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Thyroid-stimulating hormone and free thyroxine fail to predict the severity and clinical course of hyperemesis gravidarum: A prospective cohort study

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Abstract

Introduction: Little is known about the pathophysiology of hyperemesis gravidarum (HG). Proposed underlying causes are multifactorial and thyroid function is hypothesized to be causally involved. In this study, we aimed to assess the utility of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) as a marker and predictor for the severity and clinical course of HG.

Material and methods: We conducted a prospective cohort study including women admitted for HG between 5 and 20 weeks of gestation in 19 hospitals in the Netherlands. Women with a medical history of thyroid disease were excluded. TSH and FT4 were measured at study entry. To adjust for gestational age, we calculated TSH multiples of the median (MoM). We assessed HG severity at study entry as severity of nausea and vomiting (by the Pregnancy Unique Quantification of Emesis and nausea score), weight change compared with prepregnancy weight, and quality of life. We assessed the clinical course of HG as severity of nausea and vomiting and quality of life 1 week after inclusion, duration of hospital admissions, and readmissions. We performed multivariable regression analysis with absolute TSH, TSH MoMs, and FT4.

Results: Between 2013 and 2016, 215 women participated in the cohort. TSH, TSH MoM, and FT4 were available for, respectively, 150, 126, and 106 of these women. Multivariable linear regression analysis showed that lower TSH MoM was significantly associated with increased weight loss or lower weight gain at study entry (ΔKg; β = 2.00, 95% CI 0.47-3.53), whereas absolute TSH and FT4 were not. Lower TSH, not lower TSH MoM or FT4, was significantly associated with lower nausea and vomiting scores 1 week after inclusion (β = 1.74, 95% CI 0.36-3.11). TSH and FT4 showed no association with any of the other markers of the severity or clinical course of HG. Twenty-one out of 215 (9.8%) women had gestational transient thyrotoxicosis. Women with gestational transient thyrotoxicosis had a lower quality of life 1 week after inclusion than women with no gestational transient thyrotoxicosis (p = 0.03).

Conclusions: Our findings show an inconsistent role for TSH, TSH MoM, or FT4 at time of admission and provide little guidance on the severity and clinical course of HG.

KEYWORDS
disease severity marker, free thyroxine, hyperemesis gravidarum, nausea and vomiting in pregnancy, thyroid function, thyroid-stimulating hormone

1 | INTRODUCTION

Hyperemesis gravidarum (HG) is a severe form of nausea and vomiting in pregnancy (NVP) affecting 0.3%-3.6% of pregnancies.[1,2] HG is the most common reason for hospital admission in early pregnancy, but evidence-based effective treatment options are currently limited.[3,4] Because of the major impact of HG on maternal well-being and quality of life, a marker that could help to identify the severity and clinical course of HG would be of value for assessing a patient's prognosis and individualizing patient care.[5-8]

Little is known about the pathophysiology of HG. Proposed underlying causes are multifactorial and related to maternal endocrine

> **Key message**
>
> Thyroid measurement in women admitted for hyperemesis gravidarum provides little guidance on predicting disease severity and course.

and placental function as well as to gastrointestinal conditions, although recently genetic causes, including involvement of the growth differentiation factor-15 gene (*GDF15*), a cachexia gene, and its receptor have been implicated.[9,10]

Increased human chorionic gonadotropin (hCG) has been hypothesized to be causally involved in NVP and HG—hCG rises in the first trimester, which coincides with the peak in occurrence of NVP and HG.[11] However, the putative association of increased hCG with NVP symptoms was not confirmed upon systematic review, which found an association in only half of the included studies.[12] An explanation for the apparent discrepancy in findings could lie in the fact that hCG and thyroid-stimulating hormone (TSH) have biosimilar effects on the TSH receptor, which can result in hCG-induced thyroid stimulation, leading to a clinically relevant rise in free thyroxine (FT4) and subsequent suppression of TSH levels, a condition known as gestational transient thyrotoxicosis (GTT).[13] Hyperthyroidism can produce nausea, vomiting, and weight loss. Therefore, FT4 and TSH might be important factors in the etiology of HG.[14] A systematic review by Niemeijer et al[12] found few studies assessing the effect of TSH on the severity and clinical course of HG. We updated this systematic review[12] in order to put our findings in context, as shown in the Supporting Information (Appendix S1 and Table S1). Available evidence concerning possible associations between TSH and FT4 and measures of HG severity and clinical course shows conflicting results. None of the studies took gestational fluctuations of TSH into account. Niemeijer et al[12] called for better investigation of the use of TSH adjusted for pregnancy duration in future studies and currently no adjusted reference interval is available for gestational fluctuations of TSH.

In the present study, we aimed to assess the association between absolute TSH (without adjustments for gestational fluctuations), TSH multiple of the median (MoM), and FT4 and the severity and clinical course of HG to evaluate whether it is useful to measure thyroid function in order to predict the severity and clinical course of HG.

2 | MATERIAL AND METHODS

Our study used data from the Maternal and Offspring outcomes after Treatment of HyperEmesis by Refeeding (MOTHER) trial and associated cohort and is a prospective observational cohort study carried out between 2013 and 2016 that included women admitted for HG to 19 hospitals in the Netherlands.[15] The MOTHER trial, a multicenter open-label randomized controlled trial (RCT), aimed to evaluate the effect of early enteral tube feeding in addition to standard care for HG patients requiring hospital inpatient care, including intravenous fluid and anti-emetic medication. Women who were eligible for the RCT but who declined participation were asked to participate in the cohort. As early enteral tube feeding had no effect on perinatal and maternal outcomes, we deemed it appropriate to combine data of the RCT and cohort into one study population for the present study.[15] Participants of both trial and cohort provided informed consent.

We included women of 18 years and older who had been admitted to the hospital for HG between 5 and 20 weeks of gestation. Women were diagnosed with HG if they had severe nausea

and vomiting necessitating admission. More detailed description of study methodology has been previously published.[15]

2.1 | Thyroid-stimulating hormone and free thyroxine

According to local protocol, maternal blood was taken during routine laboratory testing on the first day of admission and analyzed; it was also stored frozen in the biobank, as reported in the previously published MOTHER protocol.[16] If TSH was included in local routine workup for HG, TSH was assessed in local laboratory at baseline. In August 2019, available frozen stored maternal samples from baseline were used to assess FT4 in one central laboratory.

We assessed TSH unadjusted for gestational fluctuations (absolute TSH), but we also calculated TSH MoMs in order to account for physiological fluctuation of TSH during pregnancy. To do so, we used data from the CATS study from Bestwick et al,[17] the largest available study in Europe, which assessed TSH medians in healthy pregnant women between 7 and 15 weeks of gestation. We calculated MoMs by dividing the participants' observed absolute TSH concentration by the expected TSH median for corresponding gestational age, as published by Bestwick et al.[17] GTT was defined as FT4 above 22.0 pmol/L according to the central laboratory's reference interval.[18]

2.2 | Data collection

Trained research staff completed a Case Report Form (CRF) to extract and report information from medical and obstetric antenatal files including age, parity, gestational age, weight, and comorbidity at study entry. Prepregnancy weight, ethnicity, and education level were self-reported at baseline, and if not reported, extracted from medical file, if available.

Severity of HG was measured at baseline by evaluating weight change, symptom severity, and quality of life. Weight change was defined as weight at baseline minus prepregnancy weight. Symptom severity and quality of life were measured by three self-reported validated questionnaires, filled out on the first day of inclusion. The Pregnancy Unique Quantification of Emesis and nausea (PUQE-24) measures the severity of nausea and vomiting: a higher PUQE-24 score (PUQE-24 ≥13) indicates severe vomiting.[19] The Hyperemesis Impact of Symptoms (HIS) questionnaire determines the impact of nausea and vomiting.[20] The Nausea and Vomiting in Pregnancy Quality of Life questionnaire (NVPQoL) measures the impact of nausea and vomiting specifically on quality of life.[21] A higher NVPQoL or HIS score indicates a lower quality of life or higher impact on maternal well-being.

The clinical course of HG was measured as symptom severity and quality of life 1 week after inclusion, duration of hospital admissions, and readmissions. We measured symptom severity by PUQE-24 score 1 week after inclusion and quality of life by NVPQoL and HIS

score 1 week after inclusion. Data on duration of hospital admissions and readmissions were collected from medical files. Duration of hospital admissions was measured in days; the day of admission and discharge both counted as 1 day.

2.3 | Statistical analyses

Normally distributed continuous variables are presented as means with standard deviations and skewed distributions as medians with interquartile ranges. Dichotomous and categorical variables are presented as frequencies with percentages.

We performed univariable and multivariable linear regression analyses to assess the association between absolute TSH, TSH MoM, and FT4 and continuous outcome variables. NVPQoL one week after inclusion and total days of hospital admission were not normally distributed and were logarithmically transformed to achieve normality. These logarithmically transformed variables were back-transformed and reported in proportionate differences and 95% CIs (expressed as percentages); normally distributed variables were reported in differences (β) and 95% CI. Dichotomous outcome variables were analyzed using univariable and multivariable logistic regression analyses and are reported as odds ratios with 95% CI. In the first model, we performed a univariable regression analysis. In the second model, we performed a multivariable regression analysis adjusted for age, pre-pregnancy BMI, ethnicity, and maternal education. Weight change was added as a confounder in the multivariable analysis for clinical course of HG based on available literature.[22]

A sensitivity analysis was used for assessing whether baseline characteristics and measures of the severity and clinical course of HG differed between included and excluded participants in our study. We also assessed whether baseline characteristics and measures of the severity and clinical course of HG differed between women with and without GTT, using chi-squared test, Fisher's exact test, Mann-Whitney U test, and independent Student's t test. Values of p that were <0.05 were considered statistically significant. SPSS Statistics 25.0 for Windows (IBM Corp.) was used for all analyses.

2.4 | Ethical approval

The MOTHER trial and cohort were registered at www.trialregister.nl (NTR4197) and have been approved by the research ethics committee of the Academic Medical Center (NL41011.018.12) on 3 April 2013.

3 | RESULTS

In total, 215 women were included in the combined cohort: 115 women in the RCT and another 100 women in the associated observational cohort. Nine women with a medical history of hypo- or hyperthyroidism or with a clinical hypothyroidism (TSH ≥4.0 mE/L) at

time of inclusion were excluded from the analysis (Figure 1). TSH at time of inclusion was measured in 150 women. We were able to calculate TSH MoMs for 126 women, based on TSH medians available from Bestwick et al,[17] and we were able to measure FT4 in 106 women, based on the number of frozen stored blood samples available.

Baseline characteristics and measurements of the clinical course of HG and disease severity of participants are shown in Table 1. First admission at inclusion significantly differed between women with (92.7%) and without (80.0%) absolute TSH levels available ($p = 0.01$) (Table S2). Gestational age ($p < 0.01$) and first admission ($p = 0.03$) at inclusion significantly differed between women with and without TSH MoM available, but measurements of the severity and clinical course of HG did not (Table S3). We did not find any significant differences in baseline characteristics and outcome variables between women with and without FT4 available (Table S4).

Lower TSH MoM was significantly associated with increased weight loss at baseline compared with prepregnancy weight (kg; $\beta = 2.00$, 95% CI 0.47-3.53, $p = 0.01$), whereas absolute TSH and FT4 were not (Tables 2 and 3). Neither TSH, nor TSH MoM, nor FT4 were significantly associated with other markers of HG severity at baseline including the PUQE-24, HIS, and NVPQoL scores.

Regarding the association between TSH and FT4 and the clinical course of HG, we found that lower absolute TSH was significantly associated with lower nausea and vomiting scores 1 week after inclusion in multivariable regression analysis ($\beta = 1.74$, 95% CI 0.36-3.11, $p = 0.01$) (Table 2a). Lower TSH MoM was only significantly associated with lower nausea and vomiting scores 1 week after inclusion in univariable regression analysis ($\beta = 1.41$, 95% CI 0.11-2.72, $p = 0.03$) (Table 2b). FT4 was not associated with the severity of nausea and vomiting 1 week after inclusion (Table 3). No significant association was found between TSH, TSH MoM, or FT4 and quality of life 1 week after inclusion, duration of hospital admissions, and readmissions.

Comparing women with and without GTT at baseline, we found that women with GTT (n = 21) had a higher HIS score 1 week after inclusion then women with no GTT ($p = 0.03$) as shown in Table 4. No significant differences in baseline characteristics or other outcome variables were found between women with and without GTT.

4 | DISCUSSION

We found that, in line with expectations, women who had lower TSH MoM, had more weight loss upon hospitalization with HG. Furthermore, 10% of women hospitalized with HG had concurrent GTT, associated with higher HIS scores 1 week after inclusion. In contrast to the literature, and not in line with expectations, lower TSH was also associated with markedly lower nausea and vomiting scores 1 week after baseline. Thyroid function showed no association with any of the other outcome measures of disease severity or course of HG. The fact that our findings present an inconsistent role for thyroid function in HG does not support the use of thyroid measurements as marker or predictor for HG disease severity and clinical course.
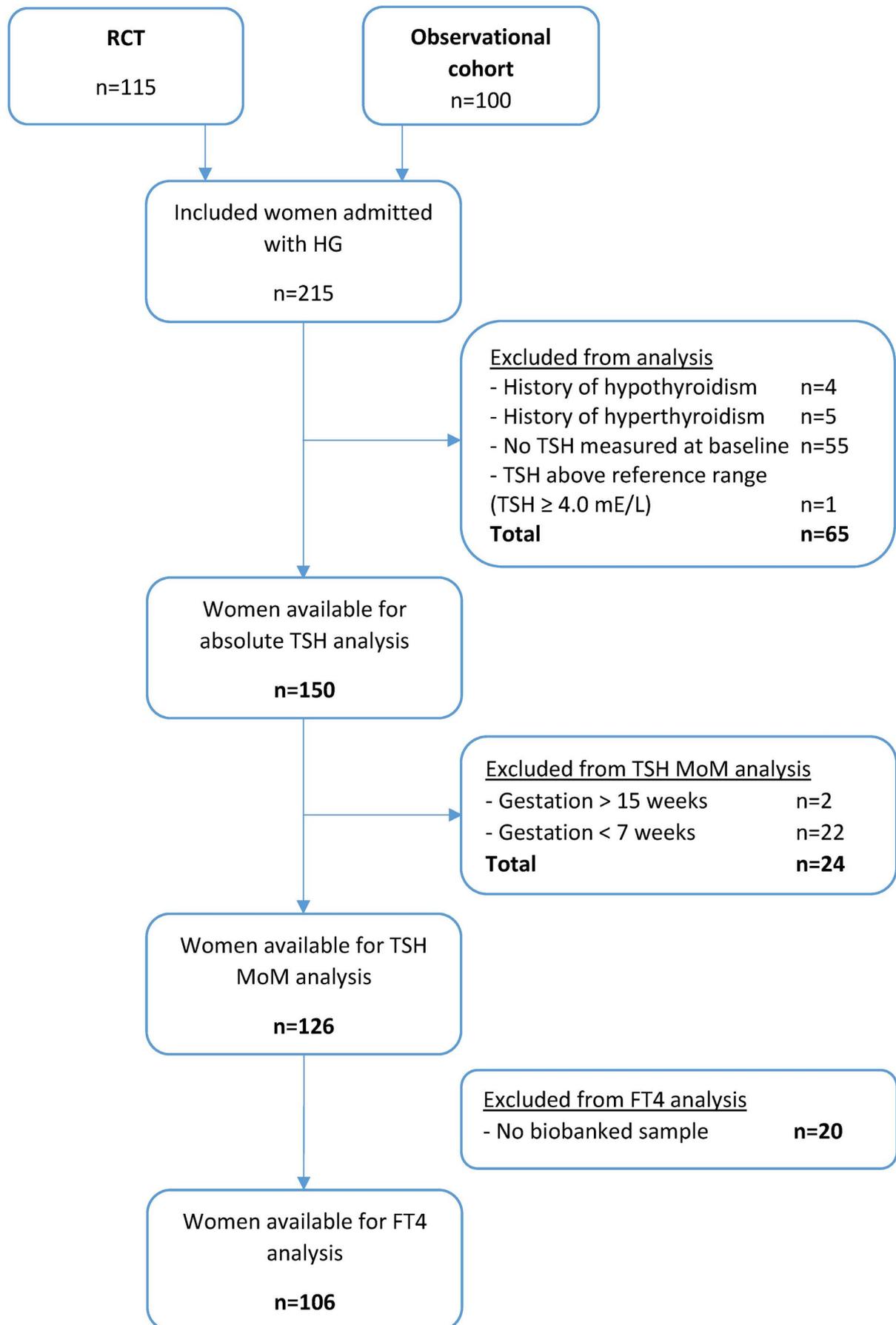
FIGURE 1 Flowchart of study population inclusions and exclusions

	N = 215	% Missing
Demographics		
Age (years)	28.83 ± 4.83	0.0%
Prepregnancy weight (kg)	71.11 ± 15.02	2.3%
Prepregnancy BMI (kg/m^2)	25.12 ± 4.89	3.7%
Ethnic origin		
Western	123 (57.2%)	18.1%
Non-western	53 (24.7%)	
Education level		
Primary or secondary	86 (40.0%)	34.0%
Higher	56 (26.0%)	
Mental health disorder in medical history[a]	41 (19.1%)	0.0%
HG in previous pregnancy[b]	68 (45.0%)	15.2%
HG in previous pregnancy requiring hospital admission[b]	37 (24.5%)	10.3%
Thyroid-stimulating hormone	0.78 ± 0.61	30.2%
Free thyroxine	19.26 ± 4.76	50.7%
Pregnancy characteristics		
Primigravida	64 (29.8%)	0.0%
Twin pregnancy	5 (2.3%)	0.0%
Gestational age at onset of symptoms of HG (weeks)	6.00 (5.25-7.00)	23.3%
Gestational age at inclusion	9.00 (7.00-11.00)	0.0%
First admission at study entry	191 (88.8%)	0.0%
Outcomes		
HG severity at baseline		
Weight change (kg)	−2.92 ± 4.07	2.8%
PUQE–24	10.01 ± 3.30	37.2%
NVPQoL	173.44 ± 23.43	34.9%
HIS	27.77 ± 3.86	34.4%
Clinical course of HG		
PUQE–24 1 week after inclusion	9.00 (6.00-11.00)	45.6%
NVPQoL 1 week after inclusion	76.00 (61.00-100.50)	49.3%
HIS 1 week after inclusion	25.71 ± 3.82	49.3%
Duration of first admission (days)	4.00 (3.00-5.00)	0.0%
Total days of hospital admission for HG	5.00 (3.00-8.00)	0.0%
Readmitted	71 (33.0%)	0.0%
Readmitted two or more times	29 (13.5%)	0.0%

TABLE 1 Baseline characteristics for women admitted for hyperemesis gravidarum included in this cohort

Data represented with mean ± standard deviation and median (interquartile range), unless stated otherwise; frequency (%).

Abbreviations: BMI, body mass index; HG, hyperemesis gravidarum; PUQE-24, 24-hour Pregnancy Unique Quantification of Emesis and nausea score. Weight change is weight at baseline minus prepregnancy weight and can be <0 if women lost weight and can be >0 if women gained weight. HIS, Hyperemesis Impact of Symptoms; NVPQoL, Nausea and Vomiting in Pregnancy Quality of Life. A higher PUQE-24, HIS- or NVPQoL-score indicates more severe symptoms or lower quality of life.

[a]Mental health disorder consists of an eating disorder, anxiety disorder, or a depressive disorder.

[b]Percentage shown is frequency divided by number of multigravidas.

In our search to identify markers of disease severity among newly diagnosed HG patients, our study found that lower TSH MoM was associated with increased weight loss in women admitted for HG, but FT4 was not. This is in contrast with existing literature that hypothesized that hyperthyroidism, and hence increased FT4, leads to weight loss.[14,23,24] However, an alternative explanation may be more likely: in healthy pregnant women without HG, lower maternal weight gain is also associated with lower TSH, when taking into account the graded decrease in TSH over the first trimester, suggesting that low TSH and not FT4 may simply be a marker of low

TABLE 2 Multivariable linear and logistic regression to assess the association between absolute TSH (a) and TSH MoM (b) and measures of the severity and clinical course of HG

	Model 1			Model 2		
	β	95% CI	p	β	95% CI	p
(a) Absolute TSH						
HG severity at baseline						
Weight change	0.82	−0.20 to 1.84	0.12	0.94	−0.43 to 2.32	0.18
PUQE-24	−0.15	−1.21 to 0.91	0.78	−0.43	−1.60 to 0.74	0.47
NVPQoL	−5.71	−12.19 to 0.78	0.08	−5.63	−12.90 to 1.65	0.13
HIS	0.49	−0.67 to 1.65	0.40	1.03	−0.35 to 2.41	0.14
Clinical course of HG						
PUQE-24 1 week after inclusion	1.02	−0.03 to 2.06	0.06	1.74	0.36-3.11	0.01
NVPQoL 1 week after inclusion ∫	8.65	−5.92 to 25.36	0.26	1.11	−15.55 to 21.17	0.90
HIS 1 week after inclusion	0.09	−1.30 to 1.48	0.90	1.04	−0.69 to 2.76	0.23
Total days of hospital admission for HG ∫	2.43	−14.02 to 21.90	0.79	−0.20	−22.89 to 29.30	0.99
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Readmitted yes or no	1.55	0.90-2.68	0.11	1.87	0.85-4.13	0.12
Readmitted two or more times	1.14	0.55-2.38	0.72	0.76	0.27-2.09	0.59
	β	**95% CI**	**p**	**β**	**95% CI**	**p**
(b) TSH MoM						
HG severity at baseline						
Weight change	1.54	0.35-2.73	0.01	2.00	0.47-3.53	0.01
PUQE-24	0.24	−0.96 to 1.43	0.70	0.13	−1.26 to 1.52	0.85
NVPQoL	−2.71	−9.80 to 4.38	0.45	−4.28	−12.31 to 3.76	0.29
HIS	0.75	−0.64 to 2.14	0.29	1.33	−0.39 to 3.05	0.13
Clinical course of HG						
PUQE-24 1 week after inclusion	1.41	0.11-2.72	0.03	1.74	−0.02 to 3.50	0.05
NVPQoL 1 week after inclusion ∫	4.50	−11.22 to 23.00	0.59	−2.27	−20.71 to 20.32	0.82
HIS 1 week after inclusion	−0.07	−1.68 to 1.54	0.93	0.90	−1.08 to 2.88	0.37
Total days of hospital admission for HG ∫	−0.50	−19.99 to 23.74	0.96	−4.97	−33.30 to 35.53	0.77
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Readmitted yes or no	1.27	0.64-2.50	0.50	1.72	0.62-4.80	0.30
Readmitted two or more times	1.49	0.62-3.59	0.38	1.23	0.36-4.23	0.75

A P value <0.05 was considered significant, represented with the corresponding 95% CI. β is the unstandardized regression coefficient. OR is the odds ratio. ∫ is log transformed, back transformed and expressed in % of difference. Weight change is weight at baseline minus prepregnancy weight and can be <0 if women lost weight and can be >0 if women gained weight.

Abbreviations: BMI, body mass index; HG, hyperemesis gravidarum; HIS, hyperemesis impact score; NVPQoL, Nausea and Vomiting in Pregnancy Quality of Life, PUQE-24, 24-hour Pregnancy Unique Quantification of Emesis and nausea. A higher HIS or NVPQoL score indicates lower quality of life or higher impact on maternal well-being. A higher PUQE-24 score indicates more severe symptoms.

Measures of HG severity at baseline as outcome: Model 1: univariable regression analysis; Model 2: multivariable regression analysis adjusted for age, prepregnancy BMI, ethnicity (western or not), and education level.

Measures of the clinical course of HG as outcome: Model 1: univariable regression analysis; Model 2: multivariable regression analysis adjusted for age, prepregnancy BMI, weight change at baseline, ethnicity (western or not), and education level.

maternal weight gain, and not a cause. Literature showing decreasing TSH levels in obese non-pregnant patients who lost weight after caloric restriction or bariatric surgery supports this theory.[25-27] Our study did not track TSH and maternal weight over time before HG symptoms developed, so we were unable to test this hypothesis.

We also sought to identify whether TSH or FT4 could be helpful in identifying women with HG who were to have a more severe or prolonged course of illness. In contrast to what had been suggested by the literature, our study found that only a lower TSH at baseline was associated with lower nausea and vomiting scores (PUQE-24 <13) 1 week after inclusion, whereas FT4 was not. An explanation could be that an increased energy intake during this period led to an increase and normalization of TSH levels, because there is evidence that there is a direct relation between TSH and energy intake.[28]

TABLE 3 Multivariable linear and logistic regression to assess the association between FT4 and measures of the severity and clinical course of hyperemesis gravidarum

	Model 1			Model 2		
	β	95% CI	p	β	95% CI	p
HG severity at baseline						
Weight change	−0.13	−0.29 to 0.04	0.13	−0.14	−0.35 to 0.06	0.16
PUQE-24	−0.05	−0.19 to 0.10	0.52	−0.05	−0.23 to 0.12	0.54
NVPQoL	0.65	−0.40 to 1.70	0.22	0.55	−0.63 to 1.74	0.35
HIS	−0.02	−0.19 to 0.15	0.81	−0.06	−0.26 to 0.14	0.55
Clinical course of HG						
PUQE-24 1 week after inclusion	−0.03	−0.21 to 0.15	0.72	0.01	−0.21 to 0.23	0.94
NVPQoL 1 week after inclusion ∫	−0.20	−2.37 to 2.12	0.87	0.80	−1.69 to 3.36	0.53
HIS 1 week after inclusion	0.15	−0.05 to 0.36	0.13	0.07	−0.15 to 0.29	0.50
Total days of hospital admission for HG ∫	2.22	−0.50 to 5.02	0.10	3.05	−0.90 to 7.04	0.13
	OR	95% CI	p	OR	95% CI	p
Readmitted yes or no	1.03	0.95-1.12	0.48	1.02	0.91-1.14	0.72
Readmitted two or more times	1.02	0.92-1.14	0.67	1.09	0.96-1.23	0.19

A p value <0.05 was considered significant, represented with the therefore corresponding 95% % CI β is the unstandardized regression coefficient. OR is the odds ratio. ∫ is log transformed, back transformed and expressed in % of difference. Weight change is weight at baseline minus prepregnancy weight and can be <0 if women lost weight and can be >0 if women gain weight.

Abbreviations: BMI, body mass index; HG, hyperemesis gravidarum; HIS, Hyperemesis Impact Score; NVPQoL, Nausea and Vomiting in Pregnancy Quality of Life; PUQE-23, 24-hour Pregnancy Unique Quantification of Emesis and nausea. A higher HIS or NVPQoL score indicates lower quality of life or higher impact on maternal wellbeing. A higher PUQE-24 score indicates more severe symptoms.

Measures of HG severity at baseline as outcome: Model 1: univariable regression analysis; Model 2: multivariable regression analysis adjusted for gestational age, age, prepregnancy BMI, ethnicity (western or not) and education level.

Measures of clinical course of HG as outcome: Model 1: univariable regression analysis; Model 2: multivariable regression analysis adjusted for gestational age, age, prepregnancy BMI, weight change at baseline, ethnicity (western or not) and education level.

Previous studies did not find an association between TSH or FT4 and readmission rates or the duration of inpatient hospital stay.[29-31] Our study confirms these findings. Unlike the three currently available studies, our study is the first that performed a multivariable regression analysis and used TSH MoMs to correct for gestational fluctuations.

Another reason why clinicians may want to be informed about thyroid function in women with HG, is to rule out clinical hyperthyroidism as an alternative explanation for severe NVP symptoms, which may require thyreostatic therapy.[32] One study in particular, which used PUQE-24 scores to quantify NVP severity, focused on ruling out thyroid dysfunction among women with HG. They found no association between hyperthyroidism (3 out of 63 women) and the PUQE-24 score and could therefore not support this alternative explanation for severe nausea and vomiting symptoms. In our study, we also found no association between TSH as well as FT4 and the PUQE-24 score at baseline. Also no differences in PUQE-24 score at baseline between women with and without GTT were found. Therefore, measuring thyroid function to rule out clinical hyperthyroidism as an explanation for severe nausea and vomiting seems unnecessary.

Our study is one of the few prospective cohort studies available including women admitted with HG using multiple measurements to assess HG severity and the clinical course of HG by using validated questionnaires. Furthermore, the women included in this study reflect a geographically representative sample of the Dutch population, because data collection was from 19 different hospitals across the Netherlands. Another strength is that we used TSH MoM to allow us to adjust for pregnancy-related fluctuations of TSH related to the rise and fall of placental hCG as pregnancy progresses.

Our study has some limitations. First and foremost, TSH values were available for only two-thirds of the included women in our study, because TSH was not always included in local routine laboratory workup for HG. We also had to exclude women for TSH MoM and FT4 analysis because of the lack of TSH medians or the lack of available frozen stored blood samples. Together with loss to follow up, including a high rate of missing data, despite multiple efforts to retrieve these data, as described in the original MOTHER study, this may have limited our power to detect associations. Potentially, there may have been selective loss to follow up, with women with severe symptoms being too unwell to complete follow-up questionnaires. However, we found no evidence for selective participation: only the baseline characteristics gestational age and first admission of HG differed between the included and excluded women. Further baseline characteristics and measures of the severity and clinical course of HG did not differ, so it is unlikely to have altered our results. Second, in this study TSH and FT4 levels were not followed up, so we were unable to investigate whether thyroid suppression normalized without treatment later in pregnancy or after delivery.

TABLE 4 Baseline characteristics and outcomes between women admitted for hyperemesis gravidarum included in this study with and without gestational thyrotoxicosis

	GTT	No GTT	
	N = 21	N = 85	p
Demographics			
Age (years)	29.67 ± 4.72	28.45 ± 4.90	0.31
Prepregnancy weight (kg)	69.40 ± 15.32	71.68 ± 15.41	0.55
Prepregnancy BMI (kg/m^2)	25.12 ± 5.41	25.54 ± 5.17	0.75
Ethnic origin			
Western	9 (42.9%)	50 (58.8%)	0.22
Non-western	8 (38.1%)	23 (27.1%)	
Education level			
Primary or secondary	5 (23.8%)	39 (45.9%)	0.13
Higher	9 (42.9%)	24 (28.2%)	
Mental health disorder in medical history[a]	2 (9.5%)	17 (20.0%)	0.35
HG in previous pregnancy[b]	9 (60%)	19 (34.5%)	0.08
HG in previous pregnancy requiring hospital admission[b]	4 (26.7%)	10 (18.2%)	1.00
Thyroid-stimulating hormone	0.33 ± 0.43	0.89 ± 0.67	0.00
Free thyroxine	26.37 ± 5.59	17.50 ± 2.26	0.00
Pregnancy characteristics			
Primigravida	6 (28.6%)	30 (35.3%)	0.56
Twin pregnancy	1 (4.8%)	2 (2.4%)	0.49
Gestational age at onset of symptoms of HG (weeks)	6.00 (5.00-6.50)	6.00 (5.00-7.00)	0.60
Gestational age at baseline	8.00 (7.50-9.50)	8.00 (7.00-10.00)	0.89
First admission at study entry	18 (85.7%)	79 (92.9%)	0.38
Outcomes			
HG severity at baseline			
Weight change (kg)	−3.87 ± 3.07	−2.96 ± 4.08	0.35
PUQE-24	9.93 ± 3.77	10.36 ± 3.02	0.65
NVPQoL	176.21 ± 14.28	173.15 ± 23.58	0.64
HIS	26.80 ± 2.83	28.13 ± 3.96	0.23
Clinical course of HG			
PUQE-24 1 week after inclusion	9.00 (7.50-10.00)	9.00 (6.00-12.00)	1.00
NVPQoL 1 week after inclusion	73.50 (57.25-84.75)	79.00 (58.75-107.25)	0.47
HIS 1 week after inclusion	27.70 ± 1.64	24.98 ± 3.65	0.03
Duration of first admission (days)	4.00 (3.00-5.00)	4.00 (3.00-5.00)	0.37
Total days of hospital admission for HG	6.00 (4.00-10.50)	5.00 (3.00-7.50)	0.20
Readmitted	9 (42.9%)	32 (37.6%)	0.66
Readmitted two or more times	4 (19.0%)	11 (12.9%)	0.49

Data represented with mean ± standard deviation and median (interquartile range), unless stated otherwise; frequency (%). A p value <0.05 was considered significant.

Abbreviations: BMI, body mass index; GTT, gestational transient thyrotoxicosis: defined as women with a free thyroxine (FT4) level above 22.0 pmol/L; HG, hyperemesis gravidarum; PUQE-24, 24-hour Pregnancy Unique Quantification of Emesis and nausea score. Weight change is weight at baseline minus prepregnancy weight and can be <0 if women lost weight and can be >0 if women gain weight; HIS, Hyperemesis Impact of Symptoms; NVPQoL, Nausea and Vomiting in Pregnancy Quality of Life. A higher PUQE-24, HIS- or NVPQoL-score indicates more severe symptoms or lower quality of life.

[a]Mental health disorder consists of an eating disorder, anxiety disorder. or a depressive disorder.

[b]Percentage shown is frequency divided by number of multigravidas.

Previous literature suggested that TSH as well as FT4 levels return to normal by the second trimester in women with HG and GTT.[33]

5 | CONCLUSION

Based on inconsistent findings from our study as well as from earlier research, there seems little utility of thyroid measurement as a marker or predictor for the severity and clinical course of HG. The clinical relevance of measuring TSH in women with HG therefore seems low, making the likelihood that the thyroid plays an important role in the etiology of HG also less likely. As advised in the HG guideline of the Nordic Federation of Societies of Obstetrics and Gynecology,[34] thyroid function assessment should be reserved to rule out thyroid disease in women with clinical signs, such as goiter, or women with symptoms of clinical hyperthyroidism, such as marked tachycardia or prolonged atypical symptoms. Further research in pursuit of a biomarker for diagnosis or as a predictor of disease course, or monitoring treatment effect in patients with HG is needed to optimize patient care and treatment.

CONFLICT OF INTEREST
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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