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RESEARCH

Recurrence of hyperemesis gravidarum across generations: population based cohort study

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ABSTRACT

Objective To estimate the risk of hyperemesis gravidarum (hyperemesis) according to whether the daughters and sons under study were born after pregnancies complicated by hyperemesis.

Design Population based cohort study.

Setting Registry data from Norway.

Participants Linked generational data from the medical birth registry of Norway (1967-2006): 544 087 units of mother and childbearing daughter and 399 777 units of mother and child producing son.

Main outcome measure Hyperemesis in daughters in mother and childbearing daughter units and hyperemesis in female partners of sons in mother and child producing son units.

Results Daughters who were born after a pregnancy complicated by hyperemesis had a 3% risk of having hyperemesis in their own pregnancy, while women who were born after an unaffected pregnancy had a risk of 1.1% (unadjusted odds ratio 2.9, 95% confidence interval 2.4 to 3.6). Female partners of sons who were born after pregnancies complicated by hyperemesis had a risk of 1.2% (1.0, 0.7 to 1.6). Daughters born after a pregnancy not complicated by hyperemesis had an increased risk of the condition if the mother had hyperemesis in a previous or subsequent pregnancy (3.2 (1.6 to 6.4) if hyperemesis had occurred in one of the mother's previous pregnancies and 3.7 (1.5 to 9.1) if it had occurred in a later pregnancy). Adjustment for maternal age at childbirth, period of birth, and parity did not change the estimates. Restrictions to firstborns did not influence the results.

Conclusions Hyperemesis gravidarum is more strongly influenced by the maternal genotype than the fetal genotype, though environmental influences along the maternal line cannot be excluded as contributing factors.

INTRODUCTION

Hyperemesis gravidarum (hyperemesis) is defined as excessive nausea and vomiting in pregnancy starting before the 22nd week of gestation, which might lead to nutritional deficiencies and weight loss.[1] Hyperemesis occurs in 0.5-2.0% of pregnancies and is the most common cause of admission to hospital in early pregnancy.[2-5] It is associated with adverse pregnancy outcomes such as low birth weight and preterm birth.[6-8] The aetiology is unknown.[2 3] A study using the medical birth registry of Norway found that the risk of hyperemesis in a woman's second pregnancy was 15.2% if hyperemesis had occurred in the first, compared with only 0.7% if it had not occurred.[9] For women with hyperemesis in the first pregnancy, the risk of hyperemesis in the second pregnancy was 10.9% after a change of partner, while it was 16.0% if the partner remained the same.[9] These findings suggest that there might be a genetic aspect to hyperemesis, possibly involving both maternal and fetal genes, although environmental factors cannot be ruled out.

To extend our understanding of the aetiology of this condition we examined the risk of hyperemesis according to whether or not the women and men under study were born after pregnancies complicated by hyperemesis. In addition, we estimated the risk of hyperemesis in women born after pregnancies not complicated by hyperemesis but where their mothers had hyperemesis in a previous or later pregnancy.

METHODS

Population under study

The medical birth registry is a population based, mandatory registry of all births in Norway and contains data from 1967 to the present, providing an opportunity to study the occurrence of birth outcomes across generations.[10-12] The midwife or physician attending the birth fills in a standardised form with demographic data on the parents, maternal health before and during pregnancy, complications and interventions during delivery, and the condition of the newborn. An antenatal card is completed for all pregnant women at the first routine examination in pregnancy, normally early in the first trimester. All complications during pregnancy are noted on the card. After birth a national identification number, which is unique for each inhabitant, is provided by the population registry of Norway. We had access to records for the period 1967-2006, comprising 2.3 million births. We linked the identification numbers for single born children (male or female) with identification numbers of mothers or fathers of single born

children, including 544 087 units of mother and childbearing daughter and 399 777 units of mother and child producing son. The lower number of mother and child producing son units was mainly because of the older average age of fathers than mothers at the birth of their children and partly because of missing paternal data. The father's identification number in the last generation was missing for 1.2%.

We also selected women who had given birth to at least two daughters, both of whom were registered with at least one pregnancy in the registry. This enabled us to examine the risk of hyperemesis in women born after pregnancies that were not complicated by hyperemesis but where their mothers had hyperemesis in a previous or later pregnancy. We identified 37 714 families and excluded 32 with hyperemesis in both pregnancies in the first generation. For these pairs of sisters the risk of recurrence was high (odds ratio 27.5, 95% confidence interval 18.5 to 40.9). Restriction of analysis to the first pair of daughters, and their first pregnancies, resulted in only one record per family and thus independence within the material.

Variables

We obtained data on hyperemesis from the registry using ICD-8 (international classification of diseases, eighth revision) codes 638.0 and 638.9 for 1967-98 and ICD-10 (10th revision) codes O 21.0, O 21.1 and O 21.9 for 1999-2006.[1] The ICD coding at the registry was based on the information the attending midwife provided according to the woman's antenatal card as well as any hospital records. Admission to hospital was not a criterion for women to be registered with hyperemesis in the registry. Maternal age was categorised for both generations as <20, 20-24, 25-29, 30-34, and ≥35. Parity was categorised as nulliparous or multiparous. The time period of birth in both generations was categorised into five year groups.

Table 1 | Risk of hyperemesis and unadjusted odds ratio for hyperemesis with 95% confidence interval in women depending on occurrence of hyperemesis in their mothers, medical birth registry of Norway 1967-2006

Hyperemesis in mother	No of pregnancies	No of daughters with hyperemesis	Risk of hyperemesis in daughters (%)	OR* (95% CI)
All mother-childbearing daughter units				
Yes	3704	111	3.00	2.90 (2.35 to 3.57)
No	540 383	5680	1.05	Reference
Total	544 087	5791	1.06	—
Restricted to firstborn in both generations				
Yes	934	30	3.21	3.20 (2.21 to 4.62)
No	113 436	1162	1.02	Reference
Total	114 370	1192	1.04	—

*OR=odds ratio based on robust clustering accounting for dependencies within data. Of first generation mothers, 58% contribute to more than one family record. Adjustment for maternal age at childbirth and period of birth in both generations and maternal parity in first generation (when not restricted to first birth order) did not change estimates.

Statistical analysis

The relative risks of hyperemesis were estimated by odds ratios, calculated with logistic regression with SPSS for Windows (version 16.0) presented in three different models. Model 1 (mother-daughter recurrence) was a woman's risk of hyperemesis if she herself was born after a pregnancy complicated by hyperemesis. Model 2 (mother-son recurrence) was the risk of hyperemesis in female partners of sons who were born after a pregnancy complicated by hyperemesis. Model 3 (mother-daughters recurrence) was risk of hyperemesis in a woman born after a pregnancy not complicated by hyperemesis but whose mother had hyperemesis in a previous or subsequent pregnancy.

We adjusted for maternal age at birth, period of birth in both generations, and parity as possible confounders. The same mother could appear in more than one unit under study if she had more than one child. This introduced dependency in the data. We therefore used clustered robust standard errors as available through Stata (release 9). All 95% confidence intervals reported are based on these standard errors where relevant.

RESULTS

Model 1 (mother-daughter recurrence): hyperemesis in women born after pregnancy complicated by hyperemesis

The mothers from 544 087 mother and childbearing daughter units delivered during 1967-1993, while the daughters delivered their babies during 1981-2006. The mean year of birth for the two generations was 1972 and 2000, respectively. From 1967 to 1993, the prevalence of hyperemesis was 0.68% (3704 cases), while from 1981 to 2006 the prevalence was 1.06% (5791 cases). If the mother had hyperemesis, the risk of hyperemesis in the daughter (recurrence risk) was 3.00% compared with 1.05% if the mother did not have hyperemesis, corresponding to an unadjusted odds ratio of 2.90 (95% confidence interval 2.35 to 3.57) (table 1). For comparison, the adjusted odds ratio was 2.91 (2.36 to 3.59). An analysis of units in which both mother and daughter were firstborn showed a slight increase in risk.

Model 2 (mother-son recurrence): hyperemesis in female partners of men who were born after pregnancy complicated by hyperemesis

In the second cohort of 399 777 mother and child producing son units, the mothers delivered their sons during 1967-1990, and the prevalence of hyperemesis was 0.57% (2290 cases). Female partners of these men delivered their babies during 1980-2006; the prevalence of hyperemesis was 1.13% (4526 cases). The female partner of the son had a risk of hyperemesis of 1.18% if his mother had had hyperemesis and 1.13% if his mother had not had hyperemesis (table 2). The odds ratio was not significantly different from the null value with an unadjusted odds ratio of 1.04 (0.68 to 1.58). Adjustment for the aforementioned possible

Table 2 | Risk of hyperemesis in female partners of sons and unadjusted odds ratio for hyperemesis with 95% confidence interval depending on occurrence of hyperemesis in man's mother, medical birth registry of Norway 1967-2006

Hyperemesis in mother	No of pregnancies	No of female partners with hyperemesis	Risk of hyperemesis in female partners (%)	OR* (95% CI)
All mother-child producing son units				
Yes	2290	27	1.18	1.04 (0.68 to 1.58)
No	397 487	4499	1.13	Reference
Total	399 777	4526	1.13	—
Restriction to firstborn in both generations				
Yes	569	7	1.23	1.15 (0.54 to 2.43)
No	83 822	896	1.07	Reference
Total	84 391	903	1.07	—

*OR=odds ratio based on robust clustering accounting for dependencies within data. Of first generation mothers, 54% contribute to more than one family record. Adjustment for maternal age at childbirth and period of birth in both generations and maternal parity in first generation (when not restricted to first birth order) did not change estimates.

confounders did not change our estimates. Restriction of the sample to firstborn in both generations did not influence the associations across generations.

Model 3 (mother-daughters recurrence): hyperemesis in women born after pregnancy not complicated by hyperemesis, but whose mother had hyperemesis in previous or subsequent pregnancy

If the mother had hyperemesis in a previous pregnancy (leading to an older sister of the woman under study) but not in the pregnancy in which the woman under study was a fetus, the risk of hyperemesis was 3.08% compared with 1.00% if the mother had never had hyperemesis, corresponding to an unadjusted odds ratio of 3.15 (1.55 to 6.41) (table 3). If the mother had hyperemesis in a later pregnancy (leading to a younger sister of the woman under study), the risk was 2.99% compared with 0.83% if the mother had never had hyperemesis; the unadjusted odds ratio was 3.70 (1.51 to 9.08) (table 3). Corresponding adjusted analyses resulted in an odds ratio of 3.18 (1.56 to 6.49) and 3.81 (1.55 to 9.36), respectively.

Table 3 | Risk of hyperemesis and unadjusted odds ratio for hyperemesis with 95% confidence interval among women born after unaffected pregnancy, depending on whether their mothers had hyperemesis in previous or subsequent pregnancy, medical birth registry of Norway 1967-2006

Hyperemesis in mother	No of pregnancies	No of daughters with hyperemesis, born after unaffected pregnancies	Risk of hyperemesis in daughters (%)	OR* (95% CI)
In previous pregnancy				
Yes	260	8	3.08	3.15 (1.55 to 6.41)
No	37 255	372	1.00	Reference
Total	37 515	380	1.01	—
In subsequent pregnancy				
Yes	167	5	2.99	3.70 (1.51 to 9.08)
No	37 255	308	0.83	Reference
Total	37 422	313	0.84	—

*OD=odds ratio based on unique family sets. Adjustment for maternal age at childbirth and period of birth in both generations did not change the estimates.

DISCUSSION

The risk of hyperemesis in a pregnant woman is threefold if the woman's mother had ever experienced hyperemesis in a pregnancy. This was regardless of whether hyperemesis had occurred in the pregnancy leading to the woman under study or in a previous or subsequent pregnancy. In contrast, female partners of men whose mother had hyperemesis during pregnancy did not have an increased risk of hyperemesis.

Strengths and limitations

Our population based cohort is based on mandatory reporting of a standardised dataset over a period of 40 years. Selection bias is not an issue. The validity of the data on hyperemesis in the registry is acceptable, as has been discussed in earlier publications.[9 13] The prevalence of hyperemesis was higher in the second generation. This finding is in line with previous studies and might be because of better registration of hyperemesis in the registry since 1999, increased awareness of the condition, or a real increase in prevalence.[9 13 14] When we adjusted for period of birth, maternal age, and parity in both generations, the association across generations did not change. Unfortunately, we did not have data on variables such as body mass index, smoking, educational attainment, and ethnic background. As most immigrants to Norway arrived after 1986, however, confounding by ethnicity in our dataset is unlikely to affect risk of recurrence across generations. In a previous study that linked data from the registry to educational information obtained from a registry in Statistics Norway, hyperemesis was not associated with maternal educational attainment.[13]

Comparison with other studies

We are not aware of any other population based studies of the recurrence of hyperemesis across generations. In a self selected sample from an internet survey there was a high degree of familial clustering of hyperemesis.[15] Other studies have reported that siblings and mothers of women with nausea and vomiting in pregnancy are more likely to have experienced the same symptoms.[16-18] A classic twin study, in which the correlation of liability towards nausea and vomiting in pregnancy was estimated for monozygotic and dizygotic twins, found that genetic variation probably explained about 50% of the population variance in this phenotype.[16] Hyperemesis is a rare condition, however, which occurs in only a few pregnancies, whereas nausea and vomiting in pregnancy is common. Currently we do not know how hyperemesis and nausea and vomiting in pregnancy are related.[3]

Implications

Hyperemesis tends to recur in pregnancies in the same woman.[9] An increased risk across generations further

WHAT IS ALREADY KNOWN ON THIS TOPIC

Women who have hyperemesis in their first pregnancy have a high risk of recurrence

This risk is reduced by change of paternity, suggesting a contribution from fetal genes

Hyperemesis has been associated with psychological disturbances and not with genetic aetiology

WHAT THIS STUDY ADDS

The risk of hyperemesis was about threefold among women whose mothers had ever experienced hyperemesis in a pregnancy

The observed pattern of familial clustering suggests that maternal genes are more important than fetal genes in the aetiology of hyperemesis

suggests that genetic factors are important. That the risk is passed on to daughters but not to female partners of sons, suggests that the maternal genotype is more important than the fetal genotype. It is possible, however, that the risk is not genetically transmitted but is caused by common environmental factors that are shared by mothers and daughters. These can be nutritional factors, other lifestyle factors, or infections.[19-22] Genomic imprinting is a possibility but is hard to establish as a cause in sex limited traits such as hyperemesis. Smoking during pregnancy is associated with a reduced risk of hyperemesis and is a candidate for social transmission to daughters.[18 23-25] The birth registry has included information on smoking since 1999 but unfortunately not for earlier births.

A previous study on consanguinity and risk of hyperemesis in the birth registry showed that consanguinity did not increase the risk, implying that fetal recessive genes are not playing a major role in the development of hyperemesis.[14] A study of recurrence of hyperemesis in successive pregnancies in the same woman showed that there was less recurrence after a change of partner, suggesting that fetal genes could have a role.[9] Lifestyles and socioeconomic conditions, however, might change along with a change of partner. The lack of information on environmental factors in our study emphasises the need for more detailed epidemiological studies.

Previously, hyperemesis was believed to be caused by psychological mechanisms, such as an unconscious rejection of the child or partner.[26] Some women experiencing this condition are still told by their healthcare providers to "quit pretending to be sick."[27] The associated psychological symptoms, however, are considered by others to be a consequence of the condition.[28] Hyperemesis is known to reduce a woman's quality of life.[29] Women who have had hyperemesis seem to be less able to welcome new pregnancies and are more likely to consider a termination.[30 31]

Conclusion and implications for clinicians

Our results show a high intergenerational risk of recurrence of hyperemesis transmitted through the mothers to the daughters. The risk of hyperemesis among the daughters was increased regardless of whether or not they themselves were born after a pregnancy complicated by hyperemesis, as long as the mother had hyperemesis in a previous or subsequent pregnancy. Female partners of men who were born after a pregnancy with hyperemesis did not have an increased risk. Our findings suggest a stronger influence of the maternal genotype than the fetal genotype or a covariation of environmental factors along the maternal line.

This study provides a new perspective on the causation of hyperemesis. It might lead to a better appreciation of the underlying biology and should stimulate research into the genetic aetiology. This, as well as an understanding of the psychological consequences of experiencing severe nausea and vomiting, could be helpful for clinicians who treat and counsel women with hyperemesis gravidarum.

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1 World Health Organization. International classification of diseases. WHO, 2009.
2 Eliakim R, Abulafia O, Sherer DM. Hyperemesis gravidarum: a current review. *Am J Perinatol* 2000;17:207-18.
3 Verberg MF, Gillott DJ, Al Fardan N, Grudzinskas JG. Hyperemesis gravidarum, a literature review. *Hum Reprod Update* 2005;11:527-39.
4 Adams MM, Harlass FE, Sarno AP, Read JA, Rawlings JS. Antenatal hospitalization among enlisted servicewomen, 1987-1990. *Obstet Gynecol* 1994;84:35-9.
5 Gazmararian JA, Petersen R, Jamieson DJ, Schild L, Adams MM, Deshpande AD, et al. Hospitalizations during pregnancy among managed care enrollees. *Obstet Gynecol* 2002;100:94-100.
6 Bailit JL. Hyperemesis gravidarium: epidemiologic findings from a large cohort. *Am J Obstet Gynecol* 2005;193:811-4.
7 Chin RK. Antenatal complications and perinatal outcome in patients with nausea and vomiting-complicated pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1989;33:215-9.
8 Dodds L, Fell DB, Joseph KS, Allen VM, Butler B. Outcomes of pregnancies complicated by hyperemesis gravidarum. *Obstet Gynecol* 2006;107:285-92.
9 Trogstad LI, Stoltenberg C, Magnus P, Skjaerven R, Irgens LM. Recurrence risk in hyperemesis gravidarum. *BJOG* 2005;112:1641-5.
10 Skjaerven R, Vatten LJ, Wilcox AJ, Ronning T, Irgens LM, Lie RT. Recurrence of pre-eclampsia across generations: exploring fetal and maternal genetic components in a population based cohort. *BMJ* 2005;331:877.
11 Nordtveit TI, Melve KK, Albrechtsen S, Skjaerven R. Maternal and paternal contribution to intergenerational recurrence of breech delivery: population based cohort study. *BMJ* 2008;336:872-6.
12 Irgens LM. The medical birth registry of Norway. Epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand* 2000;79:435-9.
13 Vikanes ÅV, Grjibovski A, Vangen S, Magnus P. Variations in prevalence of hyperemesis gravidarum by country of birth: a study of 900,074 births in Norway, 1967-2005. *Scand J Public Health* 2008;36:135-42.
14 Grjibovski AM, Vikanes A, Stoltenberg C, Magnus P. Consanguinity and the risk of hyperemesis gravidarum in Norway. *Acta Obstet Gynecol Scand* 2008;87:20-5.

15 Fejzo MS, Ingles SA, Wilson M, Wang W, MacGibbon K, Romero R, et al. High prevalence of severe nausea and vomiting of pregnancy and hyperemesis gravidarum among relatives of affected individuals. *Eur J Obstet Gynecol Reprod Biol* 2008;141:13-7.
16 Corey LA, Berg K, Solaas MH, Nance WE. The epidemiology of pregnancy complications and outcome in a Norwegian twin population. *Obstet Gynecol* 1992;80:989-94.
17 Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. *Br J Gen Pract* 1993;43:245-8.
18 Vellacott ID, Cooke EJ, James CE. Nausea and vomiting in early pregnancy. *Int J Gynaecol Obstet* 1988;27:57-62.
19 Cedergren M, Brynhildsen J, Josefsson A, Sydsjo A, Sydsjo G. Hyperemesis gravidarum that requires hospitalization and the use of antiemetic drugs in relation to maternal body composition. *Am J Obstet Gynecol* 2008;198:412-5.
20 Signorello LB, Harlow BL, Wang S, Erick MA. Saturated fat intake and the risk of severe hyperemesis gravidarum. *Epidemiology* 1998;9:636-40.
21 Golberg D, Szilagyi A, Graves L. Hyperemesis gravidarum and Helicobacter pylori infection: a systematic review. *Obstet Gynecol* 2007;110:695-703.
22 Sandven I, Abdelnoor M, Nesheim BI, Melby KK. Helicobacter pylori infection and hyperemesis gravidarum: a systematic review and meta-analysis of case-control studies. *Acta Obstet Gynecol Scand* 2009;88:1190-200.
23 Depue RH, Bernstein L, Ross RK, Judd HL, Henderson BE. Hyperemesis gravidarum in relation to estradiol levels, pregnancy outcome, and other maternal factors: a seroepidemiologic study. *Am J Obstet Gynecol* 1987;156:1137-41.
24 Källen B, Lundberg G, Aberg A. Relationship between vitamin use, smoking, and nausea and vomiting of pregnancy. *Acta Obstet Gynecol Scand* 2003;82:916-20.
25 Fell DB, Dodds L, Joseph KS, Allen VM, Butler B. Risk factors for hyperemesis gravidarum requiring hospital admission during pregnancy. *Obstet Gynecol* 2006;107:277-84.
26 Fairweather DV. Nausea and vomiting in pregnancy. *Am J Obstet Gynecol* 1968;102:135-75.
27 Poursharif B, Korst LM, Fejzo MS, Macgibbon KW, Romero R, Goodwin TM. The psychosocial burden of hyperemesis gravidarum. *J Perinatol* 2008;28:176-81.
28 Kim DR, Connolly KR, Cristancho P, Zappone M, Weinrieb RM. Psychiatric consultation of patients with hyperemesis gravidarum. *Arch Womens Ment Health* 2009;12:61-7.
29 O'Brien B, Naber S. Nausea and vomiting during pregnancy: effects on the quality of women's lives. *Birth* 1992;19:138-43.
30 Mazzotta P, Stewart DE, Koren G, Magee LA. Factors associated with elective termination of pregnancy among Canadian and American women with nausea and vomiting of pregnancy. *J Psychosom Obstet Gynaecol* 2001;22:7-12.
31 Poursharif B, Korst LM, Macgibbon KW, Fejzo MS, Romero R, Goodwin TM. Elective pregnancy termination in a large cohort of women with hyperemesis gravidarum. *Contraception* 2007;76:451-5.

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