 1:1:1 to oral treatment with mirtazapine, ondansetron, or placebo for an intervention duration of 14 days. The primary outcome was reduction of Pregnancy Unique Quantification of Emesis 24 score on day 2 in intention-to-treat analyses. The trial was registered at Clinicaltrials.gov, NCT03785691.

RESULTS: Difference in Pregnancy Unique Quantification of Emesis 24 score change from baseline to day 2 in the mirtazapine (n=21) vs the placebo (n=20) group was −1.86 (95% confidence interval, −3.61 to −0.12; *P*=.04). In ondansetron (n=18) vs placebo, the difference was −0.51 (95% confidence interval, −2.32 to 1.30), and in mirtazapin vs ondansetron, the difference was −1.35 (95% confidence interval, −3.10 to 0.40).

The differences in Pregnancy Unique Quantification of Emesis 24 score change in mirtazapine vs both ondansetron and placebo were more evident after day 4. All analyses regarding symptom severity showed a tendency toward mirtazapine being a more effective treatment than both placebo and ondansetron; however, not all results were significant.

The incidence of mild to moderate adverse events was higher with mirtazapine, and serious adverse events were few and evenly distributed.

CONCLUSION: The trial showed reduced Pregnancy Unique Quantification of Emesis 24 score in the mirtazapine group compared with the placebo group among pregnant people with hyperemesis gravidarum. Ondansetron resulted in a smaller reduction in Pregnancy Unique Quantification of Emesis 24 score that did not reach statistical significance.

Key words: antenatal care, early pregnancy, hyperemesis gravidarum, medical disorders in pregnancy, mirtazapine, nausea and vomiting of pregnancy, randomized controlled trial

Introduction

Hyperemesis gravidarum (HG) is a severe pregnancy complication and current treatment options have been introduced despite sparse evidence of effect and are often not sufficiently effective in the most severe cases.[1]

While nausea and vomiting are common and often harmless symptoms of pregnancy, HG is a severe pregnancy complication affecting up to 4% of pregnancies.[2] It is the leading cause of hospitalization in the first trimester,[3] and symptoms may last throughout pregnancy. Diagnostic criteria include inability to eat and drink normally and strong limitations in daily activities.[4] The condition can cause dehydration, nutritional deficiencies, weight loss, anxiety, and depression that may persist after pregnancy,[5] while also increasing the risk of adverse fetal outcomes, including preterm birth and small for gestational age infants,[6,7] with the greatest fetal risk being termination of a wanted pregnancy due to symptom severity.[8–10]

Several antiemetic treatment options are available; however, evidence of effect in pregnancy is scarce. Oral ondansetron, a 5-hydroxytryptamine $(HT)_3$ receptor antagonist, is recommended as a second-line treatment in several guidelines,[11,12] and in 2014, it was used in 20% of pregnancies in the United States.[13] However, there are no placebo-controlled trials with oral ondansetron in pregnancy, and only limited studies of low evidence document the effect of ondansetron comparable with that of metoclopramide and promethazine.[1]

Despite current treatment options, sufficient symptom relief is often not attainable in the most severe cases.[11] Thus, there is a need to explore alternative treatment options.

Mirtazapine might be a relevant alternative as several case reports describe an effect in treatment resistant HG.[14–23] Pharmacologically, the antiemetic effect is well explained, and effect on postoperative nausea and vomiting is documented in randomized controlled trials (RCTs).[24] Mirtazapine is an antidepressant with affinity for several receptors, and the proposed antiemetic effect is attributable to its affinity to serotonin and histamine receptors. Like ondansetron, mirtazapine is a potent $5\text{-}HT_3$ receptor antagonist; however, unlike ondansetron, it also has affinity

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AJOG at a glance

Why was this study conducted?

Current treatments for hyperemesis gravidarum are based on limited evidence and are often not sufficiently effective in severe cases.

Key findings

In this randomized controlled trial, we found that mirtazapine significantly reduced Pregnancy Unique Quantification of Emesis 24 score when compared with placebo, while ondansetron resulted in a smaller reduction in Pregnancy Unique Quantification of Emesis score, not reaching statistical significance.

What does this add to what is known?

This study adds data on the effect of a new and more effective treatment for hyperemesis gravidarum as well as providing data on an already used treatment.

for the 5-HT_{2A} and 5-HT_{2C} receptors involved in appetite regulation. Additionally, like other antiemetics, mirtazapine is a potent antihistamine with affinity for the $histamine_1$ receptor. Furthermore, it might be advantageous due to its long half-life generating a stable plasma concentration with only one administration daily.[25]

There are no controlled trials with mirtazapine in pregnancy, and literature on safety of mirtazapine in pregnancy is sparse. In a systematic review, we identified no substantial evidence indicating that mirtazapine in pregnancy was associated with adverse outcomes in pregnancy or in offspring, other than neonatal adaptation syndrome.[26]

The available observational studies suggest a safety profile similar to that of selective serotonin reuptake inhibitors,[26,27] where an increased risk of adverse pregnancy outcomes is likely owed to other factors than mirtazapine treatment.[28]

The objective of this RCT was to examine the effect of mirtazapine and ondansetron on nausea and vomiting in pregnant people with HG.

Methods

The clinical trial Validating the effect of Ondansetron and Mirtazapine In Treating hyperemesis gravidarum is an investigator-initiated multicenter randomized double-blind placebo-controlled trial, randomizing participants to 1:1:1 to treatment with mirtazapine, ondansetron, or placebo. The protocol is available in the supplementary material.

Patient and public involvement

Patient representatives from the Danish and British patient organizations were consulted in the development of the trial and reviewed early drafts of the protocol. Their input led to considerations of both ethical issues and feasibility which ultimately resulted in changes in inclusion criteria and outcome measures as well as optional continued treatment after the end of intervention.

Eligibility

Participants were recruited from departments of obstetrics and gynaecology in 7 Danish hospitals during 2019 to 2022. The main inclusion criterion was Pregnancy Unique Quantification of Emesis 24 (PUQE-24) score of $\geq$13 or PUQE-24 $\geq$7 if accompanied by (1) weight loss >5% of prepregnancy weight and/or (2) need for hospitalization due to HG. The PUQE-24 score is a validated score grading the severity of nausea and vomiting in pregnancy within 24 hours and it ranges from 3 to 15.[29]

Both inpatients and outpatients were eligible regardless of whether other antiemetics had been tried. Oral and written informed consent was obtained before any trial procedures and after detailed information on possible adverse effects for both participant and fetus associated with trial medication.

Full list of inclusion and exclusion criteria is available in Figure 1.

Trial procedures

Participants were randomly assigned 1:1:1 to oral treatment with mirtazapine, ondansetron, or placebo for an intervention duration of 14 ($\pm$1) days, and both participants and trial personnel were blinded. Participants were scheduled for visits at baseline (Day-0), after 1 week ($\pm$1 day, Day-7), and 2 weeks ($\pm$1 day, Day-14).

In the first week, oral tablets were administered twice daily. In the mirtazapine group, the morning administration contained placebo, and the bedtime administration mirtazapine 15 mg. In the ondansetron group, both morning and bedtime administrations contained ondansetron 8 mg, and in the placebo group, both morning and bedtime administrations contained placebo.

All groups were allowed rescue medication with oral metoclopramide 10 mg maximum 3 administrations daily as well as intravenous rehydration when necessary.

At Day-7, dosage increase was optional, and if desired, trial medication was administered 4 times daily. In the mirtazapine group, the tablets then contained placebo in the morning, lunch, and early evening, and mirtazapine 30 mg at bedtime, whereas in the ondansetron group all 4 tablets contained ondansetron 8 mg, and in the placebo group, all 4 tablets were placebo.

If dosage increase was not requested, the treatment regimen from the first week continued in the second week.

Participants filled out baseline questionnaires at Day-0 and started trial medication on the evening of Day-0. The daily online questionnaires included information on adherence to trial medication, PUQE-24 score, and adverse events. More extensive questionnaires were filled out at Day-7 and Day-14.

At the end of the intervention on Day-14, optional request for continuation of trial medication was registered in which case the intervention for that specific participant was unblinded.

FIGURE 1
Inclusion and exclusion criteria

Inclusion criteria

- Written informed consent obtained before any trial related procedures are performed
- Female age >18 years
- Pregnant woman with gestational age between 5+0 and 19+6
- Nausea and vomiting without other obvious reason
- PUQE-24 score ≥13 OR

  PUQE-24 score ≥7 AND
  1. weight loss >5% of pre-pregnancy weight and/or
  2. hospitalisation due to nausea and vomiting of pregnancy

Compliance with this criterion on any given day within 3 days prior to screening (possibly not compliant with this criterion on day of randomisation)

- Singleton pregnancy
- The subject must be willing and able to comply with trial protocol

Exclusion criteria

- Mola pregnancy, multiple gestation or non-vital pregnancy
- Nausea and vomiting of other aetiology than NVP
- Allergic to selective 5-HT3-receptor antagonists
- Ongoing treatment with antidepressant medication
- Pre-existing diagnosis of chronic kidney disease, diabetes type 1 or 2, significant cardiac disease (incl. long QT syndrome), epilepsy, HIV. In case of other pre-existing conditions subjects might be excluded based on individual assessment by an MD
- Elevated liver enzymes (ALAT >150 U/l)
- Elevated creatinine (>100 µmol/l)
- ECG showing long QT-syndrome (QTc >460msek)
- Weekly alcohol intake >2 units of alcohol
- Not able to take medicine orally
- Not able to understand spoken and/or written Danish
- Participation in another investigational drug trial within current pregnancy

Randomization and blinding

Trial medication was manufactured by Glostrup Pharmacy, Glostrup, Denmark and mirtazapine and ondansetron were encapsulated to appear like placebo. Randomization was performed via *randomization.com* in blocks of 3 or 6 and stratified according to study site. Unique randomization numbers were

created for each treatment unit, and the study sites received the trial medication blinded ensuring blinding for both participants, treating physicians and researchers. The randomization lists were held by Glostrup Pharmacy ensuring blinding until the end of the trial.

Outcomes

The primary outcome was change in PUQE-24 score from baseline (Day-0) to day 2 in the 3 groups. Secondary outcomes included additional patient-reported outcomes related to treatment effects filled in online by the participants at Day-0, Day-7, and Day-14 as well as premature withdrawal from the intervention due to treatment failure, request to continue trial medication after the end of the intervention and others.

The questionnaires and full list of outcomes are available in the supplementary material.

Sample size

The trial was originally dimensioned to find a difference of $\geq$2 in the primary outcomes; change in PUQE-24 score from baseline to day 2 in the mirtazapine vs the placebo group and in the ondansetron vs the placebo group tested at a significance level of 0.025 for each. The power calculation was based on a standard deviation of difference in PUQE-24 score of 3, and with an expected dropout rate of 35%, 58 participants would be required in each of the 3 groups to obtain a power of 0.8. Rounding up, we initially aimed to include a total of 180 participants in the trial.

Due to slow recruiting rates and thus compromised power, the primary outcomes were reconsidered and changed while recruiting was ongoing.

The updated primary outcomes were hierarchically arranged and were to be tested one at a time at a significance level of 0.05 to compensate for the smaller sample size. The hierarchically arranged primary outcomes were change in PUQE-24 score from baseline to day 2 in 1) mirtazapine vs placebo, 2) ondansetron vs the placebo, 3) mirtazapine vs ondansetron (inferiority), and 4) mirtazapine vs ondansetron group (superiority). If an analysis did not reach statistical significance, the subsequent outcomes were regarded as exploratory.

The changes in the planned primary outcomes are documented in the Statistical Analysis Plan (Supplementary Material).

Statistical analyses

The primary analyses were intention-to-treat consisting of a linear mixed model with intervention group and baseline PUQE-24 score as covariates. Participants were included in the intention-to-treat analysis irrespectively of adherence to protocol.

Missing data were imputed using multiple imputation with the R-package miceRanger: Fast Imputation with Random Forrest[30] where the imputation model included all available baseline variables as well as outcome variables until the time of dropout.

Registration and approvals

The trial is registered at clinicaltrials.gov (NCT03785691), and the trial design has been published.[31] The trial was approved by the Regional Committees on Health Research Ethics in the Capital Region of Denmark (H-18047191), the Danish Medicines Agency (EudraCT 2018-002285-39), and the Danish Data Protection Agency (P-2019-75).

Results

Participants

A total of 59 participants were randomized from April 2019 through July 2022; 21 participants were randomized to treatment with mirtazapine, 18 to ondansetron, and 20 to placebo. Forty participants completed the intervention as planned, 15 (71%) in the mirtazapine group, 14 (78%) in the ondansetron group, and 9 (45%) in the placebo group (Figure 2).

Baseline characteristics were similar with mean PUQE-24 scores 13.0 (standard deviation [SD], 2.36), 12.8 (SD, 2.17), and 13.1 (SD, 1.56) in the mirtazapine, ondansetron, and placebo groups, respectively (Table 1).

Efficacy

Primary outcome

Difference in PUQE-24 score change from baseline to day 2 in the mirtazapine vs placebo group was −1.86 (95% confidence interval [CI], −3.61 to −012; P=.04), thus reaching statistical significance and allowing for testing ondansetron vs placebo as a co-primary outcome. Difference in PUQE-24 score change from baseline to day 2 in the ondansetron vs placebo group was −0.51 (95% CI, −2.32 to 1.30, P=.59) allowing for no further primary outcomes. Thus, mirtazapine vs ondansetron was regarded as a secondary outcome. Difference in PUQE-24 score change from baseline to day 2 in the mirtazapine vs ondansetron group was −1.35 (95% CI, −3.10 to 0.40).

PUQE-24 scores throughout the intervention are showed in Figure 3.

Secondary outcomes

Difference in PUQE-24 score change from baseline to Day-7 was −2.93 (95% CI, −4.42 to −1.44) in the mirtazapine vs placebo group, −0.81 (95% CI, −2.41 to −0.78) in the ondansetron vs placebo group, and −2.11 (95% CI, −3.45 to −0.77) in the mirtazapine vs the ondansetron group.

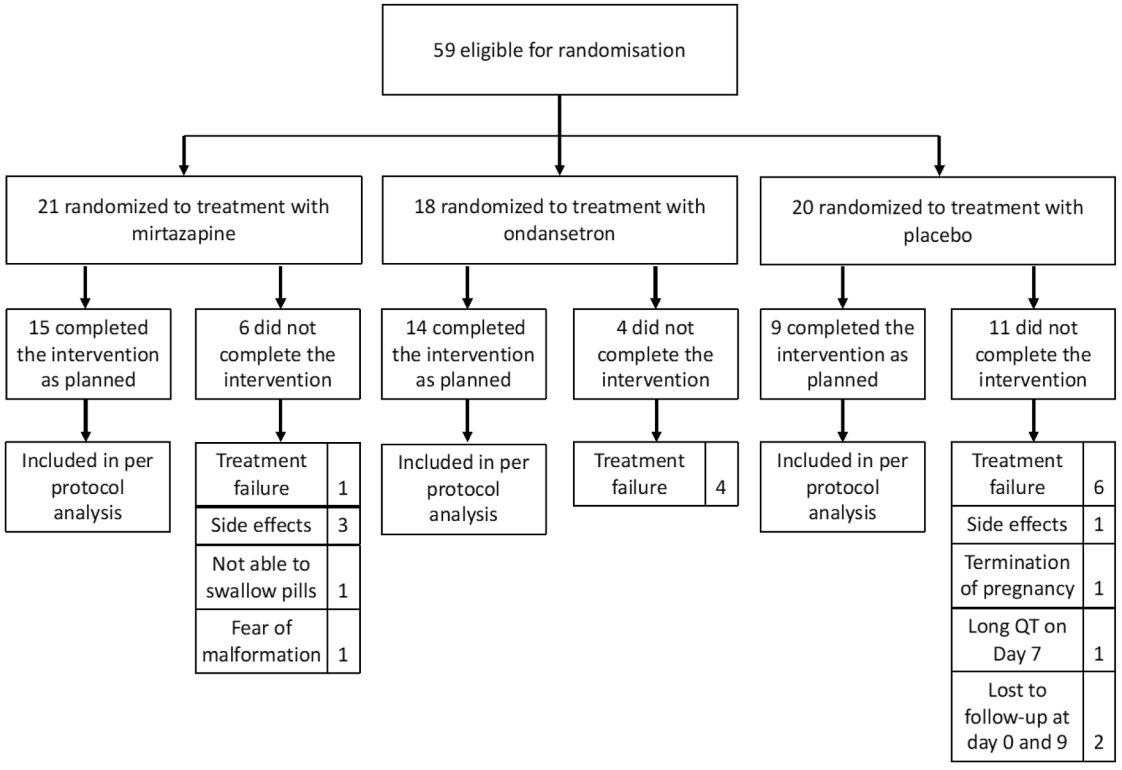
Difference in PUQE-24 score change from baseline to Day-14 was −2.43 (95% CI, −3.94 to −0.92) in the mirtazapine vs placebo group, −0.64 (95% CI, −2.26 to 0.99) in the ondansetron vs placebo group, and −1.79 (95% CI, −3.19 to −0.39) in the mirtazapine vs ondansetron group.

PUQE-24 score analyses were consistent across analyses with complete cases, imputed data, and per protocol as shown in Figure 3.

Analyses for the 2 additional questionnaires related to symptom severity, the Nausea and Vomiting of Pregnancy Quality of Life Questionnaire and the HyperEmesis Level Prediction Score Assessment, both resulted in greater symptom reduction in the mirtazapine group than the placebo and ondansetron groups on Day-7 and on Day-14.

The analyses for the EuroQol 5-Dimention 5-Level questionnaire

FIGURE 2
Flowchart of randomization and follow-up



showed no difference among the groups, and analyses for the modified Pittsburgh Sleep Quality Index showed reduced scores in the mirtazapine group when compared with the placebo and ondansetron groups.

Frequency of discontinuation of trial medication due to treatment failure was lower in the mirtazapine group when compared with the placebo group (−27.4% [95% CI, −51.0% to −3.2%]). In the mirtazapine vs the ondansetron group, the difference did not reach statistical significance (−17.5% [95% CI, −40.2% to 4.2%]).

Frequency of request for continuation of trial medication after the end of intervention was higher in the mirtazapine group than in the placebo group (36.7% [95% CI, 2.1% to 60.6%]), but the difference was not significant between the mirtazapine and the ondansetron group (18.7% [95% CI, 13.7% to 46.3%]).

Difference in the use of rescue metoclopramide, days of sick leave, amount of fluid treatments, and hospitalization was not significantly different between the groups; however, patient satisfaction with treatment on a 1 to 100 scale was higher with mirtazapine than both placebo (33.0 [95% CI, 10.2—55.9]) and ondansetron (28.9 [95% CI, 7.2—50.7]).

Primary and secondary outcomes are shown in Table 2, and Figure 3 shows PUQE-24 score in the different groups during the intervention.

Safety

Key safety end points are summarized in Table 3. The proportion of participants with any adverse event was highest in the mirtazapine group (86%), as compared with the ondansetron and placebo groups (72% and 40%, respectively). Most were mild or moderate in severity and resolved without apparent sequelae. The most common adverse events in the mirtazapine group were fatigue (48%), dizziness (24%), and headache (24%) and the most common adverse events in the ondansetron group were constipation (44%) and headache (33%).

Three participants (14%), all in the mirtazapine group, discontinued the trial due to side effects (all fatigue).

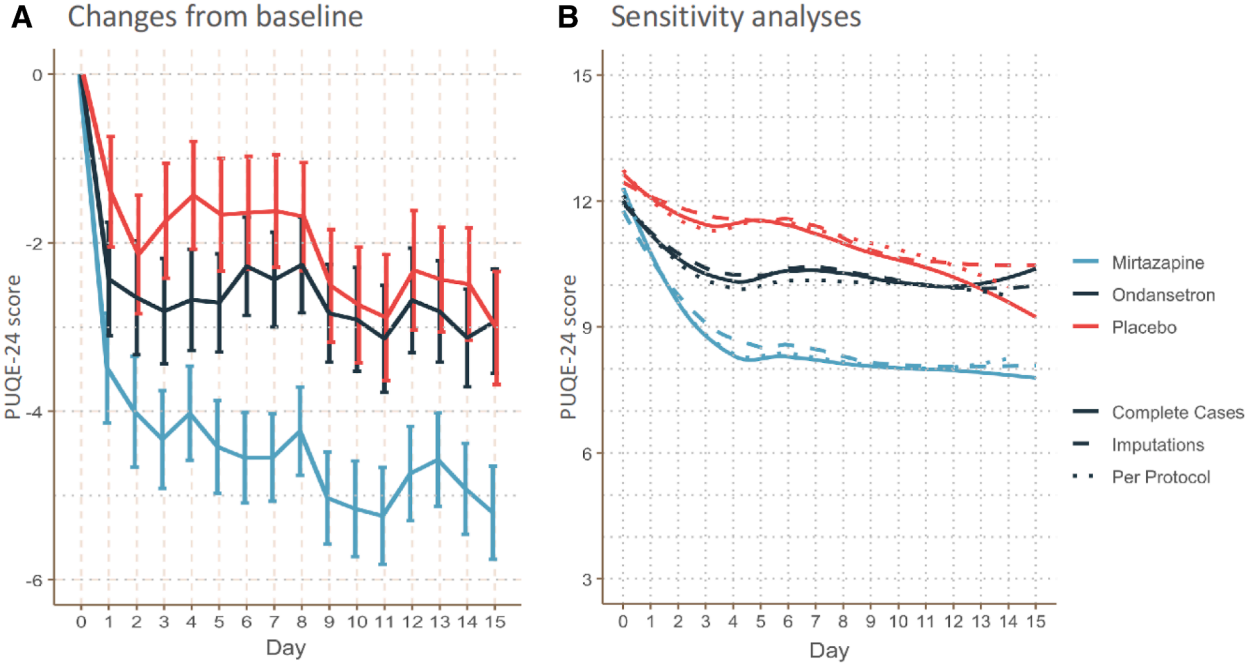
One serious adverse event was reported in each of the mirtazapine (5%) and the ondansetron (6%) groups, and 2 in the placebo (10%) group. One participant treated with mirtazapine gave birth to a child with congenital malformations. The child was diagnosed with unilateral membranous choanal atresia and stenosis of the pulmonary valve. At 2-year follow-up, no pulmonary stenosis was detectable on echocardiography, and the child had normal development. Since the maternal mirtazapine treatment was initiated at gestational age 11 weeks and

TABLE 1
Characteristics of the participants at baseline

Characteristics	Mirtazapine (n=21)	Ondansetron (n=18)	Placebo (n=20)
Age, median (minimum, maximum) y	28.1 [21.5, 35.2]	31.9 [21.7, 41.3]	28.1 [18.9, 36.3]
Inclusion week of gestation, median (minimum, maximum)	9.50 [7.00, 15.3]	9.79 [6.86, 19.6]	9.14 [6.71, 17.6]
Weight (kg), median (minimum, maximum)	69.4 [46.7, 105]	68.8 [51.6, 97.9]	67.3 [50.1, 114]
BMI (kg/m^2), median (minimum, maximum)	23.8 [16.7, 34.8]	24.6 [17.9, 34.3]	22.1 [17.8, 38.4]
Parity, n (%)			
0	7 (33.3)	7 (38.9)	9 (45.0)
1	11 (52.4)	9 (50.0)	10 (50.0)
2	2 (9.5)	2 (11.1)	0 (0.0)
3	1 (4.8)	0 (0.0)	1 (5.0)
PUQE-24 score, mean (SD)	13.0 (2.36)	12.8 (2.17)	13.1 (1.56)
History of pregnancy-related nausea and vomiting, n (%)	13 (61.9)	11 (61.1)	9 (45.0)
NVPQOL, median [minimum, maximum]	183 [146, 201]	183 [159, 205]	177 [130, 200]
HELP median [minimum, maximum]	34.0 [27.0, 42.0]	33.0 [23.0, 43.0]	34.0 [23.0, 39.0]
EQ-5D-5L, median [minimum, maximum]	0.526 [0.073, 0.912]	0.535 [-0.285, 0.778]	0.523 [0.048, 0.785]
Modified PSQI, median [minimum, maximum]	7.00 [3.00, 12.0]	10.0 [5.00, 12.0]	5.00 [3.00, 11.0]

BMI, body mass index; *EQ-5D-5L*, EuroQol-5 Dimension-5 Level; *HELP*, Hyperemesis Level Prediction; NVPQOL, Nausea and Vomiting in Pregnancy Quality of Life; PSQI, Pittsburgh Sleep Quality Index; *PUQE-24*, Pregnancy Unique Quantification of Emesis 24; *SD*, standard deviation.

FIGURE 3
PUQE-24 score during the intervention



PUQE-24, Pregnancy Unique Quantification of Emesis 24.

TABLE 2
Primary and secondary outcomes. Intention to treat

Endpoints	Mirtazapine (n=21)	Ondansetron (n=18)	Placebo (n=20)	Mirtazapine (n=21)	Ondansetron (n=18)	Placebo (n=20)
Primary		Day 2				
Least-squares mean change in PUQE-24 score [3–15 points]	−4.0 (−5.3 to −2.7)	−2.7 (−4.0 to −1.3)	−2.1 (−3.5 to −0.76)			
Least-squares mean difference vs placebo (CI)	−1.9 (−3.6 to −0.12), *P*=.04	−0.5 (−2.3–1.3), *P*=.59				
vs ondansetron (CI)	−1.4 (−3.1–0.40)					
Secondary	Day 7			Day 14		
Change in PUQE-24 [3–15 points]	−4.6 (−5.6 to −3.5)	−2.4 (−3.54 to −1.33)	−1.6 (−2.93 to −0.32)	−4.9 (−6.0 to −3.7)	−3.1 (−4.3 to −2.0)	−2.5 (−3.8 to −1.2)
Least-squares mean difference vs placebo (CI)	−2.9 (−4.4 to −1.4)	−0.81 (−2.41 to −0.78)		−2.4 (−3.9 to −0.9)	−0.64 (−2.3–0.99)	
vs ondansetron (CI)	−2.1 (−3.5 to −0.8)			−1.8 (−3.2 to −0.39)		
Change in PUQE-24 well-being score [0–10 points]	2.3 (1.5–3.0)	1.2 (0.37–1.9)	0.64 (−0.19–1.5)	2.5 (1.7–3.3)	1.4 (0.6–2.3)	1.5 (0.6–2.4)
Least-squares mean difference vs placebo (CI)	1.6 (0.64–2.6)	0.51 (−0.50–1.5)		0.99 (−0.06–2.04)	−0.05 (−1.1–1.2)	
vs ondansetron (CI)	1.1 (0.19–2.0)			1.0 (0.01–2.08)		
Change in number of daily vomiting episodes	−6.6 (−8.5 to −4.7)	−4.8 (−6.7 to −2.9)	−4.3 (−6.7 to −2.2)	−7.0 (−8.9 to −5.1)	−6.0 (−8.0 to −4.1)	−4.6 (−6.6 to −2.5)
Least-squares mean difference vs placebo (CI)	−2.4 (−4.1 to −0.64)	−0.53 (−2.3–1.3)		−2.5 (−4.2 to −0.74)	1.5 (−0.33–3.3)	
vs ondansetron (CI)	−1.8 (−3.4 to −0.20)			−0.98 (−2.6–0.61)		
Change in nausea VAS [0–100 points]	−22.5 (−30.4 to −14.6)	−8.0 (−16.6–0.55)	−8.6 (−17.9–0.60)	−28.9 (−37.3 to −20.6)	−13.3 (−22.4 to −4.3)	−21.8 (−32.3 to −11.4)
Least-squares mean difference vs placebo (CI)	−13.9 (−34.6 to −3.1)	0.59 (−11.0–12.2)		−7.1 (−19.0–4.8)	15.6 (4.5–26.8)	
vs ondansetron (CI)	−14.5 (−24.8 to −4.2)			−15.6 (−26.8 to - 4.5)		

(continued)

TABLE 2
Primary and secondary outcomes. Intention to treat *(continued)*

Endpoints	Mirtazapine (n=21)	Ondansetron (n=18)	Placebo (n=20)	Mirtazapine (n=21)	Ondansetron (n=18)	Placebo (n=20)
Change in NVPQOL (health-related quality of life for nausea and vomiting during pregnancy) [30−210 points]	−35.4 (−49.3−21.7)	−18.4 (−33.9 to −2.9)	−7.73 (−24.4−8.9)	−51.7 (−71.8 to −31.6)	−18.61 (−41.0−3.8)	−19.86 (−44.5−4.7)
Least-squares mean difference vs placebo (CI)	−27.7 (−48.9 to −6.6)	−10.7 (−33.6−12.3)		−31.8 (−62.7 to −0.95)	1.3 (−32.4−34.9)	
vs ondansetron (CI)	−17.1 (−37.7−3.5)			−33.1 (−63.0 to −3.1)		
Change in HELP (hyperemesis-level prediction) [0−50 points]	−11.7 (−15.0 to −8.45)	−7.4 (−10.9 to −3.9)	−2.9 (−7.0 to −1.1)	−12.9 (−16.6 to −9.17)	−7.02 (−11.14 to −2.90)	−6.1 (−10.6 to −1.6)
Least-squares mean difference vs placebo (CI)	−8.8 (−13.9 to −3.7))	−4.4 (−9.9−1.0)		−6.9 (−12.6 to −1.05)	−0.95 (−7.11−5.21)	
vs ondansetron (CI)	−4.4 (−9.2−0.46)			−5.9 (−11.5 to −0.33)		
Change in EQ-5D-5L (health-related quality of life) [-0,757−1 index score]	0.19 (0.07−0.30)	0.12 (0.00−0.25)	0.06 (−0.06−0.19)	0.20 (0.06−0.35)	0.07 (−0.09−0.23)	0.06 (−0.11−0.22)
Least-squares mean difference vs placebo (CI)	0.12 (−0.04−0.29)	0.06 (−0.12−0.23)		0.14 (−0.07−0.36)	0.01 (−0.22−0.24)	
vs ondansetron (CI)	0.06 (−0.10−0.23)			0.13 (−0.08−0.35)		
Change in modified PSQI (Pittsburg Sleep Quality Index) [0−21 points]	−2.2 (−3.2 to −1.1)	−1.4 (−2.5 to −0.9)	−0.43 (−1.6−0.73)	−2.1 (−3.3−0.96)	−0.73 (−2.1−0.62)	0.54 (−0.98−2.1)
Least-squares mean difference vs placebo (CI)	−1.7 (−3.3 to −0.18)	−0.96 (−2.6−0.65)		−2.6 (−4.6 to −0.72)	−1.3 (−3.3−0.76)	
vs ondansetron (CI)	−0.77 (−2.3−0.74)			−1.4 (−3.2−0.45)		
Change in weight (kg)	2.0 (1.3−2.7)	0.62 (0.10−1.3)	0.10 (−0.65−0.85)	2.5 (1.6−3.3)	0.03 (−0.89−0.95)	0.04 (−1.01−0.93)

(continued)

TABLE 2
Primary and secondary outcomes. Intention to treat *(continued)*

Endpoints	Mirtazapine (n=21)	Ondansetron (n=18)	Placebo (n=20)	Mirtazapine (n=21)	Ondansetron (n=18)	Placebo (n=20)
Least-squares mean difference vs placebo (CI)	1.9 (0.91–2.9)	0.52 (−0.53–1.6)		2.4 (1.2–3.7)	−0.01 (−1.4–1.3)	
vs ondansetron (CI)	1.4 (0.40–2.4)			2.4 (1.2–3.7)		
Area under the curve for PUQE-24 score during the intervention				129.1 (111.8–146.5)	153.9 (135.1–172.8)	166.6 (146.3–187.0)
Least-squares mean difference vs placebo (CI)				−24.8 (−50.3–0.68)	−12.7 (−40.6–15.2)	
vs ondansetron (CI)				−37.5 (−63.8 to −11.2)		
Mean patient satisfaction with treatment VAS [0–100 points]	65.9 (53.3–78.5)	50.2 (36.6–63.9)	34.7 (20.0–49.4)	68.7 (54.1–83.4)	39.8 (23.7–55.9)	35.7 (17.9–53.5)
Least-squares mean difference vs placebo (CI)	31.2 (22.2–50.1)	15.5 (−4.7–35.8)		33.0 (10.2–55.9)	4.1 (19.9–28.2)	
vs ondansetron (CI)	15.7 (2.9–34.2)			28.9 (7.2–50.7)		
Patient consideration of termination of pregnancy, n (%)	1 (4.8)	1 (5.6%)	1 (5.0)	0 (0)	1 (5.6)	0 (0)
Request for dosage increase, percentage points (95% CI)	24.6 (10.3–48.0)	57.6 (33.2–78.8)	70.20 (43.6–87.7)			
Difference vs placebo	−45.6 (−67.8 to −11.2)	−12.6 (−42.0–20.5)				
Difference vs ondansetron	−33.0 (−58.0 to −0.12)					

(continued)

TABLE 2
Primary and secondary outcomes. Intention to treat *(continued)*

Endpoints	Mirtazapine (n=21)	Ondansetron (n=18)	Placebo (n=20)	Mirtazapine (n=21)	Ondansetron (n=18)	Placebo (n=20)
Request for continuation of trial medication after end of intervention, percentage points (95% CI)				61.1 (38.5–79.8)	42.4 (21.3–66.9)	24.4 (8.8–51.9)
Difference vs placebo				36.7 (2.1–60.6)	18.0 (−15.7–46.3)	
Difference vs ondansetron				18.7 (−13.7–46.3)		
Use of rescue medication (metoclopramid pills during the last week)	5.5 (2.8–8.1)	5.3 (2.4–8.2)	5.2 (2.4–7.9)	7.3 (3.9–10.7)	6.0 (2.4–9.7)	6.5 (2.8–10.2)
Least-squares mean difference vs placebo (CI)	0.32 (−3.5–4.1)	0.13 (−3.8–4.1)		1.2 (−3.7–6.2)	−0.49 (−5.7–4.7)	
vs ondansetron (CI)	0.19 (−3.7–4.1)			0.74 (−4.3–5.6)		
Days on sick leave (days during the last week)	6.1 (5.2–7.1)	6.0 (5.0–7.0)	5.7 (4.7–6.7)	5.4 (4.3–6.5)	5.6 (4.4–6.7)	5.7 (4.5–6.9)
Least-squares mean difference vs placebo (CI)	0.44 (−0.89–1.8)	0.30 (−1.1–1.7)		−0.26 (−1.9–1.4)	−0.1 (1.8–1.6)	
vs ondansetron (CI)	0.13 (1.2–1.5)			−0.14 (−1.7–1.4)		
Amount of treatments with i.v. fluids (liter during last)	3.0 (2.0–4.1)	4.5 (3.4–5.6)	4.4 (3.3–5.5)	2.3 (1.6–3.0)	3.0 (2.3–3.8)	3.53 (2.78–4.28)
Least-squares mean difference vs placebo (CI)	−1.4 (−2.8–0.11)	0.11 (−1.4–1.7)		−1.2 (−2.2 to −0.29)	−0.51 (−1.5–0.51)	
vs ondansetron (CI)	−1.5 (−3.0–0.03)			−0.73 (−1.7–0.26)		

(continued)

TABLE 2
Primary and secondary outcomes. Intention to treat *(continued)*

Endpoints	Mirtazapine (n=21)	Ondansetron (n=18)	Placebo (n=20)	Mirtazapine (n=21)	Ondansetron (n=18)	Placebo (n=20)
Days of hospitalization (days during the last week)	0.53 (−0.06−1.1)	0.85 (0.23−1.5)	0.89 (0.27−1.5)	0.18 (−0.19−0.54)	0.50 (0.11−0.89)	0.53 (0.02−1.0)
Least-squares mean difference vs placebo (CI)	−0.37 (−1.23−0.50)	−0.05 (−0.92−0.83)		−0.35 (−0.99−0.28)	−0.03 (−0.67−0.61)	
vs ondansetron (CI)	−0.32 (−1.18−0.54)			−0.32 (−0.86−0.21)		
Occurrence of treatment failure, percentage points (95% CI)				4.8 (0.85−22.7)	22.2 (9−45.2)	32.2 (14.9−56.4)
Difference vs placebo				−27.4 (−51.3 to −3.2)	−10.0 (−36.9−18.1)	
Difference vs ondansetron				−17.5 (−40.2−4.2)		

CI, confidence interval; *EQ-5D-5L*, EuroQol-5 Dimension-5 Level; *HELP*, Hyperemesis Level Prediction; *i.v.*, intravenous; *NVPQOL*, Nausea and Vomiting in Pregnancy Quality of Life; *PSQI*, Pittsburgh Sleep Quality Index; *PUQE-24*, Pregnancy Unique Quantification of Emesis 24; *VAS*, visual analog scale.

5 days, after the development of the nasal cavities and the heart, the congenital malformations were considered unrelated to the treatment.

Birth outcomes were comparable between the groups and are available in the supplementary material.

Comment

Principal findings

This RCT showed reduced PUQE-24 score in the mirtazapine group compared with the placebo group among people with severe HG. In contrast, the tested ondansetron regimen did not reduce PUQE-24 score significantly; however, the study is potentially underpowered for this exposure and the specific dosing and interval between administrations might not be optimal.

The differences in PUQE-24 score between mirtazapine and both ondansetron and placebo are more evident after day 4, and the results are consistent across analyses with complete cases, imputed data, and per protocol. Additionally, all analyses regarding symptom severity showed a tendency toward mirtazapine being a more effective treatment than both placebo and ondansetron; however, not all results were significant.

The incidence of mild to moderate adverse events was higher with mirtazapine than with both ondansetron and placebo. Most of these adverse events were tolerable; however, few participants in the mirtazapine group discontinued treatment due to side effects. Serious adverse events were evenly distributed across the groups.

Results in the context of what is known

The present results are highly relevant, as they fill a knowledge gap in the treatment of HG. Mirtazapine is described as an effective treatment for HG in several case reports, yet so far there has been no systematically collected evidence of effect. This is the first controlled trial with mirtazapine in HG, and it is the first placebo-controlled trial with ondansetron, which is recommended as a second-line treatment.

TABLE 3
Adverse events[a]

Event	Mirtazapine (n=21)	Ondansetron (n=18)	Placebo (n=20)
	No. of patients (%)		
Any adverse event	18 (86)	13 (72)	8 (40)
Any adverse event leading to trial discontinuation	3 (14)	0	0
Any adverse event with outcome of death	0	0	0
Serious adverse events	1 (5)	1 (6)	1 (5)
Congenital malformation	1 (5)	0	0
Late miscarriage	0	1 (6)	1 (5)
Induced abortion	0	0	1 (5)
Adverse events occurring in ≥5% of the patients in either group			
Headache	5 (24)	7 (33)	2 (10)
Fatigue	10 (48)	2 (11)	0
Constipation	2 (10)	8 (44)	1 (5)
Dizziness	5 (24)	2 (11)	0
Diarrhea	3 (14)	1 (6)	0
Insomnia	1 (5)	2 (11)	1 (5)
Restlessness	0	1 (6)	2 (10)
Dry mouth	0	2 (11)	0
General discomfort	0	2 (11)	0
Palpitations	2 (10)	0	0
Back pain	0	1 (6)	0
Cough	0	1 (6)	0

[a] The safety population included all the patients who had undergone randomization and received at least one dose of any trial treatment. Adverse events were coded with the use of the preferred terms in the Medical Dictionary for Regulatory Activities, version 27.0.

Clinical and research implications

Current treatment recommendations in HG are based on scarce evidence as all available studies are small. As stated below, research in this severely ill pregnant patient population is challenging; however, optimally the present results should be confirmed in larger trials in the future. Even smaller trials allowing for subsequent meta-analyses would be valuable.

Nevertheless, the present results are likely to be incorporated in future treatment recommendations despite the limited number of participants in the trial.

Introducing mirtazapine as an evidence-based treatment option in severe cases of HG can be a step toward more efficient management. However, mirtazapine might not be tolerated by all due to side effects, and it should be noted that in our study hospitalization, treatment with intravenous fluids and days of sick leave were comparable between the groups. These outcomes represent heavy burdens to patients as well as expenses to the healthcare system.

Additionally, it should be considered that managing HG is multifaceted and treatment other than the pharmacologic should not be neglected. Management should be holistic, and lack of support from healthcare professionals is associated with adverse outcomes such as psychosocial consequences, termination of pregnancy, and suicidal ideation.[8,10,32]

Strengths and weaknesses

The present study is the first RCT investigating mirtazapine in HG, and it is the first placebo-controlled trial with ondansetron in HG. The study meets the demands of a recently published systematic review of treatments for HG, which found a need for further studies with emphasis on using validated scoring systems.[1] Additionally, a James Lind Alliance collaboration stated that investigating effective treatments for HG was a top priority for stakeholders.[33]

It is a strength that the study is placebo-controlled. As evident in Figure 3, PUQE-24 score is reduced during the intervention in all groups. This can be due to the spontaneous trajectory of HG or to the placebo effect, and it underlines the importance of doing placebo-controlled studies also in this patient population.

The compromised power is, however, an obvious limitation of this trial. This

increases the risk of type II errors, which might be the case for ondansetron.

The compromised power is partly due to COVID-19, but other factors also added to the difficulties. The patient population is challenging, and reasons for declining participation in this trial included unwillingness to consent to trial medication in pregnancy and declining because the potential participants were too debilitated to engage in a clinical trial. Additionally, trial personnel had difficulties gaining experience with the trial procedures due to the scarcity of eligible participants. Similar challenges have been reported in other clinical trials investigating treatment for HG.[34]

Conclusion

Mirtazapine demonstrated a significant reduction in PUQE-24 score among people with severe HG, while the tested ondansetron regimen did not yield a similar effect. This lack of response to ondansetron may be attributed to both compromised power and the tested treatment regimen, which may be suboptimal.

Given these findings, mirtazapine could be considered as an add-on or alternative treatment for people with treatment-resistant HG. ■

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The protocol for this trial has been presented at the International Colloquium on Hyperemesis Gravidarum 2019. The results have not been presented and are not accepted for upcoming presentation at scientific meetings.

The trial is registered at Clinicaltrials.gov.

Date of registration: December 21, 2018.

Identifier: NCT03785691.

URL: https://clinicaltrials.gov/study/NCT03785691

First patient enrolled: April 11, 2019.

Individual participant data in anonymized form (including data dictionaries) can be made available upon request. Study protocol and statistical analysis plan are available in the supplementary files.

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Supplementary material

Data completeness for all variables

Variable	Label	Total	Complete	Missing	Complete percent	Missing percent
record_id	Patient ID	59	59	0	100.00	0.00
ID	ID	59	59	0	100.00	0.00
Interventionsarm	Intervention arm	59	59	0	100.00	0.00
patient_inclusiondate	Inclusion date	59	59	0	100.00	0.00
patient_inclusion_site	Inclusion site	59	59	0	100.00	0.00
patient_age	Age at inclusion (y)	59	59	0	100.00	0.00
visit_preg_duration	Pregnancy duration at inclusion (d)	59	57	2	96.61	3.39
anamnese_prepregnancywgt	Prepregnancy weight (kg)	59	58	1	98.31	1.69
anamnese_prepregnancybmi	Prepregnancy BMI	59	58	1	98.31	1.69
vitals_weight	Weight (kg)	59	57	2	96.61	3.39
vitals_bmi	BMI	59	57	2	96.61	3.39
anamnese_pregnancynumber	Number of pregnancies	59	58	1	98.31	1.69
anamnese_birthnumber	Number of births	59	59	0	100.00	0.00
anamnese_ealiernvp	Previous pregnancy NVP	59	35	24	59.32	40.68
anamnese_ealiernnvpeffect___1	Sick leave (d) due to NVP in previous pregnancy	59	59	0	100.00	0.00
anamnese_ealiernnvpeffect___2	Sick leave (wks) due to NVP in previous pregnancy	59	59	0	100.00	0.00
anamnese_ealiernnvpeffect___3	Sick leave (mo) due to NVP in previous pregnancy	59	59	0	100.00	0.00
anamnese_ealiernnvpeffect___4	Medical treatment due to NVP in previous pregnancy	59	59	0	100.00	0.00
anamnese_ealiernnvpeffect___5	IV fluids due to NVP in previous pregnancy	59	59	0	100.00	0.00
anamnese_ealiernnvpeffect___6	Hospital admission due to NVP in previous pregnancy	59	59	0	100.00	0.00
anamnese_ealiernnvpeffect___7	Weight loss (>5%) due to NVP in previous pregnancy	59	59	0	100.00	0.00
anamnese_ealiernnvpeffect___8	Pregnancy termination due to NVP	59	59	0	100.00	0.00
anamnese_ealiernnvpeffect___9	Other effects due to NVP in previous pregnancy	59	59	0	100.00	0.00
anamnese_pre_puqe	Prehospital PUQE-24 score	59	59	0	100.00	0.00
anamnese_otherailmentdscrp	Other ailments	59	12	47	20.34	79.66
patient_occupation	Occupation	59	49	10	83.05	16.95
puqe_nausea_visit1	Nausea duration (visit 1)	59	56	3	94.92	5.08
puqe_vomit_visit1	Number of vomiting episodes (visit 1)	59	56	3	94.92	5.08
puqe_retching_visit1	Number of retching episodes (visit 1)	59	56	3	94.92	5.08
puqe_total_visit1	Total PUQE-24 score (visit 1)	59	56	3	94.92	5.08
puqe_qualityoflife_visit1	Well-being score (visit 1)	59	54	5	91.53	8.47
puqe_totalvomit_visit1	Daily vomiting episodes (visit 1)	59	51	8	86.44	13.56
puqe_averagenausea_visit1	Average nausea VAS (visit 1)	59	55	4	93.22	6.78

(continued)

Data completeness for all variables *(continued)*

Variable	Label	Total	Complete	Missing	Complete percent	Missing percent
puqe_nausea_visit2	Nausea duration (visit 2)	59	40	19	67.80	32.20
puqe_vomit_visit2	Number of vomiting episodes (visit 2)	59	40	19	67.80	32.20
puqe_retching_visit2	Number of retching episodes (visit 2)	59	40	19	67.80	32.20
puqe_total_visit2	Total PUQE-24 score (visit 2)	59	40	19	67.80	32.20
puqe_qualityoflife_visit2	Well-being score (visit 2)	59	40	19	67.80	32.20
puqe_totalvomit_visit2	Daily vomiting episodes (visit 2)	59	40	19	67.80	32.20
puqe_averagenausea_visit2	Average nausea VAS (visit 2)	59	38	21	64.41	35.59
puqe_nausea_visit3	Nausea duration (visit 3)	59	36	23	61.02	38.98
puqe_vomit_visit3	Number of vomiting episodes (visit 3)	59	36	23	61.02	38.98
puqe_retching_visit3	Number of retching episodes (visit 3)	59	36	23	61.02	38.98
puqe_total_visit3	Total PUQE-24 score (visit 3)	59	36	23	61.02	38.98
puqe_qualityoflife_visit3	Well-being score (visit 3)	59	36	23	61.02	38.98
puqe_totalvomit_visit3	Daily vomiting episodes (visit 3)	59	35	24	59.32	40.68
puqe_averagenausea_visit3	Average nausea VAS (visit 3)	59	35	24	59.32	40.68
puqe_nausea_online1	Nausea duration (day 1)	59	54	5	91.53	8.47
puqe_vomit_online1	Number of vomiting episodes (day 1)	59	54	5	91.53	8.47
puqe_retching_online1	Number of retching episodes (day 1)	59	53	6	89.83	10.17
puqe_total_online1	Total PUQE-24 score (day 1)	59	53	6	89.83	10.17
puqe_qualityoflife_online1	Well-being score (day 1)	59	53	6	89.83	10.17
puqe_totalvomit_online1	Daily vomiting episodes (day 1)	59	54	5	91.53	8.47
puqe_averagenausea_online1	Average nausea VAS (day 1)	59	52	7	88.14	11.86
puqe_nausea_online2	Nausea duration (day 2)	59	52	7	88.14	11.86
puqe_vomit_online2	Number of vomiting episodes (day 2)	59	52	7	88.14	11.86
puqe_retching_online2	Number of retching episodes (day 2)	59	52	7	88.14	11.86
puqe_total_online2	Total PUQE-24 score (day 2)	59	52	7	88.14	11.86
puqe_qualityoflife_online2	Well-being score (day 2)	59	51	8	86.44	13.56
puqe_totalvomit_online2	Daily vomiting episodes (day 2)	59	50	9	84.75	15.25
puqe_averagenausea_online2	Average nausea VAS (day 2)	59	50	9	84.75	15.25
puqe_nausea_online3	Nausea duration (day 3)	59	47	12	79.66	20.34
puqe_vomit_online3	Number of vomiting episodes (day 3)	59	47	12	79.66	20.34
puqe_retching_online3	Number of retching episodes (day 3)	59	47	12	79.66	20.34
puqe_total_online3	Total PUQE-24 score (day 3)	59	47	12	79.66	20.34
puqe_qualityoflife_online3	Well-being score (day 3)	59	46	13	77.97	22.03
puqe_totalvomit_online3	Daily vomiting episodes (day 3)	59	46	13	77.97	22.03
puqe_averagenausea_online3	Average nausea VAS (day 3)	59	42	17	71.19	28.81
puqe_nausea_online4	Nausea duration (day 4)	59	46	13	77.97	22.03
puqe_vomit_online4	Number of vomiting episodes (day 4)	59	46	13	77.97	22.03
puqe_retching_online4	Number of retching episodes (day 4)	59	46	13	77.97	22.03
puqe_total_online4	Total PUQE-24 score (day 4)	59	46	13	77.97	22.03

(continued)

Data completeness for all variables *(continued)*

Variable	Label	Total	Complete	Missing	Complete percent	Missing percent
puqe_qualityoflife_online4	Well-being score (day 4)	59	45	14	76.27	23.73
puqe_totalvomit_online4	Daily vomiting episodes (day 4)	59	45	14	76.27	23.73
puqe_averagenausea_online4	Average nausea VAS (day 4)	59	43	16	72.88	27.12
puqe_nausea_online5	Nausea duration (day 5)	59	43	16	72.88	27.12
puqe_vomit_online5	Number of vomiting episodes (day 5)	59	43	16	72.88	27.12
puqe_retching_online5	Number of retching episodes (day 5)	59	43	16	72.88	27.12
puqe_total_online5	Total PUQE-24 score (day 5)	59	43	16	72.88	27.12
puqe_qualityoflife_online5	Well-being score (day 5)	59	42	17	71.19	28.81
puqe_totalvomit_online5	Daily vomiting episodes (day 5)	59	42	17	71.19	28.81
puqe_averagenausea_online5	Average nausea VAS (day 5)	59	37	22	62.71	37.29
puqe_nausea_online6	Nausea duration (day 6)	59	43	16	72.88	27.12
puqe_vomit_online6	Number of vomiting episodes (day 6)	59	43	16	72.88	27.12
puqe_retching_online6	Number of retching episodes (day 6)	59	43	16	72.88	27.12
puqe_total_online6	Total PUQE-24 score (day 6)	59	43	16	72.88	27.12
puqe_qualityoflife_online6	Well-being score (day 6)	59	42	17	71.19	28.81
puqe_totalvomit_online6	Daily vomiting episodes (day 6)	59	41	18	69.49	30.51
puqe_averagenausea_online6	Average nausea VAS (day 6)	59	40	19	67.80	32.20
puqe_nausea_online7	Nausea duration (day 7)	59	38	21	64.41	35.59
puqe_vomit_online7	Number of vomiting episodes (day 7)	59	38	21	64.41	35.59
puqe_retching_online7	Number of retching episodes (day 7)	59	38	21	64.41	35.59
puqe_total_online7	Total PUQE-24 score (day 7)	59	38	21	64.41	35.59
puqe_qualityoflife_online7	Well-being score (day 7)	59	38	21	64.41	35.59
puqe_totalvomit_online7	Daily vomiting episodes (day 7)	59	38	21	64.41	35.59
puqe_averagenausea_online7	Average nausea VAS (day 7)	59	36	23	61.02	38.98
puqe_nausea_online8	Nausea duration (day 8)	59	39	20	66.10	33.90
puqe_vomit_online8	Number of vomiting episodes (day 8)	59	39	20	66.10	33.90
puqe_retching_online8	Number of retching episodes (day 8)	59	39	20	66.10	33.90
puqe_total_online8	Total PUQE-24 score (day 8)	59	39	20	66.10	33.90
puqe_qualityoflife_online8	Well-being score (day 8)	59	39	20	66.10	33.90
puqe_totalvomit_online8	Daily vomiting episodes (day 8)	59	39	20	66.10	33.90
puqe_averagenausea_online8	Average nausea VAS (day 8)	59	36	23	61.02	38.98
puqe_nausea_online9	Nausea duration (day 9)	59	36	23	61.02	38.98
puqe_vomit_online9	Number of vomiting episodes (day 9)	59	35	24	59.32	40.68
puqe_retching_online9	Number of retching episodes (day 9)	59	36	23	61.02	38.98
puqe_total_online9	Total PUQE-24 score (day 9)	59	35	24	59.32	40.68
puqe_qualityoflife_online9	Well-being score (day 9)	59	36	23	61.02	38.98
puqe_totalvomit_online9	Daily vomiting episodes (day 9)	59	36	23	61.02	38.98
puqe_averagenausea_online9	Average nausea VAS (day 9)	59	33	26	55.93	44.07
puqe_nausea_online10	Nausea duration (day 10)	59	32	27	54.24	45.76

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Data completeness for all variables *(continued)*

Variable	Label	Total	Complete	Missing	Complete percent	Missing percent
puqe_vomit_online10	Number of vomiting episodes (day 10)	59	32	27	54.24	45.76
puqe_retching_online10	Number of retching episodes (day 10)	59	32	27	54.24	45.76
puqe_total_online10	Total PUQE-24 score (day 10)	59	32	27	54.24	45.76
puqe_qualityoflife_online10	Well-being score (day 10)	59	32	27	54.24	45.76
puqe_totalvomit_online10	Daily vomiting episodes (day 10)	59	32	27	54.24	45.76
puqe_averagenausea_online10	Average nausea VAS (day 10)	59	30	29	50.85	49.15
puqe_nausea_online11	Nausea duration (day 11)	59	34	25	57.63	42.37
puqe_vomit_online11	Number of vomiting episodes (day 11)	59	34	25	57.63	42.37
puqe_retching_online11	Number of retching episodes (day 11)	59	34	25	57.63	42.37
puqe_total_online11	Total PUQE-24 score (day 11)	59	34	25	57.63	42.37
puqe_qualityoflife_online11	Well-being score (day 11)	59	34	25	57.63	42.37
puqe_totalvomit_online11	Daily vomiting episodes (day 11)	59	34	25	57.63	42.37
puqe_averagenausea_online11	Average nausea VAS (day 11)	59	33	26	55.93	44.07
puqe_nausea_online12	Nausea duration (day 12)	59	34	25	57.63	42.37
puqe_vomit_online12	Number of vomiting episodes (day 12)	59	34	25	57.63	42.37
puqe_retching_online12	Number of retching episodes (day 12)	59	34	25	57.63	42.37
puqe_total_online12	Total PUQE-24 score (day 12)	59	34	25	57.63	42.37
puqe_qualityoflife_online12	Well-being score (day 12)	59	34	25	57.63	42.37
puqe_totalvomit_online12	Daily vomiting episodes (day 12)	59	34	25	57.63	42.37
puqe_averagenausea_online12	Average nausea VAS (day 12)	59	33	26	55.93	44.07
puqe_nausea_online13	Nausea duration (day 13)	59	32	27	54.24	45.76
puqe_vomit_online13	Number of vomiting episodes (day 13)	59	32	27	54.24	45.76
puqe_retching_online13	Number of retching episodes (day 13)	59	31	28	52.54	47.46
puqe_total_online13	Total PUQE-24 score (day 13)	59	31	28	52.54	47.46
puqe_qualityoflife_online13	Well-being score (day 13)	59	32	27	54.24	45.76
puqe_totalvomit_online13	Daily vomiting episodes (day 13)	59	32	27	54.24	45.76
puqe_averagenausea_online13	Average nausea VAS (day 13)	59	31	28	52.54	47.46
puqe_nausea_online14	Nausea duration (day 14)	59	23	36	38.98	61.02
puqe_vomit_online14	Number of vomiting episodes (day 14)	59	23	36	38.98	61.02
puqe_retching_online14	Number of retching episodes (day 14)	59	23	36	38.98	61.02
puqe_total_online14	Total PUQE-24 score (day 14)	59	23	36	38.98	61.02
puqe_qualityoflife_online14	Well-being score (day 14)	59	23	36	38.98	61.02
puqe_totalvomit_online14	Daily vomiting episodes (day 14)	59	23	36	38.98	61.02
puqe_averagenausea_online14	Average nausea VAS (day 14)	59	21	38	35.59	64.41
puqe_nausea_online15	Nausea duration (day 15)	59	14	45	23.73	76.27
puqe_vomit_online15	Number of vomiting episodes (day 15)	59	14	45	23.73	76.27
puqe_retching_online15	Number of retching episodes (day 15)	59	14	45	23.73	76.27
puqe_total_online15	Total PUQE-24 score (day 15)	59	14	45	23.73	76.27
puqe_qualityoflife_online15	Well-being score (day 15)	59	14	45	23.73	76.27

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Data completeness for all variables *(continued)*

Variable	Label	Total	Complete	Missing	Complete percent	Missing percent
puqe_totalvomit_online15	Daily vomiting episodes (day 15)	59	14	45	23.73	76.27
puqe_averagenausea_online15	Average nausea VAS (day 15)	59	13	46	22.03	77.97
effectgoal_ab_pro_visit1	Abortion consideration due to NVP (visit 1)	59	54	5	91.53	8.47
effectgoal_ab_pro_visit2	Abortion consideration due to NVP (visit 2)	59	41	18	69.49	30.51
effectgoal_sickleavedays_visit2	Sick leave days (visit 2)	59	41	18	69.49	30.51
effectgoal_sickleavereason_visit2	Sick leave due to NVP (visit 2)	59	38	21	64.41	35.59
effectgoal_hospitaldays_visit2	Hospital days (visit 2)	59	41	18	69.49	30.51
effectgoal_hospitalreason_visit2	Hospitalization due to NVP (visit 2)	59	11	48	18.64	81.36
effectgoal_intravenous_visit2	IV fluid requirement (visit 2)	59	41	18	69.49	30.51
effectgoal_intravenous_l_visit2	IV fluid volume (L) (visit 2)	59	25	34	42.37	57.63
effectgoal_treat_sastifact_visit2	Satisfaction with treatment (visit 2)	59	39	20	66.10	33.90
vitals_weight_visit2	Weight (kg) (visit 2)	59	44	15	74.58	25.42
drug_treatment_incre_visit2	Dose increase request (visit 2)	59	42	17	71.19	28.81
effectgoal_ab_pro_visit3	Abortion consideration due to NVP (visit 3)	59	36	23	61.02	38.98
effectgoal_sickleavedays_visit3	Sick leave days (visit 3)	59	36	23	61.02	38.98
effectgoal_sickleavereason_visit3	Sick leave due to NVP (visit 3)	59	31	28	52.54	47.46
effectgoal_hospitaldays_visit3	Hospital days (visit 3)	59	36	23	61.02	38.98
effectgoal_hospitalreason_visit3	Hospitalization due to NVP (visit 3)	59	6	53	10.17	89.83
effectgoal_intravenous_visit3	IV fluid requirement (visit 3)	59	36	23	61.02	38.98
effectgoal_intravenous_l_visit3	IV fluid volume (L) (visit 3)	59	13	46	22.03	77.97
effectgoal_treat_sastifact_visit3	Satisfaction with treatment (visit 3)	59	36	23	61.02	38.98
vitals_weight_visit3	Weight (kg) (visit 3)	59	38	21	64.41	35.59
drug_continue_visit3	Continue medication request (visit 3)	59	59	0	100.00	0.00
medadm_meto_online1	Metoclopramide use (day 1)	59	53	6	89.83	10.17
medadm_meto_online2	Metoclopramide use (day 2)	59	52	7	88.14	11.86
medadm_meto_online3	Metoclopramide use (day 3)	59	47	12	79.66	20.34
medadm_meto_online4	Metoclopramide use (day 4)	59	44	15	74.58	25.42
medadm_meto_online5	Metoclopramide use (day 5)	59	42	17	71.19	28.81
medadm_meto_online6	Metoclopramide use (day 6)	59	42	17	71.19	28.81
medadm_meto_online7	Metoclopramide use (day 7)	59	38	21	64.41	35.59
medadm_meto_online8	Metoclopramide use (day 8)	59	40	19	67.80	32.20
medadm_meto_online9	Metoclopramide use (day 9)	59	37	22	62.71	37.29
medadm_meto_online10	Metoclopramide use (day 10)	59	31	28	52.54	47.46
medadm_meto_online11	Metoclopramide use (day 11)	59	35	24	59.32	40.68
medadm_meto_online12	Metoclopramide use (day 12)	59	35	24	59.32	40.68
medadm_meto_online13	Metoclopramide use (day 13)	59	31	28	52.54	47.46
medadm_meto_online14	Metoclopramide use (day 14)	59	23	36	38.98	61.02
medadm_meto_online15	Metoclopramide use (day 15)	59	11	48	18.64	81.36
studyend_reason	Reason for study end	59	58	1	98.31	1.69

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Data completeness for all variables *(continued)*

Variable	Label	Total	Complete	Missing	Complete percent	Missing percent
date_visit1	Visit 1 date	59	59	0	100.00	0.00
studyend_intervention_date	Intervention end date	59	59	0	100.00	0.00
studyend_length	Intervention duration (d)	59	57	2	96.61	3.39
partum_alive	Live birth	59	58	1	98.31	1.69
partum_weight	Birthweight (g)	59	55	4	93.22	6.78
partum_preg_days	Gestation days at birth	59	55	4	93.22	6.78
partum_preg_weeks	Gestation weeks at birth	59	55	4	93.22	6.78
partum_offspring_sex	Offspring sex	59	56	3	94.92	5.08
partum_birthmethod	Birth method	59	58	1	98.31	1.69
partum_complications	Complications at birth	59	52	7	88.14	11.86
partum_apgar_1_minut	Apgar at 1 min	59	55	4	93.22	6.78
partum_apgar_5_minut	Apgar at 5 min	59	55	4	93.22	6.78
partum_apgar_10_minut	Apgar at 10 min	59	28	31	47.46	52.54
partum_ph_vein	Umbilical vein pH	59	49	10	83.05	16.95
partum_ph_artery	Umbilical artery pH	59	43	16	72.88	27.12
partum_placenta_weight	Placenta weight (g)	59	49	10	83.05	16.95
partum_hospitalized	Neonatal hospitalization	59	52	7	88.14	11.86
partum_hospitalized_days	Neonatal hospitalization days	59	51	8	86.44	13.56
partum_malformation	Congenital malformation	59	53	6	89.83	10.17
eqd5d5l_mobility_visit1	EQ-5D-5L mobility (visit 1)	59	54	5	91.53	8.47
eqd5d5l_per_care_visit1	EQ-5D-5L personal care (visit 1)	59	54	5	91.53	8.47
eqd5d5l_activities_visit1	EQ-5D-5L usual activities (eg, work, study, household, family, or leisure) (visit 1)	59	54	5	91.53	8.47
eqd5d5l_pain_visit1	EQ-5D-5L pain/discomfort (visit 1)	59	54	5	91.53	8.47
eqd5d5l_anxiety_visit1	EQ-5D-5L anxiety/depression (visit 1)	59	54	5	91.53	8.47
eqd5d5l_health_visit1	EQ-5D-5L how good or bad is your health today? (visit 1)	59	51	8	86.44	13.56
eqd5d5l_mobility_visit2	EQ-5D-5L mobility (visit 2)	59	41	18	69.49	30.51
eqd5d5l_per_care_visit2	EQ-5D-5L personal care (visit 2)	59	41	18	69.49	30.51
eqd5d5l_activities_visit2	EQ-5D-5L usual activities (eg, work, study, household, family, or leisure) (visit 2)	59	41	18	69.49	30.51
eqd5d5l_pain_visit2	EQ-5D-5L pain/discomfort (visit 2)	59	41	18	69.49	30.51
eqd5d5l_anxiety_visit2	EQ-5D-5L anxiety/depression (visit 2)	59	41	18	69.49	30.51
eqd5d5l_health_visit2	EQ-5D-5L how good or bad is your health today? (visit 2)	59	35	24	59.32	40.68
eqd5d5l_mobility_visit3	EQ-5D-5L mobility (visit 3)	59	36	23	61.02	38.98
eqd5d5l_per_care_visit3	EQ-5D-5L personal care (visit 3)	59	36	23	61.02	38.98
eqd5d5l_activities_visit3	EQ-5D-5L usual activities (eg, work, study, household, family, or leisure) (visit 3)	59	36	23	61.02	38.98
eqd5d5l_pain_visit3	EQ-5D-5L pain/discomfort (visit 3)	59	36	23	61.02	38.98

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Data completeness for all variables *(continued)*

Variable	Label	Total	Complete	Missing	Complete percent	Missing percent
eqd5d5l_anxiety_visit3	EQ-5D-5L anxiety/depression (visit 3)	59	36	23	61.02	38.98
eqd5d5l_health_visit3	EQ-5D-5L how good or bad is your health today? (visit 3)	59	36	23	61.02	38.98
nvpqol1_visit1	NVPQOL-1 nausea (visit 1)	59	54	5	91.53	8.47
nvpqol2_visit1	NVPQOL-2 stomach discomfort (visit 1)	59	54	5	91.53	8.47
nvpqol3_visit1	NVPQOL-3 vomiting (visit 1)	59	54	5	91.53	8.47
nvpqol4_visit1	NVPQOL-4 retching without producing anything (visit 1)	59	54	5	91.53	8.47
nvpqol5_visit1	NVPQOL-5 poor appetite (visit 1)	59	53	6	89.83	10.17
nvpqol6_visit1	NVPQOL-6 worse symptoms in the evening (visit 1)	59	54	5	91.53	8.47
nvpqol7_visit1	NVPQOL-7 long periods without food intake (visit 1)	59	53	6	89.83	10.17
nvpqol8_visit1	NVPQOL-8 feeling worse when exposed to specific smells (visit 1)	59	54	5	91.53	8.47
nvpqol9_visit1	NVPQOL-9 feeling worse when exposed to certain foods (visit 1)	59	54	5	91.53	8.47
nvpqol10_visit1	NVPQOL-10 feeling exhausted (visit 1)	59	54	5	91.53	8.47
nvpqol11_visit1	NVPQOL-11 feeling worn out and without energy (visit 1)	59	54	5	91.53	8.47
nvpqol12_visit1	NVPQOL-12 feeling burnt out (visit 1)	59	53	6	89.83	10.17
nvpqol13_visit1	NVPQOL-13 feeling tired (visit 1)	59	54	5	91.53	8.47
nvpqol14_visit1	NVPQOL-14 feeling emotionally unstable (visit 1)	59	54	5	91.53	8.47
nvpqol15_visit1	NVPQOL-15 less interest in sex (visit 1)	59	54	5	91.53	8.47
nvpqol16_visit1	NVPQOL-16 feeling drained, sad, or depressed (visit 1)	59	54	5	91.53	8.47
nvpqol17_visit1	NVPQOL-17 feeling frustrated (visit 1)	59	54	5	91.53	8.47
nvpqol18_visit1	NVPQOL-18 feeling that you have had enough of feeling unwell (visit 1)	59	54	5	91.53	8.47
nvpqol19_visit1	NVPQOL-19 feeling that your symptoms are not part of a normal pregnancy (visit 1)	59	54	5	91.53	8.47
nvpqol20_visit1	NVPQOL-20 feeling that you cannot enjoy your pregnancy (visit 1)	59	54	5	91.53	8.47
nvpqol21_visit1	NVPQOL-21 everything requires effort (visit 1)	59	54	5	91.53	8.47
nvpqol22_visit1	NVPQOL-22 feeling that you have achieved less than you would like (visit 1)	59	53	6	89.83	10.17
nvpqol23_visit1	NVPQOL-23 things take longer to accomplish than usual (visit 1)	59	53	6	89.83	10.17
nvpqol24_visit1	NVPQOL-24 difficulties performing work and activities (visit 1)	59	54	5	91.53	8.47
nvpqol25_visit1	NVPQOL-25 difficulties maintaining normal social activities (visit 1)	59	54	5	91.53	8.47

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Data completeness for all variables *(continued)*

Variable	Label	Total	Complete	Missing	Complete percent	Missing percent
nvpqol26_visit1	NVPQOL-26 being dependent on your partner to do things you would normally do (visit 1)	59	54	5	91.53	8.47
nvpqol27_visit1	NVPQOL-27 having difficulty maintaining your home (visit 1)	59	54	5	91.53	8.47
nvpqol28_visit1	NVPQOL-28 having difficulty shopping (visit 1)	59	54	5	91.53	8.47
nvpqol29_visit1	NVPQOL-29 having difficulty cooking (visit 1)	59	54	5	91.53	8.47
nvpqol30_visit1	NVPQOL-30 having to reduce the time spent on work and other activities (visit 1)	59	54	5	91.53	8.47
nvpqol_totalscore_visit1	NVPQOL total score (visit 1)	59	51	8	86.44	13.56
nvpqol1_visit2	NVPQOL-1 nausea (visit 2)	59	41	18	69.49	30.51
nvpqol2_visit2	NVPQOL-2 stomach discomfort (visit 2)	59	41	18	69.49	30.51
nvpqol3_visit2	NVPQOL-3 vomiting (visit 2)	59	41	18	69.49	30.51
nvpqol4_visit2	NVPQOL-4 retching without producing anything (visit 2)	59	41	18	69.49	30.51
nvpqol5_visit2	NVPQOL-5 poor appetite (visit 2)	59	41	18	69.49	30.51
nvpqol6_visit2	NVPQOL-6 worse symptoms in the evening (visit 2)	59	41	18	69.49	30.51
nvpqol7_visit2	NVPQOL-7 long periods without food intake (visit 2)	59	40	19	67.80	32.20
nvpqol8_visit2	NVPQOL-8 feeling worse when exposed to specific smells (visit 2)	59	41	18	69.49	30.51
nvpqol9_visit2	NVPQOL-9 feeling worse when exposed to certain foods (visit 2)	59	41	18	69.49	30.51
nvpqol10_visit2	NVPQOL-10 feeling exhausted (visit 2)	59	41	18	69.49	30.51
nvpqol11_visit2	NVPQOL-11 feeling worn out and without energy (visit 2)	59	41	18	69.49	30.51
nvpqol12_visit2	NVPQOL-12 feeling burnt out (visit 2)	59	41	18	69.49	30.51
nvpqol13_visit2	NVPQOL-13 feeling tired (visit 2)	59	41	18	69.49	30.51
nvpqol14_visit2	NVPQOL-14 feeling emotionally unstable (visit 2)	59	40	19	67.80	32.20
nvpqol15_visit2	NVPQOL-15 less interest in sex (visit 2)	59	40	19	67.80	32.20
nvpqol16_visit2	NVPQOL-16 feeling drained, sad, or depressed (visit 2)	59	41	18	69.49	30.51
nvpqol17_visit2	NVPQOL-17 feeling frustrated (visit 2)	59	41	18	69.49	30.51
nvpqol18_visit2	NVPQOL-18 feeling that you have had enough of feeling unwell (visit 2)	59	41	18	69.49	30.51
nvpqol19_visit2	NVPQOL-19 feeling that your symptoms are not part of a normal pregnancy (visit 2)	59	41	18	69.49	30.51
nvpqol20_visit2	NVPQOL-20 feeling that you cannot enjoy your pregnancy (visit 2)	59	41	18	69.49	30.51
nvpqol21_visit2	NVPQOL-21 everything requires effort (visit 2)	59	41	18	69.49	30.51
nvpqol22_visit2	NVPQOL-22 feeling that you have achieved less than you would like (visit 2)	59	41	18	69.49	30.51

(continued)

Data completeness for all variables *(continued)*

Variable	Label	Total	Complete	Missing	Complete percent	Missing percent
nvpqol23_visit2	NVPQOL-23 things take longer to accomplish than usual (visit 2)	59	41	18	69.49	30.51
nvpqol24_visit2	NVPQOL-24 difficulties performing work and activities (visit 2)	59	41	18	69.49	30.51
nvpqol25_visit2	NVPQOL-25 difficulties maintaining normal social activities (visit 2)	59	41	18	69.49	30.51
nvpqol26_visit2	NVPQOL-26 being dependent on your partner to do things you would normally do (visit 2)	59	41	18	69.49	30.51
nvpqol27_visit2	NVPQOL-27 having difficulty maintaining your home (visit 2)	59	41	18	69.49	30.51
nvpqol28_visit2	NVPQOL-28 having difficulty shopping (visit 2)	59	40	19	67.80	32.20
nvpqol29_visit2	NVPQOL-29 having difficulty cooking (visit 2)	59	41	18	69.49	30.51
nvpqol30_visit2	NVPQOL-30 having to reduce the time spent on work and other activities (visit 2)	59	41	18	69.49	30.51
nvpqol_totalscore_visit2	NVPQOL total score (visit 2)	59	38	21	64.41	35.59
nvpqol1_visit3	NVPQOL-1 nausea (visit 3)	59	36	23	61.02	38.98
nvpqol2_visit3	NVPQOL-2 stomach discomfort (visit 3)	59	36	23	61.02	38.98
nvpqol3_visit3	NVPQOL-3 vomiting (visit 3)	59	36	23	61.02	38.98
nvpqol4_visit3	NVPQOL-4 retching without producing anything (visit 3)	59	36	23	61.02	38.98
nvpqol5_visit3	NVPQOL-5 poor appetite (visit 3)	59	36	23	61.02	38.98
nvpqol6_visit3	NVPQOL-6 worse symptoms in the evening (visit 3)	59	35	24	59.32	40.68
nvpqol7_visit3	NVPQOL-7 long periods without food intake (visit 3)	59	36	23	61.02	38.98
nvpqol8_visit3	NVPQOL-8 feeling worse when exposed to specific smells (visit 3)	59	35	24	59.32	40.68
nvpqol9_visit3	NVPQOL-9 feeling worse when exposed to certain foods (visit 3)	59	36	23	61.02	38.98
nvpqol10_visit3	NVPQOL-10 feeling exhausted (visit 3)	59	36	23	61.02	38.98
nvpqol11_visit3	NVPQOL-11 feeling worn out and without energy (visit 3)	59	36	23	61.02	38.98
nvpqol12_visit3	NVPQOL-12 feeling burnt out (visit 3)	59	36	23	61.02	38.98
nvpqol13_visit3	NVPQOL-13 feeling tired (visit 3)	59	36	23	61.02	38.98
nvpqol14_visit3	NVPQOL-14 feeling emotionally unstable (visit 3)	59	36	23	61.02	38.98
nvpqol15_visit3	NVPQOL-15 less interest in sex (visit 3)	59	36	23	61.02	38.98
nvpqol16_visit3	NVPQOL-16 feeling drained, sad, or depressed (visit 3)	59	36	23	61.02	38.98
nvpqol17_visit3	NVPQOL-17 feeling frustrated (visit 3)	59	36	23	61.02	38.98
nvpqol18_visit3	NVPQOL-18 feeling that you have had enough of feeling unwell (visit 3)	59	35	24	59.32	40.68
nvpqol19_visit3	NVPQOL-19 feeling that your symptoms are not part of a normal pregnancy (visit 3)	59	36	23	61.02	38.98

(continued)

Data completeness for all variables *(continued)*

Variable	Label	Total	Complete	Missing	Complete percent	Missing percent
nvpqol20_visit3	NVPQOL-20 feeling that you cannot enjoy your pregnancy (visit 3)	59	36	23	61.02	38.98
nvpqol21_visit3	NVPQOL-21 everything requires effort (visit 3)	59	36	23	61.02	38.98
nvpqol22_visit3	NVPQOL-22 feeling that you have achieved less than you would like (visit 3)	59	36	23	61.02	38.98
nvpqol23_visit3	NVPQOL-23 things take longer to accomplish than usual (visit 3)	59	36	23	61.02	38.98
nvpqol24_visit3	NVPQOL-24 difficulties performing work and activities (visit 3)	59	36	23	61.02	38.98
nvpqol25_visit3	NVPQOL-25 difficulties maintaining normal social activities (visit 3)	59	36	23	61.02	38.98
nvpqol26_visit3	NVPQOL-26 being dependent on your partner to do things you would normally do (visit 3)	59	36	23	61.02	38.98
nvpqol27_visit3	NVPQOL-27 having difficulty maintaining your home (visit 3)	59	36	23	61.02	38.98
nvpqol28_visit3	NVPQOL-28 having difficulty shopping (visit 3)	59	36	23	61.02	38.98
nvpqol29_visit3	NVPQOL-29 having difficulty cooking (visit 3)	59	36	23	61.02	38.98
nvpqol30_visit3	NVPQOL-30 having to reduce the time spent on work and other activities (visit 3)	59	35	24	59.32	40.68
nvpqol_totalscore_visit3	NVPQOL total score (visit 3)	59	33	26	55.93	44.07
help_1_visit1	HELP-1 nausea level most of the time (visit 1)	59	54	5	91.53	8.47
help_2_visit1	HELP-2 average number of vomiting episodes per day (visit 1)	59	54	5	91.53	8.47
help_3_visit1	HELP-3 retching episodes per day (without producing anything) (visit 1)	59	54	5	91.53	8.47
help_4_visit1	HELP-4 how often do you urinate? (visit 1)	59	53	6	89.83	10.17
help_5_visit1	HELP-5 average nausea/vomiting level 1 hour after medication or without medication (visit 1)	59	53	6	89.83	10.17
help_6_visit1	HELP-6 number of hours unable to work adequately at work and/or home (visit 1)	59	53	6	89.83	10.17
help_7_visit1	HELP-7 how well have you managed your nausea and vomiting? (visit 1)	59	53	6	89.83	10.17
help_8_visit1	HELP-8 able to eat/drink and keep it down for at least 1 hour (visit 1)	59	54	5	91.53	8.47
help_9_visit1	HELP-9 can you keep your antinausea medication down? (visit 1)	59	53	6	89.83	10.17
help_10_visit1	HELP-10 symptoms compared to last week? (visit 1)	59	54	5	91.53	8.47
help_total_visit1	HELP total score (visit 1)	59	51	8	86.44	13.56
help_1_visit2	HELP-1 nausea level most of the time (visit 2)	59	41	18	69.49	30.51
help_2_visit2	HELP-2 average number of vomiting episodes per day (visit 2)	59	41	18	69.49	30.51
help_3_visit2	HELP-3 retching episodes per day (without producing anything) (visit 2)	59	41	18	69.49	30.51
help_4_visit2	HELP-4 how often do you urinate? (visit 2)	59	40	19	67.80	32.20

(continued)

Data completeness for all variables *(continued)*

Variable	Label	Total	Complete	Missing	Complete percent	Missing percent
help_5_visit2	HELP-5 average nausea/vomiting level 1 hour after medication or without medication (visit 2)	59	41	18	69.49	30.51
help_6_visit2	HELP-6 number of hours unable to work adequately at work and/or home (visit 2)	59	40	19	67.80	32.20
help_7_visit2	HELP-7 how well have you managed your nausea and vomiting? (visit 2)	59	40	19	67.80	32.20
help_8_visit2	HELP-8 able to eat/drink and keep it down for at least 1 hour (visit 2)	59	41	18	69.49	30.51
help_9_visit2	HELP-9 can you keep your antinausea medication down? (visit 2)	59	41	18	69.49	30.51
help_10_visit2	HELP-10 symptoms compared to last week? (visit 2)	59	41	18	69.49	30.51
help_total_visit2	HELP total score (visit 2)	59	40	19	67.80	32.20
help_1_visit3	HELP-1 nausea level most of the time (visit 3)	59	36	23	61.02	38.98
help_2_visit3	HELP-2 average number of vomiting episodes per day (visit 3)	59	36	23	61.02	38.98
help_3_visit3	HELP-3 retching episodes per day (without producing anything) (visit 3)	59	36	23	61.02	38.98
help_4_visit3	HELP-4 how often do you urinate? (visit 3)	59	36	23	61.02	38.98
help_5_visit3	HELP-5 average nausea/vomiting level 1 hour after medication or without medication (visit 3)	59	35	24	59.32	40.68
help_6_visit3	HELP-6 number of hours unable to work adequately at work and/or home (visit 3)	59	35	24	59.32	40.68
help_7_visit3	HELP-7 how well have you managed your nausea and vomiting? (visit 3)	59	36	23	61.02	38.98
help_8_visit3	HELP-8 able to eat/drink and keep it down for at least 1 hour (visit 3)	59	36	23	61.02	38.98
help_9_visit3	HELP-9 can you keep your antinausea medication down? (visit 3)	59	36	23	61.02	38.98
help_10_visit3	HELP-10 symptoms compared to last week? (visit 3)	59	36	23	61.02	38.98
help_total_visit3	HELP total score (visit 3)	59	34	25	57.63	42.37
psqi1_visit1	PSQI-1 time to fall asleep (in min) (visit 1)	59	54	5	91.53	8.47
psqi2_visit1	PSQI-2 hours of actual sleep at night (visit 1)	59	49	10	83.05	16.95
psqi3a_visit1	PSQI-3a difficulty falling asleep within 30 minutes (visit 1)	59	54	5	91.53	8.47
psqi3b_visit1	PSQI-3b waking up during the night or early morning (visit 1)	59	54	5	91.53	8.47
psqi3c_visit1	PSQI-3c need to go to the toilet (visit 1)	59	53	6	89.83	10.17
psqi3d_visit1	PSQI-3d nausea and/or vomiting (visit 1)	59	54	5	91.53	8.47
psqi3e_visit1	PSQI-3e other sleep problems (visit 1)	59	53	6	89.83	10.17
psqi3e_andet_visit1	PSQI-3e other sleep problems, please describe (visit 1)	59	19	40	32.20	67.80
psqi4_visit1	PSQI-4 overall sleep quality (visit 1)	59	54	5	91.53	8.47

(continued)

Data completeness for all variables *(continued)*

Variable	Label	Total	Complete	Missing	Complete percent	Missing percent
psqi1_visit2	PSQI-1 time to fall asleep (in min) (visit 2)	59	41	18	69.49	30.51
psqi2_visit2	PSQI-2 hours of actual sleep at night (visit 2)	59	37	22	62.71	37.29
psqi3a_visit2	PSQI-3a difficulty falling asleep within 30 minutes (visit 2)	59	41	18	69.49	30.51
psqi3b_visit2	PSQI-3b waking up during the night or early morning (visit 2)	59	41	18	69.49	30.51
psqi3c_visit2	PSQI-3c need to go to the toilet (visit 2)	59	41	18	69.49	30.51
psqi3d_visit2	PSQI-3d nausea and/or vomiting (visit 2)	59	41	18	69.49	30.51
psqi3e_visit2	PSQI-3e other sleep problems (visit 2)	59	41	18	69.49	30.51
psqi3e_andet_visit2	PSQI-3e other sleep problems, please describe (visit 2)	59	8	51	13.56	86.44
psqi4_visit2	PSQI-4 overall sleep quality (visit 2)	59	41	18	69.49	30.51
psqi1_visit3	PSQI-1 time to fall asleep (in min) (visit 3)	59	36	23	61.02	38.98
psqi2_visit3	PSQI-2 hours of actual sleep at night (visit 3)	59	33	26	55.93	44.07
psqi3a_visit3	PSQI-3a difficulty falling asleep within 30 minutes (visit 3)	59	36	23	61.02	38.98
psqi3b_visit3	PSQI-3b waking up during the night or early morning (visit 3)	59	36	23	61.02	38.98
psqi3c_visit3	PSQI-3c need to go to the toilet (visit 3)	59	36	23	61.02	38.98
psqi3d_visit3	PSQI-3d nausea and/or vomiting (visit 3)	59	36	23	61.02	38.98
psqi3e_visit3	PSQI-3e other sleep problems (visit 3)	59	36	23	61.02	38.98
psqi3e_andet_visit3	PSQI-3e other sleep problems, please describe (visit 3)	59	9	50	15.25	84.75
psqi4_visit3	PSQI-4 overall sleep quality (visit 3)	59	36	23	61.02	38.98
visit2_dag	Null	59	46	13	77.97	22.03
visit3_dag	Null	59	39	20	66.10	33.90
medadm_morning.day1	Did you take your morning medication today? (day 1)	59	55	4	93.22	6.78
medadm_evening.day1	Did you take your evening medication today? (day 1)	59	55	4	93.22	6.78
medadm_morning.day2	Did you take your morning medication today? (day 2)	59	53	6	89.83	10.17
medadm_evening.day2	Did you take your evening medication today? (day 2)	59	53	6	89.83	10.17
medadm_morning.day3	Did you take your morning medication today? (day 3)	59	48	11	81.36	18.64
medadm_evening.day3	Did you take your evening medication today? (day 3)	59	48	11	81.36	18.64
medadm_morning.day4	Did you take your morning medication today? (day 4)	59	45	14	76.27	23.73
medadm_evening.day4	Did you take your evening medication today? (day 4)	59	45	14	76.27	23.73
medadm_morning.day5	Did you take your morning medication today? (day 5)	59	43	16	72.88	27.12

(continued)

Data completeness for all variables *(continued)*

Variable	Label	Total	Complete	Missing	Complete percent	Missing percent
medadm_evening.day5	Did you take your evening medication today? (day 5)	59	43	16	72.88	27.12
medadm_morning.day6	Did you take your morning medication today? (day 6)	59	43	16	72.88	27.12
medadm_lunch.day6	Did you take your lunch medication today? (day 6)	59	5	54	8.47	91.53
medadm_evening.day6	Did you take your evening medication today? (day 6)	59	43	16	72.88	27.12
medadm_morning.day7	Did you take your morning medication today? (day 7)	59	38	21	64.41	35.59
medadm_lunch.day7	Did you take your lunch medication today? (day 7)	59	31	28	52.54	47.46
medadm_evening.day7	Did you take your evening medication today? (day 7)	59	38	21	64.41	35.59
medadm_morning.day8	Did you take your morning medication today? (day 8)	59	40	19	67.80	32.20
medadm_lunch.day8	Did you take your lunch medication today? (day 8)	59	36	23	61.02	38.98
medadm_evening.day8	Did you take your evening medication today? (day 8)	59	40	19	67.80	32.20
medadm_morning.day9	Did you take your morning medication today? (day 9)	59	37	22	62.71	37.29
medadm_lunch.day9	Did you take your lunch medication today? (day 9)	59	34	25	57.63	42.37
medadm_evening.day9	Did you take your evening medication today? (day 9)	59	37	22	62.71	37.29
medadm_morning.day10	Did you take your morning medication today? (day 10)	59	33	26	55.93	44.07
medadm_lunch.day10	Did you take your lunch medication today? (day 10)	59	30	29	50.85	49.15
medadm_evening.day10	Did you take your evening medication today? (day 10)	59	33	26	55.93	44.07
medadm_morning.day11	Did you take your morning medication today? (day 11)	59	35	24	59.32	40.68
medadm_lunch.day11	Did you take your lunch medication today? (day 11)	59	32	27	54.24	45.76
medadm_evening.day11	Did you take your evening medication today? (day 11)	59	35	24	59.32	40.68
medadm_morning.day12	Did you take your morning medication today? (day 12)	59	35	24	59.32	40.68
medadm_lunch.day12	Did you take your lunch medication today? (day 12)	59	32	27	54.24	45.76
medadm_evening.day12	Did you take your evening medication today? (day 12)	59	35	24	59.32	40.68
medadm_morning.day13	Did you take your morning medication today? (day 13)	59	32	27	54.24	45.76

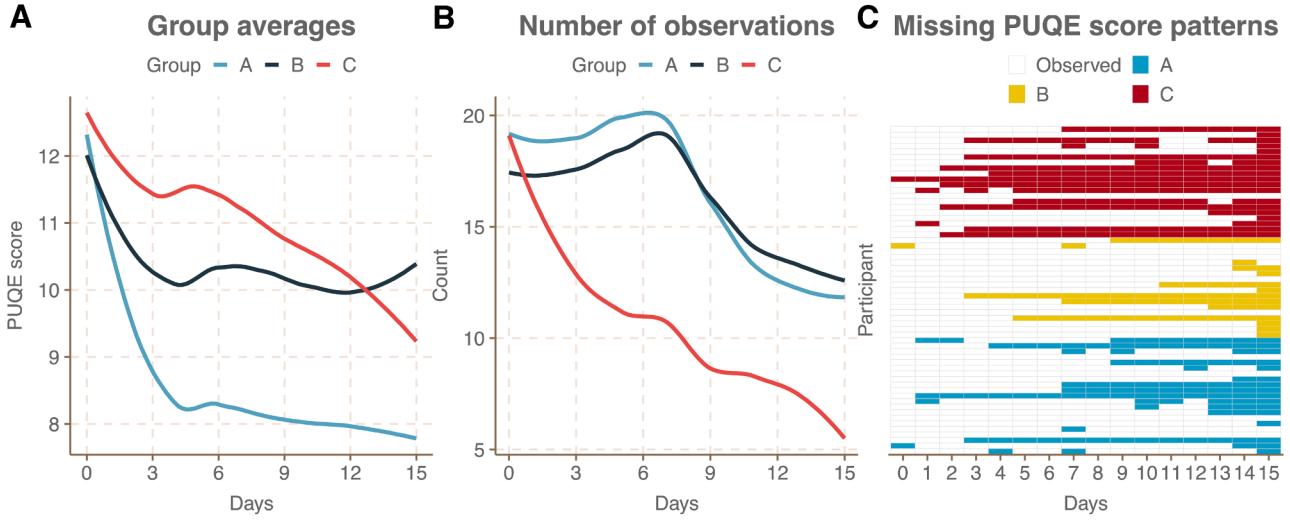
(continued)

Data completeness for all variables *(continued)*

Variable	Label	Total	Complete	Missing	Complete percent	Missing percent
medadm_lunch.day13	Did you take your lunch medication today? (day 13)	59	30	29	50.85	49.15
medadm_evening.day13	Did you take your evening medication today? (day 13)	59	32	27	54.24	45.76
medadm_morning.day14	Did you take your morning medication today? (day 14)	59	23	36	38.98	61.02
medadm_lunch.day14	Did you take your lunch medication today? (day 14)	59	21	38	35.59	64.41
medadm_evening.day14	Did you take your evening medication today? (day 14)	59	23	36	38.98	61.02
medadm_morning.day15	Did you take your morning medication today? (day 15)	59	11	48	18.64	81.36
medadm_lunch.day15	Did you take your lunch medication today? (day 15)	59	11	48	18.64	81.36
medadm_evening.day15	Did you take your evening medication today? (day 15)	59	11	48	18.64	81.36

BMI, body mass index; *EQ-5D-5L*, EuroQol-5 Dimension-5 Level; *HELP*, Hyperemesis Level Prediction; *IV*, intravenous; *NVPQOL*, Nausea and Vomiting in Pregnancy Quality of Life; *PSQI*, Pittsburgh Sleep Quality Index; *PUQE-24*, Pregnancy Unique Quantification of Emesis 24; *VAS*, visual analog scale.

SUPPLEMENTAL FIGURE 1
Data completeness



PUQE-24 score. (**A**) Mirtazapine, (**B**) Ondansetron, (**C**) Placebo.

SUPPLEMENTAL TABLE 1

Descriptive statistics for categorical and continuous partum outcomes and results for chi-square test for categorical partum outcomes across treatment groups

Partum outcomes	Mirtazepine (n=21)	Ondansetron (n=18)	Placebo (n=20)	Chi-square statistic
Birthweight (g), mean (SD)	3450 (644)	3550 (445)	3410 (601)	
Gestational age (wks), mean (SD)	38.8 (1.24)	38.3 (4.68)	37.6 (6.62)	
Umbilical vein pH, mean (SD)	7.33 (0.07)	7.35 (0.09)	7.33 (0.06)	
Umbilical artery pH, mean (SD)	7.24 (0.06)	7.24 (0.9)	7.25 (0.07)	
Placenta weight (g), mean (SD)	653 (136)	671 (122)	649 (135)	
Neonatal admission within the first month of life, n (%)	5 (23.8)	5 (27.8)	4 (20.0)	0.17, *P*=.85
Neonatal admission within the first month of life (d), mean (SD)	1.39 (4.00)	1.24 (3.27)	2.31 (5.07)	
Apgar score at 5 min <7, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Offspring gender (female), n (%)	14 (66.7)	9 (50.0)	10 (50.0)	0.85, *P*=.43
Mode of delivery, n (%)				1.08, *P*=.37
Vaginal	17 (81.0)	14 (77.8)	10 (50.0)	
Vacuum extraction	0 (0.0)	1 (5.6)	1 (5.0)	
Elective cesarean	1 (4.8)	1 (5.6)	3 (15.0)	
Acute cesarean	2 (9.5)	1 (5.6)	4 (20.0)	
Spontaneous abortion	0 (0.0)	0 (0.0)	1 (5.0)	
Elective abortion	0 (0.0)	1 (5.6)	1 (5.0)	
Delivery complications, n (%)	7 (33.3)	5 (27.8)	8 (40.0)	0.44, *P*=.65
Congenital malformations, n (%)	1 (4.8)	0 (0.0)	0 (0.0)	0.92, *P*=.40
Loss/termination of pregnancy, n (%)	0 (0.0)	1 (5.6)	2 (10.0)	1.06, *P*=.34

SD, standard deviation.

Birth outcome

SUPPLEMENTAL TABLE 2
Linear regression results for continuous partum outcomes across treatment groups (intention-to-treat population)

Continuous partum outcomes	Mirtazapine (n=21)	Ondansetron (n=18)	Placebo (n=20)
Birthweight (g)	3455.94 (3210.71–3701.16)	3533.60 (3268.40–3798.80)	3409.81 (3156.37–3663.24)
Least-squares mean difference vs placebo (CI)	77.66 (−284.06–439.39)	123.79 (−243.06–490.65)	
vs ondansetron (CI)	−46.13 (−398.36–306.10)		
Pregnancy duration (d)	272.29 (258.37–286.21)	268.06 (253.05–283.06)	263.83 (249.54–278.12)
Least-squares mean difference vs placebo (CI)	8.46 (−11.48–28.40)	4.23 (−16.49–24.95)	
vs ondansetron (CI)	4.23 (−16.23–24.70)		
Pregnancy duration (wks)	38.90 (36.91–40.89)	38.29 (36.15–40.44)	37.69 (35.65–39.73)
Least-squares mean difference vs placebo (CI)	1.21 (−1.64–4.06)	0.60 (−2.36–3.56)	
vs ondansetron (CI)	0.60 (−2.32–3.53)		
Apgar score at 1 min	9.64 (9.13–10.15)	9.59 (9.04–10.14)	9.20 (8.68–9.73)
Least-squares mean difference vs placebo (CI)	0.44 (−0.30–1.17)	0.38 (−0.38–1.14)	
vs ondansetron (CI)	0.05 (−0.70–0.80)		
Apgar score at 5 min	9.90 (9.75–10.06)	9.99 (9.81–10.16)	9.80 (9.64–9.96)
Least-squares mean difference vs placebo (CI)	0.10 (−0.12–0.33)	0.19 (−0.05–0.43)	
vs ondansetron (CI)	−0.08 (−0.32–0.16)		
Apgar score at 10 min	NA	NA	NA
Least-squares mean difference vs placebo (CI)	NA	NA	
vs ondansetron (CI)	NA		
Umbilical vein (pH)	7.34 (7.30–7.37)	7.34 (7.31–7.38)	7.33 (7.29–7.37)
Least-squares mean difference vs placebo (CI)	0.01 (−0.04–0.06)	0.01 (−0.04–0.07)	
vs ondansetron (CI)	−0.01 (−0.06–0.04)		
Umbilical artery (pH)	7.24 (7.20–7.27)	7.24 (7.20–7.28)	7.25 (7.21–7.29)
Least-squares mean difference vs placebo (CI)	−0.01 (−0.06–0.04)	−0.01 (−0.06–0.05)	
vs ondansetron (CI)	0.00 (−0.06–0.05)		
Placenta weight (g)	651.83 (598.52–705.14)	666.94 (609.13–724.74)	646.49 (591.14–701.85)
Least-squares mean difference vs placebo (CI)	5.33 (−71.66–82.33)	20.44 (−59.75–100.63)	
vs ondansetron (CI)	−15.11 (−93.67–63.45)		
Infant/mother hospitalized postpartum (d)	1.24 (−0.49–2.97)	1.39 (−0.51–3.30)	2.06 (0.24–3.87)
Least-squares mean difference vs placebo (CI)	−0.81 (−3.31–1.70)	−0.66 (−3.27–1.94)	
vs ondansetron (CI)	−0.15 (−2.73–2.43)		

CI, confidence interval; *NA*, not applicable.