

## Recurrence Risk of Hyperemesis Gravidarum

### Abstract

The purpose of this study is to describe the recurrence risk for hyperemesis gravidarum (HG). Women who registered on a website sponsored by the Hyperemesis Education and Research Foundation as having had one HG-complicated pregnancy were contacted to follow-up on a subsequent pregnancy. One hundred women responded. Fifty-seven had become pregnant again, 2 were trying to conceive, 37 were not willing to get pregnant again due to HG, and 4 did not have a 2<sup>nd</sup> pregnancy for other reasons. Among the 57 women who responded that they had become pregnant again, 81% reported having severe nausea and vomiting in their second pregnancy. Among the women reporting recurrent HG, 98% reported losing weight and taking prescribed medication for HG, 83% reported treatment with IV fluids, 20% reported treatment with TPN or NG tube feeding, and 48% reported hospitalization for HG. This study demonstrates both a high recurrence rate and a large percentage of women who change reproductive plans due to their experience with hyperemesis gravidarum.

### Keywords

Hyperemesis Gravidarum; Recurrence; Nausea; Pregnancy

## INTRODUCTION

Hyperemesis Gravidarum (HG), or severe nausea and vomiting of pregnancy, is the most common cause of hospitalization in the first half of pregnancy and is second only to preterm labor as a reason for hospitalization in pregnancy overall.<sup>1</sup> HG can be associated with serious maternal and fetal morbidity such as Wernicke's encephalopathy<sup>2</sup>, fetal growth restriction, and even maternal and fetal death.<sup>3,4</sup>

The definition of HG is highly variable leading to poor estimates of incidence. These range from 0.5% (based on 520,739 births in a California-based study that defined HG as hospitalization with a primary diagnosis of excessive vomiting in pregnancy) to 10.8% (based on 1867 singleton live births in Shanghai, China, where prenatal care records reported severe vomiting).<sup>4,5</sup> As many as 46% of hospital admissions of pregnant women do not have an obstetric code as the primary code,<sup>6</sup> suggesting that HG may not be completely recorded. Finally, HG is often treated in an outpatient setting and is not always diagnosed. Among 1224 self-reported women with HG defined as severe and debilitating nausea and vomiting with weight loss, 37% of respondents were not treated by hospitalization and 16% were never diagnosed as having HG.<sup>7</sup>

The cause of HG is unknown, but a biologic component to the condition has been suggested from animal studies. Anorexia of early pregnancy has been observed in various mammals including monkeys.<sup>8</sup> In dogs, anorexia can be accompanied by vomiting and can be severe enough to require pregnancy termination.<sup>9</sup>

Several lines of evidence support a genetic predisposition to nausea and vomiting in pregnancy (NVP). In the only study of NVP in twins, concordance rates were more than twice as high for monozygotic compared to dizygotic twins.<sup>10</sup> Approximately one-third of women affected with HG have an affected mother, and 1 out of 5 have an affected sister.<sup>7</sup>

Finally, the higher frequency of severe NVP in patients with certain genetically-determined conditions such as defects in taste sensation,<sup>11,12</sup> glycoprotein hormone receptor defects,<sup>13–15</sup> or latent disorders in fatty acid transport or mitochondrial oxidation,<sup>16,17</sup> suggests that some portion of women affected with HG may be related to discrete, genetically transmitted disease states that are unmasked or exacerbated in pregnancy. Overall, these data suggest that genetic predisposition may play a role in the development of nausea and vomiting of pregnancy. Given these observations, it is perplexing that the published recurrence risk for Hyperemesis Gravidarum is reportedly only 15.2%.<sup>18</sup> However, this report was based on repeat hospitalization for severe nausea of pregnancy with diagnosis. As noted, this may represent an underestimate of recurrence because HG is often not diagnosed, not properly recorded, and/or not treated by hospitalization.

The aim of this study was to estimate a recurrence risk of severe nausea of pregnancy in a registry of women who reported HG in their first pregnancy independent of hospitalization. Understanding the recurrence risk has implications for both counseling, treatment, and disease etiology.

## MATERIALS AND METHODS

The nonprofit Hyperemesis Education and Research (HER) Foundation was established in 2002. As part of its mission, it created a registry for women with HG and has undertaken a variety of on-line surveys about their experiences. One extensive survey, which was offered from 2003 to 2006, questioned women regarding their symptoms, treatments, and outcomes.<sup>7,19,20,21,22</sup> Respondents found the survey on the internet, and registered for the survey by answering the question “Have you ever experienced severe nausea or vomiting (HG) while pregnant? HG is characterized by significant weight loss and debility, and typically requires medications and/or IV fluids for treatment.”

Respondents answering “YES” to this question and answering that they lost weight below their pre-pregnancy weight were included in this study. Survey participants who answered “NO” to this question and/or participants who reported no weight loss in any pregnancy were excluded.

The survey included questions on demographics (age, ethnicity, level of education), diagnoses made by a physician or midwife (HG, morning sickness, other), treatments (including total parenteral nutrition (TPN), nasogastric feeding (NG) tube, intravenous (IV) fluids, and medications), weight loss, emotional and physical conditions and diagnoses preceding, during, and following pregnancy, maternal and child outcomes, and family history as reported previously.<sup>7,19,20,21,22</sup> Participants in the 2003–2006 survey who reported HG in their first and only pregnancy (304 women) were contacted by email in 2008 to request a follow-up reproductive history. This was obtained via a short survey that included a multiple choice question to determine whether the participant had had a subsequent pregnancy. If so, the participant was asked to answer questions relating to their second pregnancy (e.g. due date, intravenous fluid treatment due to nausea and vomiting, weight loss due to nausea and vomiting). Only the multiple choice question regarding occurrence of a subsequent pregnancy and questions answered via “yes” or “no” were included in the analysis.

All data analyzed in this study were derived from self-reports; medical records were not obtained to confirm diagnosis or reported symptoms, treatments, and outcomes. An initial version of the survey was piloted and revised prior to data collection for this study.

The study was approved by the Institutional Review Board of the University of Southern California HS06-00056.

## RESULTS

Of the original 304 survey participants who reported HG in their first pregnancy, 100 (33%) responded to the follow-up survey, 151 (50%) did not respond to the email, and 53 (17%) emails were returned as undeliverable. Table 1 describes the originally collected demographic data for all three groups, including country of origin, education, ethnicity, age at survey, average height, average weight, average year of birth/loss, and pregnancy weeks.

Of the 100 women who responded to the follow-up questionnaire, 57 had become pregnant again, 2 were trying to conceive, 37 reported they were not willing to get pregnant again due to HG, and 4 did not have a 2<sup>nd</sup> pregnancy for other reasons (Figure 1). Among the 57 women who had become pregnant again, 46 (81%) reported having severe nausea and vomiting in their second pregnancy. Among the women reporting recurrent HG, all reported the same partner, 45 (98%) reported losing weight due to nausea and vomiting, 45 (98%) reported taking prescribed medication for HG, 38 (83%) reported treatment with IV fluids for HG, 9 (20%) reported treatment with TPN or NG tube feeding, and 22 (48%) reported hospitalization in their second pregnancy for HG (TABLE 2).

## DISCUSSION

A common concern of women who have suffered from HG is whether or not they will have a recurrence in a subsequent pregnancy (HER Foundation, personal communication). In this survey, one-third of women affected by hyperemesis gravidarum in their first pregnancy chose not to become pregnant again because of that experience. This is consistent with reports of the severe psychosocial impact of HG and a retrospective study finding that 37% of women affected by HG reportedly consider or plan no more pregnancies.<sup>20</sup>

Of note, this study suggests a markedly higher recurrence risk (81%) of severe nausea and vomiting in pregnancy than previously reported (15%).<sup>18</sup> One difference between the two studies is that Trostad's recurrence rate was based on hospitalizations for HG, while the current study draws a recurrence rate from self-report of women in the community. Although our data are drawn from a selected sample of women who chose to register and complete a survey on a hyperemesis-oriented website, there are no striking differences among those who responded to the follow-up survey, and non-responders or those whose emails were returned. This does not suggest a biased reporting of recurrence risk in the group of responders, and our results may be generalizable to affected individuals with similar characteristics to those reported in Table I.

Trogstad et al. analyzed data from 547,238 women in the Medical Birth Registry of Norway and found the overall proportion of hyperemesis pregnancies to be 0.8%. The authors noted that the Norwegian Mother and Child Cohort Study reports 1.3% of pregnant women are hospitalized for HG and suggested that HG may be underreported in the Medical Birth Registry. Among 4796 women with hyperemesis in their first pregnancy, 731, or 15%, had a recurrence in their second pregnancy, defined as persistent nausea and vomiting associated with ketosis and weight loss >5% of pre-pregnancy weight. This recurrence risk was based on more stringent clinical criteria (diagnosis and hospitalization), while our study is based on self-reports.

The higher risk reported in our study is more consistent with recently reported familial incidence that suggests HG may have a genetic component.<sup>7</sup> It is also worth noting that in our cohort, although only 48% of recurrent patients were hospitalized in their second pregnancy for HG, 98% reported being treated for severe nausea and vomiting with medication, 83% with IV fluids, and 20% with TPN or NG tube. This supports a higher recurrence risk based on clinical criteria that can profoundly affect a woman's quality of life.

Thus, although the risk for hospitalization in subsequent HG pregnancies is likely lower than 79%, the risk for recurrent HG, when defined by treatment with medication and/or IV fluids, is no doubt much higher than the commonly reported 15% recurrence risk. Other differences between the Norwegian Study and our study is that our cohort is primarily based in the United States where treatment with intravenous fluids and/or prescribed medication is more common than outside the United States,<sup>19</sup> and the limitations of a birth registry, which include incomplete reporting and outcome misclassification.<sup>23</sup>

On the other hand, we recognize that this study is based on self-identification, self-report and a small proportion of eligible participants who responded to the survey. Women who join online support groups and respond to on-line surveys by e-mail may be somewhat different as a group. They may be more health literate and thus more likely to seek care for HG at an earlier gestational age than women who do not frequently use computers for health information. The 33% response rate in this study may have created a selection bias, which may lead to an overestimate of actual recurrence risk. If we assume that the non-respondents (whose emails were undeliverable) all became pregnant and none had HG, the estimated recurrence rate would drop to 22%. Conversely, if the same proportion of non-responders became pregnant again and all suffered recurrent HG, the recurrence rate would be as high as 94%.

Despite these limitations, we believe it is important for counseling purposes that affected individuals be aware that the published recurrence risk based on hospitalization may be a gross underestimate of the actual recurrence risk of severe nausea and vomiting of pregnancy requiring medical intervention. Due to this potentially high risk of recurrence, we recommend that women with a previous history of HG and their providers may want to discuss a treatment plan prior to pregnancy. Women with previous HG may need to be seen more frequently in early pregnancy to facilitate more rapid diagnosis and treatment. In addition, providers caring for non-pregnant women should identify individuals who have suffered from HG who may be afraid to get pregnant again.

Women with a history of severe HG who are considering their future reproductive plans can be provided with information and support by their providers, or referred to informational supportive websites.<sup>24</sup> Providers should work with these women to ensure prompt diagnosis and treatment in a subsequent pregnancy or discuss other options such as adoption or surrogacy to complete their family. All providers caring for women should be aware that the high recurrence rate and large percentage of women who change reproductive plans due to their experience with hyperemesis gravidarum has important implications for counseling, treatment, and risk assessment.

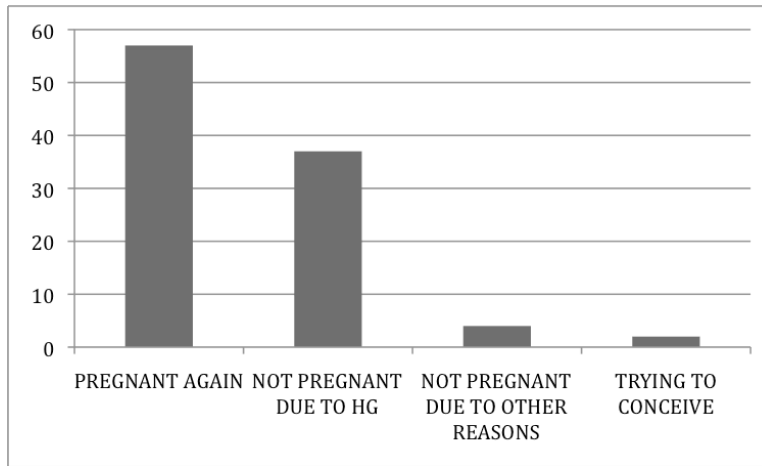
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**FIGURE 1.** SUMMARY OF FOLLOW-UP RESPONSES FROM WOMEN WITH A PREVIOUS HISTORY OF HYPEREMESIS GRAVIDARUM WITH RESPECT TO SUBSEQUENT PREGNANCIES (N=100).

**TABLE 1**

Demographic Characteristics Of Women With Previous Hyperemesis Gravidarum Who Were Recruited For The Study Of Subsequent Pregnancy<sup>a</sup>.

DEMOGRAPHIC CHARACTERISTICS	RESPONDENTS	NON-RESPONDENTS	EMAIL UNDELIVERED
	n=100	n=151	n=53
<b>RESIDENCE, n (%)</b>			
UNITED STATES	82 (82)	119 (79)	37 (70)
GREAT BRITAIN	6 (6)	14 (9)	5 (9)
OTHER COUNTRIES	11 (11)	18 (12)	11 (21)
MISSING	1 (1)	0	0
<b>EDUCATION, n (%)</b>			
NO COLLEGE DEGREE	42 (42)	46 (30)	19 (36)
COLLEGE DEGREE	29 (29)	51 (34)	16 (30)
ADVANCED DEGREE <sup>b</sup>	27 (27)	45 (30)	16 (30)
MISSING	2 (2)	9 (6)	2 (4)
<b>RACE/ETHNICITY, n (%)</b>			
WHITE/NON-HISPANIC	82 (82)	115 (76)	47 (89)
OTHER	16 (16)	27 (18)	4 (8)
MISSING	2 (2)	9 (6)	2 (4)
<b>AVG # OF YEARS SINCE INDEX PREGNANCY</b>	5	5	6
<b>GESTATIONAL AGE AT DELIVERY OF INDEX PREGNANCY, n (%)</b>			
TERM (>=37 WEEKS)	81 (81)	114 (75)	44 (83)
26-36 WEEKS	16 (16)	22 (15)	6 (11)
<26 WEEKS	3 (3)	9 (6)	3 (6)
MISSING	0	6 (4%)	0

<sup>a</sup>Three-hundred and four women who reported HG in their first and only pregnancy were e-mailed to request a follow-up reproductive history.

<sup>b</sup>Currently pursuing or completed

**TABLE 2**

Treatment Of Nausea/Vomiting Reported By 46 Women With Recurrent Hyperemesis Gravidarum

TREATMENT	N (%)
Prescription Medication	45 (98)
Intravenous Fluids	38 (83)
Hospitalization	22 (48)
Total Parental Nutrition or Nasogastric tube feeding	9 (20)