OBSTETRICS

Recurrence patterns of hyperemesis gravidarum

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BACKGROUND: Hyperemesis gravidarum, excessive vomiting in pregnancy, affects approximately 0.3—3.0% of all pregnancies, but the risk is considerably higher in pregnancies following a hyperemetic pregnancy. The reported recurrence rate of hyperemesis gravidarum is wide, ranging from 15—81%, depending on study settings. Factors affecting recurrence of hyperemesis gravidarum are as yet insufficiently studied.

OBJECTIVE: We sought to evaluate the recurrence rate of hyperemesis gravidarum in subsequent pregnancies, to elucidate chronological patterns of recurrence of the condition, and to analyze maternal, environmental, and pregnancy-related factors associated with recurring hyperemesis gravidarum.

STUDY DESIGN: Out of all pregnancies ending in delivery in Finland from 2004 through 2011, data of women who had at least 1 pregnancy ending in delivery following a pregnancy diagnosed with hyperemesis gravidarum were retrieved from hospital discharge register and medical birth register (1836 women, 4103 pregnancies; 1836 index pregnancies and 2267 subsequent pregnancies). The first pregnancy with hyperemesis gravidarum diagnosis was chosen as the index pregnancy, and recurrence rate was calculated by comparing the number of hyperemetic pregnancies that followed the index pregnancy to the total number of pregnancies that followed the index pregnancy. Recurrence patterns of hyperemesis gravidarum were illustrated by presenting the chronological order of the women's pregnancies beginning from the index pregnancy to the end of the follow-up period. The associations between recurring hyperemesis and age, parity, prepregnancy body mass index, smoking, marital and socioeconomic status, domicile, month of delivery, assisted reproductive technology, sex, and number of fetuses were analyzed in both the index pregnancies and in pregnancies following the index pregnancy.

RESULTS: There were 544 pregnancies with a hyperemesis diagnosis and 1723 pregnancies without a hyperemesis diagnosis following the index pregnancies. The overall recurrence rate of hyperemesis gravidarum in pregnancies following the index pregnancy was 24%. In case of >1 subsequent pregnancy, 11% of women were diagnosed with hyperemesis in all of their pregnancies. In the index pregnancies, recurrence of hyperemesis gravidarum was more common among women with parity of 2 than parity of 1 (adjusted odds ratio, 1.33, $P = .046$). Overweight women (adjusted odds ratio, 0.58, $P = .036$) or women who smoked after the first trimester (adjusted odds ratio, 0.27, $P < .001$) had lower recurrence of hyperemesis. In the comparison of the subsequent pregnancies, quitting smoking in the first trimester (adjusted odds ratio, 0.32, $P = .010$) and smoking continued after the first trimester (adjusted odds ratio, 0.38, $P = .002$) were associated with lower odds of recurring hyperemesis. Female sex of the fetus was associated with higher odds of recurring hyperemesis (adjusted odds ratio, 1.29, $P = .012$).

CONCLUSION: In the majority of pregnancies following an earlier hyperemetic pregnancy, hyperemesis gravidarum does not recur, but hyperemetic pregnancies occur in the next pregnancies with little predictability. Only few factors associated with recurring hyperemesis could be identified. Although estimating the probability of recurrence of hyperemesis gravidarum in a subsequent pregnancy based on a woman's first hyperemetic pregnancy turned out not to be feasible, it is reassuring to know that hyperemesis does not appear to become more likely with each pregnancy and that after 1 pregnancy with hyperemesis, the following pregnancy may be different.

Key words: hyperemesis, hyperemesis gravidarum, nausea, pregnancy, recurrence, vomiting

Introduction

Hyperemesis gravidarum (HG), excessive vomiting in pregnancy, is the most common cause of hospitalization in the first trimester of pregnancy.[1] HG occurs in approximately 0.3—3.0% of all pregnancies.[2—4] The likelihood of recurrence of HG in an eventual subsequent pregnancy is not yet well established. There are 2 previous register studies that have estimated the recurrence of HG: Trogstad et al[5] found a recurrence of 15% in second pregnancies, and Fiaschi et al[6] found a recurrence of 26% in second pregnancies. Lack of a universally accepted definition of HG causes methodological challenges, and differences in defining HG may lead to variation in study groups and results between different studies.[7] In a survey-based study, Fejzo et al[8,9] found that self-reported HG symptoms reoccurred in 46 of 57 subsequent pregnancies (81%), and 22 of the 57 pregnancies (39%) involved hospitalization due to HG.

The role of the contributing factors is of interest in order to recognize those women who are at an elevated risk of recurring HG. Several maternal, environmental, and pregnancy-related factors are known to be associated with HG in general. Previous results regarding parity and gravidity are conflicting: according to some studies, primiparous women appear more likely to need hospital care due to HG,[6,10,11] while according to others, HG is associated with an increase in gravidity.[12] Body mass index (BMI) may have some effect on HG; underweight women have been shown to be more susceptible to HG,[13,14] whereas results about obesity are conflicting: both higher[14] and lower[13] risk of HG has been reported. Several studies indicate that smoking is associated with a lower risk of HG.[14—16] Assisted reproduction technology (ART) may have an impact on HG.[11,15,16] Furthermore, HG

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AJOG at a Glance

Why was this study conducted?

To evaluate the recurrence rate of hyperemesis gravidarum, to elucidate recurrence patterns of hyperemesis, and to analyze factors associated with recurring hyperemesis.

Key findings

Overall recurrence rate of hyperemesis was 24%, and 11% of women were diagnosed with hyperemesis in all of their pregnancies. Smoking was associated with lower odds of recurring hyperemesis (adjusted odds ratio, 0.27, $P < .001$); female sex of the fetus increased the odds (adjusted odds ratio, 1.29, $P = .012$).

What does this add to what is known?

Our results present various chronological recurrence patterns of hyperemesis in the course of several consecutive pregnancies. Hyperemesis gravidarum does not appear to worsen with each pregnancy. Comparisons of the women's first hyperemetic pregnancies revealed that there were very few differences between hyperemesis survivors, irrespective of whether they were diagnosed with hyperemesis in their subsequent pregnancies or not.

has been found to be more common in multiple pregnancies[10,17] as well as in pregnancies with a female fetus.[3,6] As for recurring HG, knowledge about contributing factors is limited. In the study by Fiaschi et al,[6] Asian or black ethnicity and thyroid dysfunction were associated with elevated odds of HG reoccurrence. Trogstad et al[5] found a change in paternity to be associated with reduced odds of recurrent HG, but in a study by Fejzo et al,[8] change of paternity did not affect recurrence of hyperemesis.

HG may have an effect on family planning and even mother-child relationships,[18] and the need for reliable data about recurrence rate of HG was emphasized in a recent systematic review protocol.[19]

The aims of our study were to evaluate the recurrence rate of HG in subsequent pregnancies and to analyze how maternal, environmental, and pregnancy-related factors such as age, parity, maternal prepregnancy BMI, smoking during pregnancy, marital status, socioeconomic status, municipality, month of delivery, ART, and the number and sex(es) of the fetuses are associated with recurring HG.

Materials and Methods

The data were compiled using Finnish health care registers with permission of the Finnish National Institute for Health and Welfare (THL/658/5.05.00/2012). Ethical committee of Hospital District of Southwest Finland evaluated and approved the study plan (43/180/2011).

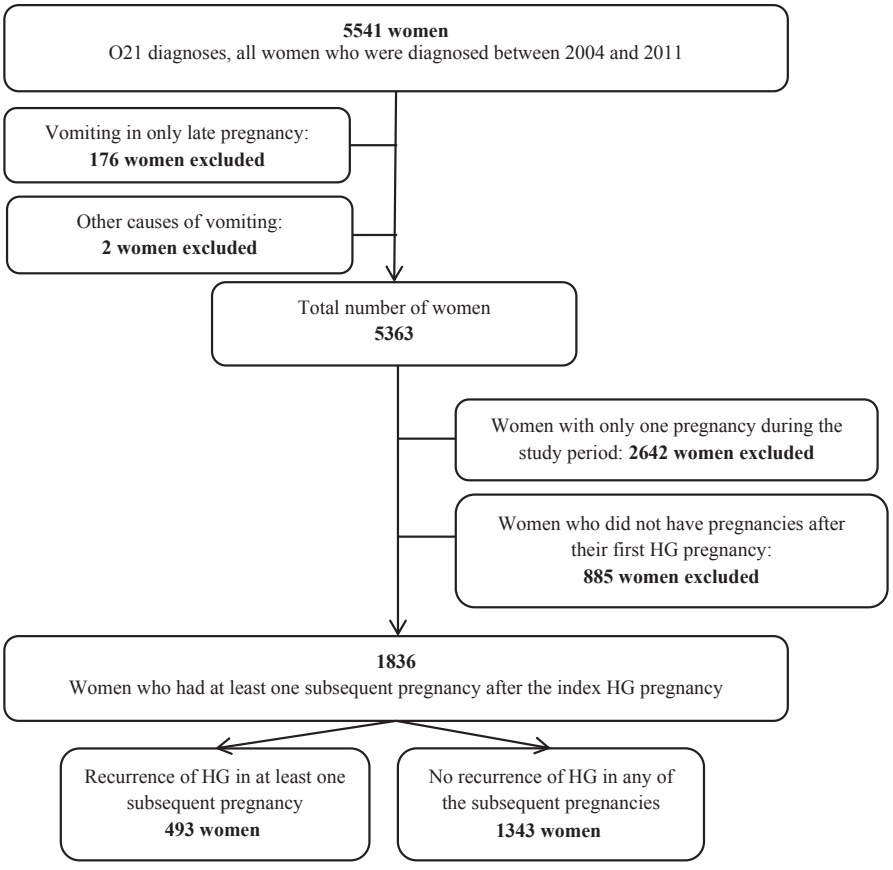
All pregnancies ending in delivery with a HG discharge diagnosis in the first 20 weeks of pregnancy (*International Statistical Classification of Diseases, 10th Revision* [*ICD-10*] diagnosis codes O21 [excessive vomiting in pregnancy], O21.0 [HG, mild or unspecified, starting before the end of the 22nd week of gestation], O21.1 [HG, starting before the end of the 22nd week of gestation, with metabolic disturbance such as carbohydrate depletion, dehydration, or electrolyte imbalance], and O21.9 [vomiting of pregnancy, unspecified][20] in the Finnish Hospital Discharge Register) from the years 2004 through 2011 were included in the study. In Finland, all persons entering the public health care system from any entry point (local health care center, emergency department, specialized clinic, or hospital ward) are given a mandatory main diagnosis and optional secondary diagnoses. These are first registered in the local health care data system to permit efficient treatment and follow-up of the patient, and, subsequently, registered in the national registers for research and statistical purposes. Our study group consists thus of women who have been diagnosed with HG with or without hospitalization. Women who had only 1 pregnancy during the study period (2642) and women who did not have pregnancies after their first pregnancy with a HG diagnosis (885) were excluded (Figure 1). Data on maternal, environmental, and pregnancy-related factors in all pregnancies ending in delivery were obtained from the Finnish Medical Birth Register: maternal age in years, parity (current pregnancy included), prepregnancy BMI (calculated from height and prepregnancy weight and categorized into <18.5; 18.5−24.9; 25−29.9; 30−34.9, and ≥ 35 kg/m^2), smoking (did not smoke; smoked but quit in the first trimester; continued smoking after the first trimester), living with partner (yes/no), socioeconomic status (based on maternal occupation), size of municipality (entered in the database as the community identification code; categorized in the analysis according to the population count: $<10{,}000$, 10,000−99,999, or $\geq 100{,}000$ inhabitants), month of delivery, ART (including insemination, follicle stimulation, and embryo transfer), and the number and sex of fetuses. Two pregnancies with another cause of vomiting than HG (1 case of gallstones and 1 case of pancreatitis) were excluded. Discharge diagnoses in subsequent pregnancies were analyzed to assess whether HG recurred in the new pregnancies.

The first pregnancy with a HG diagnosis of each woman was chosen as the index pregnancy. To calculate the average recurrence rate of HG, all pregnancies that followed the index pregnancy were divided into those that involved a HG diagnosis and those without a HG diagnosis. To assess the chronological occurrence of pregnancies with HG diagnosis and pregnancies without HG diagnosis after the index pregnancy, and to calculate the frequency of each combination, a recurrence pattern chart of HG was compiled (Figure 2).

Statistical analysis

Factors associated with recurring HG were analyzed in 2 parts: index pregnancy comparisons and subsequent pregnancy comparisons (Table).

FIGURE 1
Flowchart of study



Primary source of hyperemesis gravidarum (HG) diagnoses was Finnish Hospital Discharge Register (FHDR) (officially Care Register for Health Care), in which all health care visit diagnoses are collected, and secondary source was Finnish Medical Birth Register (FMBR), in which diagnoses given during routine maternal follow-up visits are collected. Out of 1836 women, 1828 were identified in FHDR and 374 in FMBR (366 women in both registers, 1462 only in FHDR and 8 only in FMBR). Out of 496 women with recurrence of HG, 490 were identified in FHDR and 121 in FMBR (115 women in both registers, 372 only in FHDR and 6 only in FMBR). Out of 1343 women without recurrence of HG, 1341 were identified in FHDR and 253 in FMBR (251 women in both registers, 1090 only in FHDR and 2 only in FMBR).

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First, the index pregnancies were compared to identify factors that could predict HG recurrence in the future based on the woman's first pregnancy with a HG diagnosis. The women were divided into 2 groups based on the pregnancies following the index pregnancy: (1) those with a HG diagnosis in at least 1 pregnancy following the index pregnancy (HG recurrence group); and (2) those without HG diagnosis in any of the pregnancies following the index pregnancy (no-recurrence group). The associations of factors with the HG recurrence were analyzed using univariable and multivariable binary logistic regression. Factors with a P value $<.10$ in the univariable analysis were included in the multivariable model.

In the second part of the analysis, the following pregnancies were compared to identify factors differentiating pregnancies with recurring HG from pregnancies without recurring HG. The subsequent pregnancies were divided in 2 groups: (1) pregnancies with HG diagnosis; and (2) pregnancies without HG diagnosis. One woman could have >1 pregnancy after the index pregnancy during the study period, some with HG and some without HG (Figure 2), and thus the groups were compared using binary logistic regression with generalized estimating equation to take into account the dependency between the pregnancies of a same woman. The associations of factors with the HG diagnosis were analyzed using univariable and multivariable logistic regression. Factors with a P value $<.10$ in the univariable analysis were included in the multivariable model.

Statistical analysis was performed with software (SAS System for Windows, Version 9.4; SAS Institute Inc, Cary, NC).

Results

We identified 1836 women who had at least 1 subsequent pregnancy after their index HG pregnancy. Among these women, 493 (26.9%) were diagnosed with HG in at least 1 of their following pregnancies, and 1343 (73.1%) had no HG diagnosis in any of their following pregnancies. The women had altogether 2267 pregnancies following the index HG pregnancy, and HG reoccurred in 544 of these pregnancies. The overall recurrence rate of HG was thus 24.0%.

In the chronological distribution of pregnancies with a HG diagnosis among pregnancies ending in delivery, the most frequent pattern was that none of the pregnancies following the index pregnancy were diagnosed with HG. Among women who had 1 pregnancy after the index pregnancy, HG reoccurred in 25% of the second pregnancies. There were 333 women who had >1 pregnancy after the index pregnancy, and among them, 11% had a HG diagnosis in all of their subsequent pregnancies, 22% had a HG diagnosis in at least 1 but not all of their subsequent pregnancies, and 67% had no HG diagnosis in any of their subsequent pregnancies. In all, 11% of women who had >1 pregnancy after the index pregnancy had ≥ 1 pregnancies without HG diagnosis occurring between following pregnancies with HG diagnosis; eg, HG − no HG − HG (Figure 2).

In the comparison of index pregnancies, parity was not associated with

FIGURE 2
Chronological patterns of recurrence of hyperemesis gravidarum (HG) in pregnancies following index pregnancy

One pregnancy after HG, n=1499

HG	no	75%
HG	HG	25%

Two pregnancies after HG, n=255

HG	no	no	65%
HG	HG	HG	13%
HG	HG	no	13%
HG	no	HG	9%

Three pregnancies after HG, n=60

HG	no	no	no	70%
HG	no	no	HG	7%
HG	HG	HG	no	5%
HG	HG	HG	HG	5%
HG	no	HG	HG	3%
HG	HG	no	no	3%
HG	HG	no	HG	3%
HG	no	HG	no	3%

Four pregnancies after HG, n=16

HG	no	no	no	no	75%
HG	HG	no	no	no	13%
HG	HG	HG	HG	HG	6%
HG	no	HG	HG	HG	6%

Five pregnancies after HG, n=2

HG	no	no	no	no	no	100%

HG	Index pregnancy: the first HG pregnancy during the study period.
HG	Subsequent pregnancy with HG diagnosis.
no	Subsequent pregnancy without HG diagnosis.

Pregnancies ending in delivery in 2004 through 2011 of those women who had at least 1 pregnancy after their first HG pregnancy during study period were included in analysis.

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recurrence of HG in the univariable analysis, but in the multivariable model, the recurrence of HG was more common among women with parity of 2 than parity of 1 (adjusted odds ratio [OR], 1.33, $P = .046$). The recurrence of HG (adjusted OR, 0.58, $P = .036$) was less common in overweight women compared to normal-weight women, but the other BMI classes had no associations to either direction. Women who smoked after the first trimester had lower recurrence of HG than women in the nonsmoking group (adjusted OR, 0.27, $P < .001$). Other factors were not associated with recurrence of HG.

In the comparison of the subsequent pregnancies, smoking was associated with lower odds of recurring HG. Age of 36–40 years, living in a city with >100,000 inhabitants, ART, and female sex of the fetus were associated with higher odds of recurring HG in the univariable analysis. Smoking (smoked, but quit in the first trimester vs nonsmoking: adjusted OR, 0.32, $P = .010$; continued smoking after the first trimester vs nonsmoking: adjusted OR, 0.38, $P = .002$) and female sex of the fetus (adjusted OR, 1.29, $P = .012$) remained significant in the multivariable analysis.

Comment

The recurrence rate of HG, 24%, was moderate: three-fourths of the women in our study were not diagnosed with HG in their following pregnancies. However, women who had had an earlier pregnancy with a HG diagnosis had HG considerably more frequently compared to the general population. Comparisons of the index pregnancies, all of which involved a HG diagnosis, revealed that there were very few differences between HG survivors, irrespective of whether they had HG in any of their subsequent pregnancies or not. Further, comparison of the subsequent pregnancies suggested that only few maternal, pregnancy-related, or environmental factors are consistently associated with recurring HG.

Comparison of recurrence rates is complicated by lack of universally accepted definition of HG, and, hence, a lack of common understanding of what is counted as recurrence of HG. In our study, we used the clinical diagnoses based on the *ICD-10* diagnostic system that was used in Finnish health care units during the whole study period. In the Norwegian register study of 4796 women with HG, the recurrence rate of HG was lower than ours, 15%.[5] Their study period was broader than ours, 1967 through 1998, and changes in the incidence of HG diagnosis varied during the years being lowest in the beginning and higher toward the end of the study period, possibly reflecting changes in diagnostic practices over time. In the British study,[6] the recurrence rate was

TABLE

Comparisons of maternal, environmental, and pregnancy-related factors in index pregnancies (hyperemesis gravidarum recurrence group vs no-recurrence group) and following pregnancies (pregnancies with hyperemesis gravidarum diagnosis vs pregnancies without hyperemesis gravidarum diagnosis)

	1. Comparison between index pregnancies						2. Comparisons between pregnancies after first HG pregnancy					
	HG recurrence,[a] N = 493 % (N)	No recurrence,[b] N = 1343 % (N)	OR univariable (95% CI)	*P*	OR multivariable[c] (95% CI)	*P*	HG diagnosis, N = 544 % (N)	No HG diagnosis, N = 1723 % (N)	OR univariable (95% CI)	*P*	OR multivariable[d] (95% CI)	*P*
Maternal factors												
Age, y												
≤20	9.7 (48)	8.7 (117)	1.09 (0.75–1.59)	.644			2.4 (13)	1.6 (28)	1.46 (0.73–2.91)	.285	1.51 (0.74–3.09)	.261
21–25	31.2 (154)	33.1 (445)	0.92 (0.72–1.18)	.519			19.5 (106)	22.6 (390)	0.93 (0.72–1.21)	.594	1.03 (0.79–1.35)	.835
26–30	38.5 (190)	37.7 (506)	1				35.7 (194)	37.3 (643)	1		1	
31–35	15.4 (76)	16.2 (218)	0.93 (0.68–1.27)	.639			29.6 (161)	28.5 (491)	1.11 (0.88–1.40)	.359	1.10 (0.86–1.40)	.445
36–40	4.5 (22)	3.9 (52)	1.13 (0.67–1.91)	.656			11.4 (62)	8.2 (142)	1.45 (1.04–2.01)	.028	1.35 (0.96–1.90)	.084
≥41	0.6 (3)	0.4 (5)	1.60 (0.38–6.75)	.524			1.5 (8)	1.7 (29)	1.00 (0.38–2.09)	.802	0.82 (0.34–1.99)	.668
Parity												
1	63.7 (314)	67.8 (908)	1		1							
2	22.7 (112)	19.5 (261)	1.24 (0.96–1.60)	.098	1.33 (1.00–1.76)	.046	53.9 (293)	54.4 (937)	1			
3	6.5 (32)	6.6 (89)	1.04 (0.68–1.59)	.857	1.13 (0.71–1.80)	.619	26.8 (146)	25.8 (444)	1.03 (0.84–1.3)	.775		
4	3.5 (17)	2.8 (37)	1.33 (0.74–2.39)	.344	1.40 (0.73–2.69)	.317	10.1 (55)	10.2 (176)	1.01 (0.75–1.4)	.944		
≥5	3.7 (18)	3.4 (45)	1.16 (0.66–2.03)	.611	1.02 (0.53–1.95)	.958	9.2 (50)	9.6 (166)	1.02 (0.73–1.4)	.901		
Prepregnancy BMI, kg/m^2												
<18.5	6.5 (28)	5.1 (62)	1.23 (0.77–1.96)	.391	1.38 (0.85–2.22)	.190	4.8 (25)	4.3 (71)	0.87 (0.54–1.42)	.580	0.91 (0.55–1.51)	.711
18.5–24.9	63.8 (275)	60.9 (747)	1		1		59.4 (312)	55.3 (920)	1		1	
25–29.9	20.7 (89)	22.2 (272)	0.88 (0.67–1.17)	.403	0.93 (0.70–1.23)	.601	21.5 (113)	24.2 (403)	0.81 (0.63–1.03)	.086	0.80 (0.63–1.03)	.089
30–34.9	4.9 (21)	8.3 (102)	0.56 (0.34–0.91)	.020	0.58 (0.35–0.96)	.036	9.1 (48)	11.1 (185)	0.76 (0.54–1.08)	.128	0.77 (0.54–.11)	.163
≥35	4.2 (18)	3.6 (44)	1.11 (0.63–1.96)	.715	1.32 (0.74–2.38)	.348	5.1 (27)	5.2 (86)	0.86 (0.54–1.37)	.517	0.91 (0.56–1.48)	.709
Unknown	62	116					19	58				

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(continued)

TABLE

Comparisons of maternal, environmental, and pregnancy-related factors in index pregnancies (hyperemesis gravidarum recurrence group vs no-recurrence group) and following pregnancies (pregnancies with hyperemesis gravidarum diagnosis vs pregnancies without hyperemesis gravidarum diagnosis) *(continued)*

	1. Comparison between index pregnancies						2. Comparisons between pregnancies after first HG pregnancy					
	HG recurrence,[a] N = 493 % (N)	No recurrence,[b] N = 1343 % (N)	OR univariable (95% CI)	*P*	OR multivariable[c] (95% CI)	*P*	HG diagnosis, N = 544 % (N)	No HG diagnosis, N = 1723 % (N)	OR univariable (95% CI)	*P*	OR multivariable[d] (95% CI)	*P*
Smoking during pregnancy												
No	95.4 (460)	88.3 (1158)	1		1		96.8 (512)	90.2 (1499)	1		1	
Yes, but quit in first trimester	2.5 (12)	4.1 (54)	0.56 (0.30–1.05)	.073	0.55 (0.28–1.07)	.079	0.9 (5)	3.1 (51)	0.32 (0.14–0.74)	.008	0.32 (0.14–0.76)	.010
Yes, continued after first trimester	2.1 (10)	7.6 (99)	0.25 (0.13–0.49)	<.001	0.27 (0.13–0.54)	<.001	2.3 (12)	6.7 (112)	0.33 (0.18–0.61)	<.001	0.38 (0.21–0.71)	.002
Unknown	11	32					15	61				
Marital status												
Living with partner	95.7 (464)	94.8 (1236)	1				96.2 (507)	96.4 (1619)	1			
Not living with partner	4.3 (21)	5.2 (68)	0.82 (0.50–1.36)	.445			3.8 (20)	3.6 (60)	1.02 (0.60–1.74)	.946		
Unknown	8	39					17	44				
Environmental factors												
Socioeconomic status												
Employed	73.9 (272)	76.1 (801)	1				83.7 (293)	81.3 (968)	1			
Unemployed/at home	26.1 (96)	23.9 (252)	1.12 (0.85–1.47)	.408			16.3 (57)	18.7 (222)	0.84 (0.61–1.15)	.276		
Unknown	125	290					194	533				
Domicile population												
<10,000 Inhabitants	45.2 (223)	41.1 (551)	1		1		43.8 (238)	36.5 (628)	1		1	
10,000–99,999 Inhabitants	39.8 (196)	39.9 (536)	1.26 (0.93–1.71)	.139	1.21 (0.87–1.67)	.253	39.7 (216)	43.4 (748)	1.12 (0.84–1.49)	.454	1.10 (0.81–1.48)	.553
≥100,000 Inhabitants	15.0 (74)	19.0 (255)	1.39 (1.03–1.89)	.031	1.21 (0.87–1.67)	.256	16.5 (90)	20.1 (347)	1.41 (1.06–1.88)	.019	1.33 (0.99–1.80)	.061
Unknown		1										

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(continued)

TABLE

Comparisons of maternal, environmental, and pregnancy-related factors in index pregnancies (hyperemesis gravidarum recurrence group vs no-recurrence group) and following pregnancies (pregnancies with hyperemesis gravidarum diagnosis vs pregnancies without hyperemesis gravidarum diagnosis) *(continued)*

	1. Comparison between index pregnancies						2. Comparisons between pregnancies after first HG pregnancy					
	HG recurrence,[a] N = 493 % (N)	No recurrence,[b] N = 1343 % (N)	OR univariable (95% CI)	*P*	OR multivariable[c] (95% CI)	*P*	HG diagnosis, N = 544 % (N)	No HG diagnosis, N = 1723 % (N)	OR univariable (95% CI)	*P*	OR multivariable[d] (95% CI)	*P*
Pregnancy-related factors												
Month of delivery												
January through March	24.7 (332)	24.3 (120)	1				19.8 (108)	23.2 (400)	1			
April through June	24.8 (333)	26.8 (132)	1.10 (0.82–1.47)	.533			26.7 (145)	23.8 (410)	1.24 (0.95–1.62)	.111		
July through September	25.8 (347)	25.8 (127)	1.01 (0.76–1.36)	.933			27.0 (147)	26.5 (456)	1.15 (0.88–1.51)	.316		
October through December	24.7 (457)	23.1 (144)	0.95 (0.71–1.28)	.751			26.5 (144)	26.5 (457)	1.09 (0.83–1.43)	.554		
Assisted reproductive technology[e]												
No	96.4 (1294)	96.4 (475)	1				97.1 (528)	98.6 (1699)	1		1	
Yes	3.6 (24)	3.6 (16)	1.00 (0.58–1.74)	.998			2.9 (16)	1.4 (24)	2.10 (1.08–4.09)	.029	1.74 (0.88–3.47)	.114
Number of fetuses												
One fetus	98.0 (483)	96.4 (1294)	1				97.8 (532)	98.7 (1700)	1			
Two fetuses	2.0 (10)	3.6 (24)	1.05 (0.50–2.19)	.900			2.2 (12)	1.3 (23)	1.59 (0.77–3.29)	.207		
Sex of fetus, all pregnancies[f]												
Male	46.3 (228)	45.1 (606)	1		1		49.3 (268)	54.0 (931)	1		1	
Female	53.75 (265)	54.9 (737)	0.96 (0.78–1.18)	.668	0.93 (0.71–1.22)	.597	50.7 (276)	46.0 (792)	1.26 (1.05–1.52)	.014	1.29 (1.06–1.56)	.012
Sex of fetus, singleton pregnancies[g]												
One fetus, male	45.5 (224)	44.3 (594)	1				48.6 (264)	53.5 (921)	1			
One fetus, female	52.6 (259)	53.9 (723)	0.95 (0.77–1.17)	.631			49.4 (268)	45.2 (779)	1.26 (1.04–1.51)	.018		

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(continued)

TABLE
Comparisons of maternal, environmental, and pregnancy-related factors in index pregnancies (hyperemesis gravidarum recurrence group vs no-recurrence group) and following pregnancies (pregnancies with hyperemesis gravidarum diagnosis vs pregnancies without hyperemesis gravidarum diagnosis) *(continued)*

	1. Comparison between index pregnancies					2. Comparisons between pregnancies after first HG pregnancy				
	HG recurrence,[a] N = 493 % (N)	No recurrence,[b] N = 1343 % (N)	OR univariable (95% CI)	*P*	OR multivariable[c] (95% CI)	*P*	HG diagnosis, N = 544 % (N)	No HG diagnosis, N = 1723 % (N)	OR univariable (95% CI)	*P*	OR multivariable[d] (95% CI)	*P*
Sex of fetuses, twin pregnancies[g]												
Two males	0.4 (2)	0.6 (8)	1				0.2 (1)	0.5 (8)	1			
Two females	0.8 (4)	0.8 (11)	1.45 (0.21–9.98)	.703			1.1 (6)	0.3 (5)	1.94 (0.25–15.02)	.527		
One male, one female	0.6 (3)	0.5 (6)	2.00 (0.25–15.99)	.513			0.7 (4)	0.5 (9)	6.93 (1.19–40.41)	.031		

BMI, body mass index; *CI*, confidence interval; *HG*, hyperemesis gravidarum; *OR*, odds ratio.

[a] In this group, at least 1 subsequent pregnancy had HG diagnosis; [b] In this group, no subsequent pregnancies had HG diagnosis; [c] Multivariable logistic regression analysis of index pregnancies: parity, BMI, smoking, and size of municipality included in model; [d] Multivariable logistic regression analysis of subsequent pregnancies: age, BMI, smoking, size of municipality, assisted reproductive technology, and sex of fetus included in model; [e] Yes = insemination, follicle stimulation, embryo transfer, or combination of these; [f] In twin pregnancies, sex of firstborn fetus was included in analysis; [g] Additional analyses, not included in multivariable model due to collinearity with sex and number of fetuses.

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similar to ours, 26%, and their study period, 1997 through 2012, overlapped ours. Both previous register studies analyzed the first and the second pregnancies of their study population. In contrast, we included all pregnancies during the study period in the analysis, revealing patterns of HG recurrence where ≥1 pregnancy without a HG diagnosis between 2 HG pregnancies may occur. In the US study, the self-reported recurrence rate, 81%, was substantially higher than in our study, and the recurrence rate according to hospitalization, 39%, was closer to our results.[8,9] Their data were collected retrospectively with a questionnaire to HG patients who had visited a HG support Internet site and been treated with intravenous hydration in their first pregnancy. The study group may thus have differed from the general population and possible bias toward overestimation of the recurrence cannot be excluded, or, since their study was small (57 pregnancies after an earlier hyperemetic pregnancy), the difference may stem from general variation. The discovery of potential HG-associated candidate genes[21] has provided a new element for predicting recurrence of HG. For instance, the G allele of the gene GDF15 is more frequently found among HG patients compared to symptom-free women (approximately 80% vs 70%), as well as the A allele of the gene IGFBP7 (approximately 70% vs 65%), and thus examining these associations in the context of recurring hyperemesis will be of interest; in theory, recurrence of hyperemesis may be more common among those with a genetic predisposition to the condition. However, since the alleles associated with HG are found in more than half of women without HG, too, it is not yet possible to estimate whether the genes would explain the observed one-fourth chance of recurrence.

Maternal factors that have earlier been found to be associated with HG in general, such as parity or BMI, did not give constant results in our study setting, and warrant more studies. Smoking showed a consistent association with recurrence of HG. The lower odds of recurring HG

associated with smoking is presumably due to its effect on the placenta, for instance inhibiting healthy placental growth and possibly affecting placental proteins that may play a role in HG, such as GDF15 and IGFBP7.[14,21,22]

In the univariate analysis, municipality of residence appeared to have an effect on recurring HG: women living in bigger communities experienced recurrent HG more often than women living in smaller communities. However, this finding disappeared in the multivariable analysis. These results warrant further studying, since in Finland, although health care services are universal and mostly free of charge during pregnancy, the population density and distance to health care services are quite dissimilar in different parts of the country: in the less densely populated areas of Finland, especially in the North, distance to the nearest health care unit may be several hundred miles. Communities with population count of at least 100,000 inhabitants are fairly large in the Finnish scale; there were only 9 such cities during the study period. It can be hypothesized that in large towns, where health care services are more easily accessible, women are more likely to seek assistance and be diagnosed. On the other hand, women living in small communities may more often live near their relatives compared to women who have, eg, moved to largest cities, and thus have better support networks. There may also be different treatment policies in different parts of the country, which may have influenced our results.

Among the pregnancy-related factors, ART was associated with recurring HG in the univariable analysis, but in the multivariable model, the association was statistically insignificant. Further analysis of the role of ART is of interest, as an association between HG and ART has been described previously.[11,15,16] The higher odds of HG associated with a female fetus has also been reported previously.[3,6] There may be a common mechanism of action related with both ART and a female fetus: serum levels of hCG higher than average have been found in pregnancies with ART, as well as in pregnancies with a female fetus.[14,22] The role of hCG levels in HG remains unclear with statistical evidence both for and against the hypothesis that hCG, or individual susceptibility to hCG, or some of its biochemical isoforms, may cause or aggravate symptoms of HG in some women.[16,23] A detailed analysis of 4372 pregnancies after in vitro fertilization did not show any association between hCG levels and HG[24] and in the light of new evidence that other placental genes may be involved in development of HG,[21] the association between HG and hCG levels may turn out to be incidental. Further studies are needed to fully understand these associations.

Our register data did not permit analysis of all factors that have been studied earlier in association with recurring HG, such as ethnicity or migrant background, thyroid function,[6] or change in paternity.[5] Nevertheless, our results were in accordance with the earlier findings that age[5,6] or socioeconomic status[6] do not seem to be associated with the recurrence of HG.

Strengths and weaknesses

Our data were drawn from registers. According to validation studies, the accountability and coverage of the Finnish health care register data are high and reliable.[25] Data about visits to health care clinics and hospital admissions are systematically collected into nationwide centralized registers. Data provision is obligatory, and all institutions use the same data collection protocols established by the National Institute for Health and Welfare.[26] The HG patients entered in this study were diagnosed in the general health care system, in maternity health care clinics, in maternity outpatient care clinics, or in the hospital. On the other hand, all women with symptoms of HG may not have sought medical care and thus may not have been diagnosed, leading to some level of underestimation. Our results can thus be interpreted to represent a lower limit of recurrence of HG, and the true recurrence can be higher. The duration of follow-up, 8 years, did not necessarily cover the entire reproductive history of all women, and thus continuation of follow-up of the women in our study would be of interest.

Meaning of the study

Knowledge about the recurrence of HG in a subsequent pregnancy is of importance, since severe HG may have an effect on family planning[19] and mother-child relationship.[18] Some factors affecting HG recurrence can be identified, but there is not yet a reliable way to predict whether HG will reoccur in a subsequent pregnancy. The lack of a trend toward HG getting more likely with each new pregnancy is encouraging. Even though it is challenging to estimate the recurrence risk of HG in a subsequent pregnancy by evaluating the conditions in a woman's first HG pregnancy, knowing that HG does not necessarily reoccur may be reassuring when considering a new pregnancy. ■

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