




Recurrence, postponing pregnancy, and termination rates after hyperemesis gravidarum: Follow up of the MOTHER study

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Abbreviations: CI, confidence interval; HG, hyperemesis gravidarum; IQR, interquartile range; MOTHER, Maternal and Offspring outcomes after Treatment for HyperEmesis by Refeeding; OR, odds ratio; PUQE-24, 24-hour Pregnancy Unique Quantification of Emesis score; RCT, randomized controlled trial; SD, standard deviation.

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Abstract

Introduction: Hyperemesis gravidarum (HG) complicates 1% of pregnancies and has a major impact on maternal quality of life and well-being. We know very little about HG's long-term impact after an affected pregnancy, including recurrence rates in future pregnancies, which is essential information for women considering subsequent pregnancies. In this study, we aimed to prospectively measure the recurrence rate of HG and the number of postponed and terminated subsequent pregnancies due to HG. We also aimed to evaluate if there were predictive factors that could identify women at increased risk for HG recurrence, and postponing and terminating subsequent pregnancies.

Material and methods: We conducted a prospective cohort study. A total of 215 women admitted for HG to public hospitals in the Netherlands were enrolled in the original MOTHER randomized controlled trial and associated observational cohort. Seventy-three women were included in this follow-up study. Data were collected through an online questionnaire. Recurrent HG was defined as vomiting symptoms accompanied by any of the following: multiple medication use, weight loss, admission, tube feeding or if nausea and vomiting symptoms were severe enough to affect life and/or work. Outcome measures were recurrence, postponing, and termination rates due to HG. Univariable logistic regression analysis was used to identify predictive factors associated with HG recurrence, and postponing and terminating subsequent pregnancies.

Results: Thirty-five women (48%) became pregnant again of whom 40% had postponed their pregnancy due to HG. HG recurred in 89% of pregnancies. One woman terminated and eight women (23%) considered terminating their pregnancy because of recurrent HG. Twenty-four out of 38 women did not get pregnant again because of HG in the past. Univariable logistic regression analysis identifying possible predictive factors found that having a western background was associated with having weight loss due to recurrent HG in subsequent pregnancies (odds ratio 12.9, 95% CI 1.3–130.5, $p = 0.03$).

Conclusions: High rates of HG recurrence and a high number of postponed pregnancies due to HG were observed. Women can be informed of a high chance of recurrence to enable informed family planning.

KEYWORDS

hyperemesis gravidarum, induced abortion, pregnancy outcome, recurrence, reproductive behavior, risk assessment, risk factors, secondary prevention

1 | INTRODUCTION

Hyperemesis gravidarum (HG) is a severe complication of pregnancy affecting around 1% of pregnancies globally.¹ HG can cause significant physical and psychological morbidity for mothers.² A lack of effective treatment makes HG a challenging condition to manage and therapeutic termination is commonly reported.^{3,4}

A history of HG is the single most important risk factor for developing HG.⁵ The recurrence rate has been reported to be well above

Key message

Women admitted for hyperemesis gravidarum in a previous pregnancy have a high chance of recurrence (89%) and often postpone subsequent pregnancies (40%). There are also women who considered terminating or actually terminated subsequent pregnancies due to recurrent HG (23%).

baseline risk, but literature shows a wide range varying from 15% to 81%.⁵ A recent systematic review failed to produce an aggregate recurrence rate due to the contributing studies' methodological shortcomings, including poor external validity and significant heterogeneity.⁶

Such a wide risk prediction bracket for a condition with substantial biopsychosocial impacts makes informed decision-making regarding subsequent pregnancies difficult. Patients have expressed a desire for research to provide a definitive recurrence risk and recently this was also recognized as a priority research question by a priority-setting partnership.^{6,7} Furthermore, there is evidence suggesting that early treatment and lifestyle preparation strategies may reduce the overall severity of the condition.^{8,9} For such interventions to be appropriately implemented, the recurrence rate must be understood.⁶

Both overestimating and underestimating the recurrence rate can have substantial impacts on people's lives. There are reports of families curtailing future pregnancies believing HG is unavoidable as well as reports of women deciding to terminate on the assumption that their risk in a future pregnancy is that of the general population.^{3,10,11}

In this study, we aimed to prospectively measure the self-reported recurrence rate of HG, the postponement of pregnancy because of previous HG, and pregnancies terminated due to recurrent HG. Additionally, we aimed to identify predictive factors associated with an increased risk of HG recurrence, and postponing and terminating subsequent pregnancies.

2 | MATERIAL AND METHODS

This study is a prospective cohort follow-up study of the Maternal and Offspring outcomes after Treatment for HyperEmesis by Refeeding (MOTHER) randomized control trial (RCT) and associated observational cohort.¹²

The original MOTHER RCT assessed whether early enteral tube feeding in addition to standard care for women admitted with HG improved neonatal and maternal outcomes.¹² Women admitted for HG between 5 and 20 weeks of gestation in 19 different hospitals in the Netherlands between 2013 and 2016 were recruited. In total, 115 women were randomized and 100 women, who declined randomization, were recruited to an associated observational cohort. Early enteral tube feeding did not affect maternal and perinatal outcomes,¹² so we combined the RCT and cohort into one study population for this follow-up study. Detailed information about data collection can be found in the original study protocol and earlier published results of the MOTHER RCT.^{12,13}

The MOTHER follow-up study consisted of a single, self-reported, online questionnaire that assessed health and reproductive outcomes after participating in the MOTHER study. Participants who gave consent to be approached for follow-up studies were emailed with a link to the online questionnaire. Both Dutch and English language options were available. In case of no response, a reminder was sent after 1, 3, and 6 weeks. Individual informed consent had been obtained during both the MOTHER and follow-up studies.

For the full questionnaire please see Appendix S1. Women self-reported whether they had conceived again since participating in the MOTHER study. Those who had not had a further pregnancy were asked whether they had curtailed or postponed any future pregnancies due to fear of recurrent HG. For those who had subsequent pregnancies, nausea and vomiting symptoms were assessed with a series of questions regarding the onset of symptoms, hospital admission including duration and frequency, anti-emetic use, and tube feeding. We considered that HG had recurred if vomiting symptoms were reported with multiple HG medication use (two or more, including anti-emetics and corticosteroids, see full list in Appendix S1), weight loss during pregnancy, admission for HG, requiring tube feeding, or symptoms severe enough to affect their life and/or work. The HG definition we used was based on the recently internationally developed WINDSOR HG definition (unpublished results, manuscript currently submitted for publication). Weight loss was reported as lowest weight during pregnancy compared with prepregnancy weight and reported as any weight loss and more than 5% weight loss. We also assessed whether pregnancies had ended as miscarriages or ectopic pregnancies and if women had considered terminating or had terminated their pregnancy due to recurrent HG. Because of ethical considerations, we were unable to verify answers to the questionnaire with medical records. The follow-up questionnaire also included questions about depression, anxiety, and post-traumatic stress disorder symptoms after having HG in the index pregnancy. These results will be discussed in a different manuscript that is currently submitted for publication.

We also assessed if we could identify factors that could predict which women were at increased risk of developing recurrent HG, to postpone subsequent pregnancies, or to terminate or consider terminating subsequent pregnancies because of severe recurrent HG with use of univariable regression analysis. For this analysis, recurrent HG in subsequent pregnancies was broken down into the following outcome measures: being admitted to the hospital, having weight loss, and receiving tube feeding due to recurrent HG in subsequent pregnancies.

We assessed the following possible predictive factors: maternal age, ethnicity, and several measures of HG severity in the index pregnancy, when participating in the MOTHER study. Measures of HG severity in the index pregnancy as predictor variables were: higher symptom severity (measured by the self-reported, validated 24-hour Pregnancy Unique Quantification of Emesis [PUQE-24] score at baseline),^{14,15} lower weight gain at inclusion in the MOTHER study compared with prepregnancy weight, higher total duration of hospital admissions, and admission after the first trimester. The PUQE-24 score can vary from 3 to 15 with a higher score indicating more severe symptoms.

2.1 | Statistical analyses

Continuous variables were presented as means with standard deviations if they were normally distributed, or otherwise presented as

medians with interquartile ranges. Dichotomous and categorical variables were presented as frequencies with percentages. A sensitivity analysis was performed to assess differences in demographic and clinical characteristics of the index pregnancy between participating and non-participating women in this follow-up study. Independent Student's *t* test, Mann-Whitney *U* test, and chi-squared test were used for analyses.

Univariable logistic regression analysis was used to identify possible predictive factors for an increased risk of HG recurrence, or postponing or terminating subsequent pregnancies. Due to the low number of events, we were not able to perform multivariable logistic regression analysis and adjust for confounders.¹⁶

As described earlier, we deemed it appropriate to combine the MOTHER RCT and associated observational cohort into one combined study population. However, as this study is a follow up of an RCT, we felt it was necessary, for ethical reasons, to also assess whether there were differences in recurrence, postponement, and termination rates between the RCT arms. Methods and results of these analyses can be found in Appendix S2. Values of *p* less than 0.05 were considered statistically significant and SPSS Statistics 26.0 for Windows (IBM Corp., Armonk, NY, USA) was used for analyses.

2.2 | Patient and public involvement

Patients have been involved in this research from the inception of the MOTHER study when patients expressed a desire for the research question. The Dutch HG patient charity, Zwangerschapsmisselijkheid en Hyperemesis Gravidarum, was consulted at various points, including piloting the survey questions. Desire for a prospective study to address the recurrence rate of HG is well documented by one of the authors, who is a patient representative (CD)⁶ and has given patient perspective on the results and interpretation of this study.

2.3 | Ethical approval

The MOTHER trial was registered at www.trialregister.nl (NTR4197) and was approved by the research ethics committee of the Amsterdam UMC, location AMC on April 3, 2013. Ethics approval was not required for the follow-up study under the Medical Research Involving Human Subjects Act (reference number W20_066 #20.094).

3 | RESULTS

Out of 215 MOTHER participants who had given consent to be contacted for follow-up studies, 190 were approached. Seventy-five participants completed the follow-up survey between March and May 2020. About half of the respondents completed the

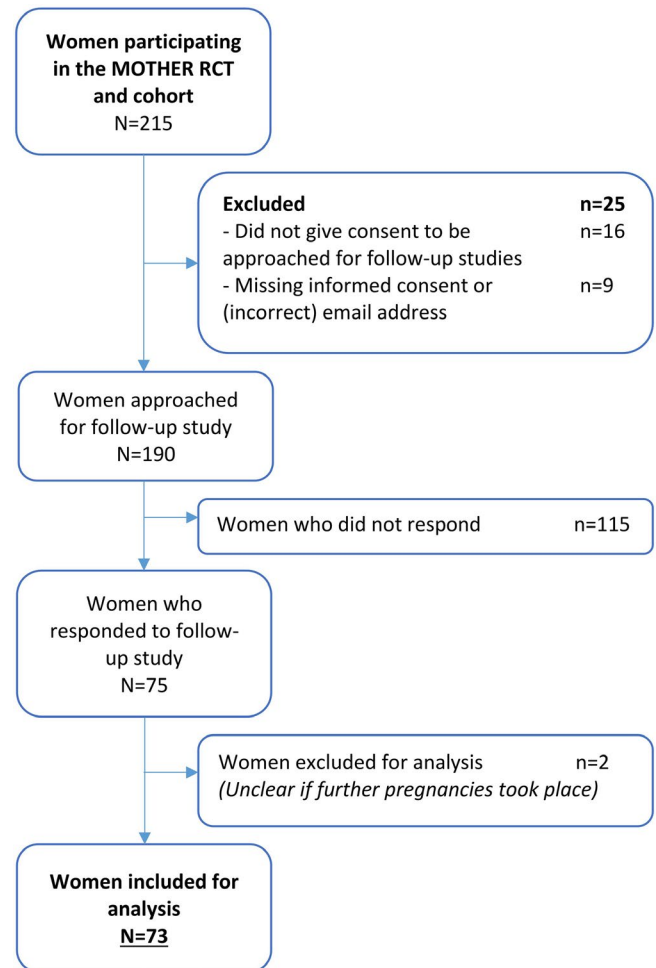


FIGURE 1 Flow of participants included and excluded for follow-up study

questionnaire after receiving the initial email invitation (40/75, 53%). Respectively, 11% (8/75), 20% (15/75), and 16% (12/75) of the participants responded after the first, second, and third reminder emails. Two women were excluded because they reported on pregnancies before the index pregnancy and not on subsequent ones in a distinguishable way. Therefore, 73 participants were included for analysis, as shown in Figure 1.

Table 1 details baseline characteristics of women included in our study. Table S1 shows a sensitivity analysis between follow-up participants and those who did not participate in the follow-up study. Participants were more highly educated ($p < 0.01$) and had had higher vomiting scores at inclusion during the index pregnancy ($p = 0.02$), than those who did not participate.

Following the index pregnancy, 38 women (52%) did not get pregnant again. Of them, two-thirds (24/38) stated that this was because of HG, while 14 women stated other reasons (Table 2). Thirty-five women conceived one or more subsequent pregnancies. Of those women, 40% (14/35) had postponed their pregnancy due to HG.

Hyperemesis gravidarum recurred in 88.6% of subsequent pregnancies (Table 2). Of the women with recurrent HG, 54% required

TABLE 1 Baseline characteristics of women included in this follow-up study

Baseline characteristics	N = 73
Age (years), mean \pm SD	29.2 \pm 4.6
Education level, n (%)	
Primary or secondary	27 (37.0%)
Higher	29 (39.7%)
Ethnicity, n (%)	
Western	52 (71.2%)
Non-western	12 (16.4%)
Primigravida at time of MOTHER inclusion, n (%)	27 (37.0%)
HG in pregnancy before MOTHER inclusion, n (%) ^a	22 (47.8%)

Note: Data presented with mean \pm SD, median (IQR) or frequency (%).

Abbreviations: HG, hyperemesis gravidarum; IQR, interquartile range; MOTHER, Maternal and Offspring outcomes after Treatment for HyperEmesis by Refeeding; SD, standard deviation.

^aPercentage shown is frequency divided by multigravidas at time of MOTHER inclusion.

two or more medications to manage their symptoms, 60% were admitted to hospital for HG and 63% experienced weight loss with an average of -4.5 ± 4.4 kg. One woman terminated her pregnancy and eight women (23%) considered terminating their subsequent pregnancy because of recurrent HG.

In six out of 45 subsequent pregnancies no vomiting symptoms were reported. Of these six pregnancies, one was an ectopic pregnancy and four ended in a miscarriage. Four of these five women went on to have another, successful, pregnancy in which they did experience vomiting symptoms. The fifth woman had three miscarriages in which she developed HG each time.

In univariable regression analysis, we assessed whether there were factors that could predict HG recurrence, postponing, and (consideration of) terminating subsequent pregnancies. Baseline characteristics of women who became pregnant again and were included in the regression analysis are shown in Table S2. Univariable logistic regression analysis showed that having a western background was associated with having weight loss due to recurrent HG in subsequent pregnancies (odds ratio 12.86, 95% CI 1.27–130.54, $p = 0.03$). No associations were found between maternal age and several measures of HG severity in the index pregnancy, and HG recurrence, and postponing and (consideration of) terminating subsequent pregnancies. (Table 3).

4 | DISCUSSION

In a well-defined prospective cohort, we found a high HG recurrence rate of 89%. Furthermore, we found high proportions of women who avoided a subsequent pregnancy (33%), postponed their pregnancy (40%), or considered terminating their pregnancy (23%) because of HG. Additionally, we found that having a western background was

associated with having weight loss due to recurrent HG in subsequent pregnancies.

Our study found an 89% recurrence rate of HG. A recent systematic review identified five previously published, prospective studies assessing the HG recurrence rate.⁶ Four were population database cohorts that used birth registry data and International Classification of Diseases 10th revision (ICD-10) codes to identify HG patients and which reported relatively low recurrence rates between 15% and 26%.^{5,17–19} Although large populations were included in their study, with the number of HG cases varying from 447 to 33 214, Dean et al.⁶ concluded that methods lacked both external validity and internal reliability. While ICD codes may seem an effective method for pregnancy data collection, attempts to validate them for identifying HG have proved unsuccessful.⁶ Norwegian researchers found that the Medical Birth Registry and ICD codes were valid for mild, but not for severe, pregnancy sickness or HG.²⁰ In our study, only 60% of women with HG were admitted in subsequent pregnancies, which would suggest that ICD codes are missing for around 30% of women with recurrent HG in the Dutch system. The fifth study, by Fejzo et al.,²¹ reported a substantially higher recurrence rate of 81% (46/57 women), but consisted of a self-reported follow up from an online survey of self-selected participants, making it prone to selection bias. Our follow-up survey was also self-reported, but the initial population was recruited with robust inclusion criteria for HG, which provided our study with a greater degree of external validity.

To our knowledge, Fejzo et al.²¹ is the only study assessing HG severity in subsequent pregnancies. They reported higher rates of tube feeding than our study (20% vs. 14.3%), but similar admission rates (48% vs. 60%), which is likely a reflection of healthcare system differences between the USA and European countries.²²

Literature regarding women curtailing pregnancies after developing HG is scarce and heterogenic. Fiaschi et al.⁵ found no evidence of women with HG curtailing any future pregnancies compared with women without HG in their population-based cohort study that included 33 214 women with HG. We consider this a surprising finding considering that Heitmann et al.²³ found that 75.7% (159/210 women) of those with severe nausea and vomiting symptoms considered never getting pregnant again. Furthermore, Fejzo et al.²¹ reported that 37% (37/100 women) had avoided any further pregnancies due to HG. Our study found that 33% of women curtailed pregnancies due to HG. We also found that 40% of the women who got pregnant again after their index pregnancy postponed their pregnancy due to HG in the past. Poursharif et al.²⁴ described that 76% (614/808) of participants in their large self-selected online-survey cohort reported a change in personal attitude to future childbearing following an HG pregnancy, including increased spacing of pregnancies or fewer children than previously desired. This phenomenon is also described in a review from Dean et al.²⁵ reporting on the effect of HG on women's lives and is recognized by our Patient and Public Involvement representatives.

Previous surveys have identified a termination rate for HG between 3% and 15%.^{3,11,26} Poursharif et al.³ reported that 6% (49/808

TABLE 2 Recurrence, postponing, and termination rates in subsequent pregnancies

Subsequent pregnancies	N = 73
Women who experienced a subsequent pregnancy, n (%)	35 (47.9%)
Number of pregnancies after MOTHER study, median (IQR)	1.0 (1.0–2.0)
one pregnancy, n (%)	26 (74.3%)
two pregnancies, n (%)	8 (22.9%)
three or more pregnancies, n (%)	1 (2.9%)
Women who did not become pregnant again due to fear for recurrent HG, n (%)	24 (32.9%)
Time interval between MOTHER and follow-up study participation (years), median (IQR)	4.5 (4.1–5.0)
Recurrence rate of HG ^a	N = 35
Recurrence of vomiting symptoms, n (%)	34 (97.1%)
Gestational age when vomiting started (weeks), median (IQR)	6.0 (4.0–7.0)
Used multiple (two or more) HG-related medications, n (%)	19 (54.3%)
Was admitted to hospital, n (%)	21 (60.0%)
Duration of hospital admissions (days), mean ± SD	6.5 ± 4.0
Had weight loss, n (%) ^b	22 (62.9%)
Had >5% weight loss, n (%)	16 (45.7%)
Average weight change (kg), mean ± SD ^b	–4.2 ± 4.3
Received tube feeding, n (%)	5 (14.3%)
NVP affected her job, n (%)	20 (57.1%)
NVP affected her life, n (%)	26 (74.3%)
Had HG, n (%) ^c	31 (88.6%)
Postponed or terminated pregnancies	
Postponed a pregnancy due to HG in the past, n (%)	14 (40.0%)
Considered terminating a pregnancy due to HG in subsequent pregnancies, n (%)	8 (22.9%)
Terminated a pregnancy due to HG in subsequent pregnancies, n (%)	1 (2.9%)

Note: Data presented with mean ± SD, median (IQR) or frequency (%). Abbreviations: HG, hyperemesis gravidarum, IQR, interquartile range; MOTHER, Maternal and Offspring outcomes after Treatment for HyperEmesis by Refeeding; NVP, nausea and vomiting in pregnancy; SD, standard deviation.

^aHG recurrence rate in any subsequent pregnancy.

^bLowest weight during pregnancy minus prepregnancy weight: can be <0 if women lost weight and can be >0 if women gained weight.

^cHG defined as: vomiting symptoms with either multiple medication use, hospital admission, weight loss during pregnancy, tube feeding or NVP affecting her job and/or life.

women) underwent multiple terminations for HG and an additional 13% “almost” terminated their pregnancy due to HG. Although in our study only one woman terminated a pregnancy due to developing HG again, we found that 23% of women considered terminating a

pregnancy, which is consistent with a rate of 26.7% (56/210 women) reported in a Scandinavian population.²³ Variation in rates reported may reflect differences in access to treatment and social support around the world. For example, women included in Poursharif et al.³ were predominantly from the USA, where sick pay and employment rights are not statutory and treatment for HG is expensive. Our study participants are from the Netherlands where treatment is covered by universal healthcare insurance and employees can make use of extended paid sick leave and are protected from termination of contract due to illness.²⁷ However, 23% of women considering termination of pregnancy due to HG is worryingly high and highlights the importance of early recognition and treatment of symptoms and supportive care.

Our study has several strengths. All participants had well-documented HG during their index pregnancy, which is of benefit compared with previous studies, which relied on hospital admission records, usually only including pregnancies that had led to a delivery. Including patient representatives in the conception and design of the research and interpretation of the results is also a strength, because this has been earlier recognized to improve the quality and relevance of research.²⁸ Our study also assessed whether subsequent pregnancies were viable and whether measures of HG severity of the index pregnancy can be used as predictive factors of recurrent HG, and postponing and termination rates. These are both recognized as important matters in clinical practice by our patient representatives, especially as, in our study, most women without vomiting symptoms had a non-viable pregnancy.

Our results are limited by the small sample size. Of the cohort of 215 women, 75 (35%) responded, despite our recruitment efforts, and only 35 women (16%) had become pregnant again. Selective participation led to women with more severe symptoms in the index pregnancy being over-represented in the current study, probably leading to selection bias. It is conceivable that those who did not participate in this follow-up study had a lower HG recurrence in subsequent pregnancies, which means that the recurrence rate presented here may be overestimated. Additionally, RCT analyses were hampered by an even smaller sample size, including 24 women who had become pregnant again. Also, the association between having a western background and having weight loss in subsequent pregnancies is likely to be affected by the size of our study, with only 6/35 women that became pregnant again having a non-western background. External validity may therefore be limited.

In this follow-up study, data were gathered through a self-reported, non-validated questionnaire, because there is no validated questionnaire available. The nature of some of the included questions could be considered to be subjective. Additionally, there was potential for recall bias on pregnancies experienced up to 7 years before participants completed the questionnaire as subsequent pregnancies could have taken place from 2013 onwards. This may have led to both under- and over-reporting of HG symptoms, although previous studies have shown that self-reporting questionnaires are well validated for reporting on pregnancy.²⁹

TABLE 3 Univariable logistic regression analysis to assess possible predictive factors, including measures of HG severity of the index pregnancy, for HG recurrence, postponing and terminating subsequent pregnancies

	Was admitted for HG in any subsequent pregnancy		Had weight loss in any subsequent pregnancy ^b		Had tube feeding in any subsequent pregnancy		Postponed subsequent pregnancies due to HG in the past		Terminated or considered terminating a subsequent pregnancy	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Possible predictive factors										
Maternal age at inclusion MOTHER study	1.00	0.85–1.17	0.95	0.81–1.12	1.08	0.87–1.33	1.00	0.85–1.17	0.94	0.77–1.15
Ethnicity (western or non-western)	1.78	0.30–10.72	12.86	1.27–130.54	— ^a	— ^a	0.79	0.13–4.68	1.25	0.12–13.24
Measures of HG severity in the index pregnancy										
Weight change (kg) at inclusion MOTHER study ^b	1.10	0.94–1.29	1.03	0.89–1.20	1.12	0.87–1.44	0.97	0.84–1.12	0.97	0.82–1.14
PUQE-24 at inclusion MOTHER study	0.88	0.67–1.16	1.29	0.96–1.73	1.21	0.80–1.84	0.99	0.76–1.29	0.96	0.70–1.30
Total duration of hospital admission(s) in the index pregnancy (days)	1.01	0.85–1.19	1.09	0.90–1.32	1.16	0.94–1.42	1.01	0.85–1.19	1.05	0.87–1.26
Admission in the second or third trimester in the index pregnancy	8.00	0.87–73.40	1.25	0.25–6.16	0.69	0.07–7.11	0.68	0.14–3.34	2.10	0.39–11.43

Note: A $p < 0.05$ is considered significant and marked in bold.

Abbreviations: HG, hyperemesis gravidarum; OR, odds ratio; PUQE, 24-hour Pregnancy Unique Quantification of Emesis and nausea (a higher PUQE-24 score indicates more severe symptoms).

^aAll women that received tube feeding in a subsequent pregnancy had a western background.

^bWeight change during index pregnancy is weight at baseline minus prepregnancy weight. Weight loss during subsequent pregnancies is prepregnancy weight minus lowest weight during pregnancy. Both can be <0 if women lost weight and >0 if women gained weight.

5 | CONCLUSION

Our study found a high recurrence rate for HG of 89%. Although it seems plausible that selective attrition has occurred and led to an overestimation, our study suggests that the recurrence rate is more likely to be at the high end of the current available range of 15%–81%. Although such findings may be distressing for women who were hoping future pregnancies would be better, it is important information to give during preconception consultations, so that people are able to make informed decisions about their family planning. Knowing that HG has a very high chance of recurrence allows families not only to plan in advance for childcare and finances, but also to discuss available treatments and the possibility of early interventions, which may make the burden of the condition easier to bear. Finally, it is important that healthcare professionals do not give false hope regarding the chance of recurrence and that they recognize the severe burden of a condition

that leads so many women to consider terminating, or to actually terminate their otherwise wanted pregnancies.

CONFLICT OF INTERESTS

BWM reports grants from the National Health and Medical Research Council (NHMRC) outside the submitted work. The rest of the authors have nothing to disclose.

AUTHOR CONTRIBUTIONS

IJG, TJR, and RCP conceived and designed the MOTHER study. KN and RCP conceived and designed the follow-up study. LMvdM helped develop the online survey tool. KN performed all statistical analyses supervised by RCP and RvE. KN and CD drafted the manuscript. The following authors were responsible for recruitment of, and data collection from the original MOTHER RCT and cohort: JMJB, CR-S, HAB, DPvdH, WMH, AH, GK, SK, JOEHvL, JL, FvdM, DP, M-JP, PJP, LvRF,

RJR, HCJS, TV, BWM, MHK, IJG, and RCP. All authors critically reviewed the manuscript and approved the final draft.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the principle investigator (r.c.painter@amsterdamc.nl) upon reasonable request.

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SUPPORTING INFORMATION

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

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