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Participants who did and did not change partners between their first and second

pregnancies, were asked to rate their first and second pregnancy in regards to symptoms of HG. Neither the ratings nor the change in rating between pregnancies was significantly different between the two groups.

**Conclusion:** Women reported HG in over 70% of their pregnancies regardless of a paternity change. Paternal genes expressed through the fetus do not have a significant effect on incidence or recurrence of HG. This study supports a strong maternal genetic factor involved in HG. However, because the recurrence risk is not 100%, other factors play a role. Identification of the predisposing gene(s) and other factors will determine the cause of this poorly understood complication of pregnancy.

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**Results:** The percentage of HG pregnancies in women with the same partner for all pregnancies was not significantly different from the percentage of HG

pregnancies in women who changed partners for at least one pregnancy (78% vs 71%,  $p>0.05$ ). Participants who did and did not change partners between their first and second pregnancies, were asked to rate their first and second pregnancy in regards to symptoms of HG. Neither the ratings nor the change in rating between pregnancies was significantly different between the two groups.

**Conclusion:** Women reported HG in over 70% of their pregnancies regardless of a paternity change. Paternal genes expressed through the fetus do not have a significant effect on incidence or recurrence of HG. This study supports a strong maternal genetic factor involved in HG. However, because the recurrence risk is not 100%, other factors play a role. Identification of the predisposing gene(s) and other factors will determine the cause of this poorly understood complication of pregnancy.

Keywords: Paternal; Genetic; Nausea; Pregnancy

### **Introduction**

Hyperemesis gravidarum (HG) accounts for over 285,000 hospital discharges in the U.S. annually, with most authors reporting an incidence of 0.5-2%.<sup>1,2</sup> HG often results in dehydration, electrolyte disturbance and nutritional deficiency in many cases, mandating intravenous hydration and, in severe cases, the use of parenteral nutrition. If left untreated, HG can result in Wernicke's encephalopathy,<sup>3</sup> central pontine myelinolysis,<sup>4</sup> hepatic dysfunction,<sup>5</sup> and renal failure.<sup>6</sup> The diagnosis of HG is also associated with low birth weight, intrauterine growth restriction, preterm delivery, and fetal and neonatal death.<sup>7-9</sup>

The most common treatment modalities include IV hydration and serotonin

inhibitors.<sup>10</sup> However, treatment is not always effective, resulting in therapeutic termination in as many as 15.2% of cases<sup>11</sup> and extreme weight loss of more than 15% of pre-pregnancy weight in more than a quarter of cases.<sup>12</sup> Furthermore, prolonged hyperemesis, nausea and vomiting lasting beyond 27 weeks' gestation is seen in as many as 22% of cases.<sup>12</sup>

The cause of HG is unknown and it is becoming increasingly clear that there is a genetic basis to the disease.<sup>13,14</sup> Recently, a case-control study showed familial aggregation of HG.<sup>13</sup> A generational study and a change in partner study also suggested a stronger influence of the maternal genotype (and/or maternal environment) than the fetal genotype (and/or paternal environment).<sup>14,15</sup> However, a role for paternal genes expressed through the fetus is controversial, as it is supported by a large population-based study that suggests a significant change in recurrence risk with change in paternity.<sup>16</sup> Therefore we sought to determine whether there is evidence for a paternal genetic component in our database of women with HG.

## 2. MATERIALS AND METHODS

### *Sample and Settings*

This study is part of a larger investigation evaluating the genetics and epidemiology of hyperemesis gravidarum. A total of 318 women with more than one pregnancy have been recruited. Eligible patients were primarily recruited through advertising on the Hyperemesis Education and Research Foundation website at [www.HelpHer.org](http://www.HelpHer.org). Another method of recruitment of affected

individuals was a recruitment video on YouTube at <http://www.youtube.com/watch?v=92NFOwvAXcI> which provided the rationale for starting this study, information about the study, and contact information. Some participants have also recruited their own affected acquaintances to participate and some participants heard about the study from articles, news stories, and pregnancy or parenting websites.

The inclusion criteria were a diagnosis of HG and treatment with IV fluids and/or total parenteral nutrition/nasogastric feeding tube. Minors (under 18 years) were not included in the study because few teens were expected to fit the study criteria for controls having had two pregnancies. Additionally, it would be difficult to justify the risks/benefits to normal control minors. Women over the age of 50 at the time of first contact were not included in a somewhat arbitrary attempt to limit the possibility of recall bias. Because multiple or chromosomally abnormal gestations may be associated with HG due to unique physiological pathways, women with these types of pregnancies were also excluded. Biological relatives of participants in the study were not included in the study.

Because this was a study of recurrence and paternity change, only participants with more than one pregnancy were included in the study.

### *Study Procedures*

Participants were asked to submit their medical records and complete an online survey regarding information on a variety of demographic characteristics (e.g. partner, age, gender, and ethnicity), pre-existing conditions, pregnancy

symptoms and treatments, and maternal and fetal outcomes. The survey instrument can be found at <http://www.helper.org/HER-Research/2007-Genetics/2007rsch-start.php>. The majority of participants joined the study and began the survey during one of their pregnancies and were sent a reminder to complete the survey pertaining to pregnancy outcome following their due date. Participants were asked to rate each pregnancy from one to five with respect to nausea and vomiting using the following definitions:

- 1) **No nausea and vomiting:** never felt nauseous and never vomited in this pregnancy.
- 2) **Very little nausea and vomiting:** felt nauseous and/or vomited for a total of 1-7 days during this pregnancy.
- 3) **Typical nausea and vomiting:** may have nausea and/or vomiting in this pregnancy but (all of the following must be true)  
did not lose weight from nausea/vomiting and  
was able to sustain normal daily routine most days with little change in productivity due to nausea/vomiting most of the time, and  
no need to consult health professional for medical treatment due to nausea and vomiting.
- 4) **More severe morning sickness:**  
persistent nausea and vomiting that interfered with normal daily routine in this pregnancy but did NOT require IV hydration or TPN due to persistent nausea/vomiting.  
May have consulted a medical professional to treat nausea and vomiting.  
May have lost a few pounds or one kg.
- 5) **Hyperemesis Gravidarum:** persistent nausea and vomiting with weight loss that interfered significantly with daily routine, and led to need for:  
IV hydration or nutritional therapy (feeding by an iv (TPN) or tube (NG) through the nose), and/or  
prescription medications to prevent weight loss and/or nausea/vomiting.

### *Statistical Analyses*

Responses from participants without a paternity change in any pregnancy were compared to participants who reported at least one paternity change for a number of variables including health issues of participants and offspring using two-sided t-tests. Variables included in demography, treatment and method of delivery were also performed using the t-test. All data were analyzed using R.

This study has been approved by Institutional Review Boards, USC IRB # HS-06-00056 and UCLA IRB # 09-08-122-01A.

## RESULTS

### *Overall Demographic Characteristics*

Three-hundred and eighteen women with HG with IV fluid treatment in at least one pregnancy participated in the study. Among these, there were two-hundred and sixty women with the same partner for each pregnancy, and fifty-eight women who changed partners between pregnancies.

As shown in Table 1, participants were well-matched and are primarily Caucasian, from the United States, currently in their mid-30s, and an average height of 65 inches. Participants were also well-matched for percentage of pregnancy losses, vaginal vs cesarean delivery, number of living children, and gender of the baby.

Participants who reported a change in paternity were more likely to weigh less, to have more pregnancies, to report a voluntary pregnancy termination, and to

report their partner was not of the same race. Regardless of these differences, women with and without a paternity change between pregnancies reported a similar percentage of HG pregnancies. Both groups reported over 70% of their pregnancies were affected with HG.

### *Characteristics for first and second pregnancies*

As shown in Table 2, participants were primarily Caucasian and born in the mid-1970s. Participants were well matched for total number of pregnancies, vaginal vs cesarean delivery, number of living children, and sex of the baby in the first and second pregnancy. Participants who changed partners between their first and second pregnancy were more likely to be younger for their first pregnancy, but were well-matched for age at the time of their second pregnancy. They were more likely to be of a different race than their partner in the first pregnancy compared to the group with no partner change, but were equally likely to have a partner of the same race in their second pregnancy. Women with a partner change between their first and second pregnancy were significantly more likely to report a voluntary termination. Regardless of these differences, both groups were equally likely to report being treated for HG in their second pregnancy.

### *HG Treatments in the second pregnancy*

At least 60% of participants regardless of partner change, required intravenous fluid treatment for HG in their second pregnancy (Table 3). The most common treatments for HG in the second pregnancy were compared between cases who



changed (N=45) and did not change (N=273) partners between the first and second pregnancy. None of the treatments were significantly different. Participants were equally likely to be treated with intravenous fluids, Phenergan, Reglan, Zofran, and Total Parenteral Nutrition, regardless of whether they had changed partners between the first and second pregnancy.

#### *HG Rating and Paternity Change*

Participants were asked to rate their first and second pregnancies in regards to nausea and vomiting on a scale of 1 to 5 using the definitions provided in the *Study Procedures*. Nausea and vomiting ratings of the first pregnancy were not significantly different between the participants that did and did not change partners between the first and second pregnancy. Nausea and vomiting ratings of the second pregnancy were also not significantly different between the participants that did and did not change partners between the first and second pregnancy. Finally, differences in nausea and vomiting ratings between the first and second pregnancy were not significantly different regardless of a paternity change (Table 4).

#### **4. Comment**

The etiology of HG is currently unknown. Finding the cause is an essential step towards developing more effective therapies or a cure. 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>17</sup> In dogs, anorexia can be accompanied by vomiting and can be severe enough to require

pregnancy termination.<sup>18</sup>

Several lines of evidence support a genetic predisposition to nausea and vomiting in pregnancy (NVP). First, in the only study of NVP in twins, concordance rates were more than twice as high for monozygotic compared to dizygotic twins.<sup>19</sup> Second, several investigators have noted that siblings and mothers of patients affected with NVP and HG are more likely to be affected than siblings and mothers of unaffected individuals.<sup>20,21</sup> Third, the higher frequency of severe NVP in patients with certain genetically determined conditions such as defects in taste sensation,<sup>22,23</sup> glycoprotein hormone receptor defects,<sup>24-26</sup> or latent disorders in fatty acid transport or mitochondrial oxidation,<sup>27,28</sup> suggests that some portion of HG cases may be related to discrete, genetically transmitted disease states that are unmasked or exacerbated in pregnancy. Additionally, there is a high prevalence of severe nausea and vomiting of pregnancy/hyperemesis gravidarum among relatives of patients with hyperemesis gravidarum.<sup>29</sup> Familial aggregation of the disease and recurrence across generations all support a genetic component.<sup>13,14</sup> However, a maternal genetic component is not the only factor involved in HG, as HG recurs in less than 100% of gestations from the same mother, suggesting other factors play a role. An increased incidence of HG has been reported with multiple gestations, gestational trophoblastic disease, fetal chromosomal abnormalities and central nervous system malformations, and for mothers of female offspring.<sup>30,31</sup> Our study is consistent with a role for female fetal genes in hyperemesis gravidarum as over 60% of babies born to women in this study were reportedly female.

Smoking during pregnancy was recently reported to decrease the risk of hyperemesis, but smoking by the partner was reported to increase the risk.<sup>30,32</sup>

Other than second-hand smoke, to our knowledge, no environmental factors have been identified that increase risk. Non-genetic maternal factors such as advanced maternal age have been associated with decreased risk, and adolescent pregnancy with increased risk for HG.<sup>33,34</sup>

Evidence for a paternal and fetal contribution has been controversial. While one study suggested that HG recurrence decreases with a change in paternity,<sup>16</sup> suggesting paternal genes expressed in the fetus may play a role, this conclusion was recently refuted by a separate study.<sup>15</sup> Additionally, a consanguinity study also found no increased risk of HG, suggesting recessive fetal genes may not be involved in HG risk.<sup>5</sup> The study herein supports the finding that paternal genes expressed through the fetus are not a significant factor in recurrence risk of hyperemesis gravidarum.

A major strength of this study stems from the collaboration with the HER Foundation, which allowed collection of information on a large sample of women affected by HG. To date, most studies of hyperemesis gravidarum have been small case series or population studies relying on hospital databases with no information on paternity and recurrence.

Admittedly, this study has some methodological concerns. One potential limitation arises from the use of an internet based survey. While internet-based research is quickly becoming scientifically recognized as a reliable recruiting tool,

the study population consists only of cases with internet-access, and thus may represent women of higher education and income. We feel, however, that the generalizability of our study results should be reasonably good since we have no reason to suspect that education level and income would affect the likelihood of having a recurrence of HG with respect to paternity.

Another limitation is that data was based on self-reports, which can lead to misclassification of disease status. However, we believe it would be highly unlikely for women to misclassify disease status as they are given definitions to classify disease and are required to have been treated with intravenous therapy for severe nausea and vomiting in at least one pregnancy.

Finally, the change in paternity group and the no change in paternity group were not perfectly matched for several characteristics, such as total number of pregnancies, voluntary terminations, and race of partner. However, these characteristics have never been shown to be related to HG recurrence, and we have no reason to believe they have any effect on HG recurrence rates reported in this study. The fact that women with no partner change weighed more on average than those with a partner change should not have an effect on the results because we have found in this same cohort that women with more severe prolonged nausea and vomiting weigh significantly more.<sup>35</sup> Therefore, this result could only bias the results in favor of the change in partner group having a significantly lower recurrence risk, which we did not find in this study. On the contrary, we suggest that the recurrence risk associated with partner change in a past study<sup>16</sup> may be due to other factors found to be significant in women having

a change in partner, such as pre-pregnancy weight, rather than paternal genes expressed in the fetus. But we can not rule out that there may be other factors associated with partner change that may confound the relationship with HG herein. We have tried to investigate many of them, but perhaps others remain. On another note, the fact that changing to a partner of a different race had no significant effect on recurrence suggests paternal ethnic differences are not likely to play a role in risk of HG.

Currently the cause of nausea and vomiting in pregnancy is unknown although there is strong evidence linking human chorionic gonadotropin or estrogens as well as genetic susceptibility possibly mediated through the vestibuloocular reflex pathway.<sup>36,37</sup> While spontaneous abortion rates may not be significantly different in women with or without HG,<sup>38</sup> it can lead to long-term effects on the patient including postpartum post-traumatic stress symptoms and difficulty producing breast milk,<sup>39</sup> and recent research suggests it may be linked to permanent neurobehavioral abnormalities in the exposed fetus.<sup>40</sup> Herein we report that recurrence of HG is higher than 70% regardless of a change in paternity, and future work should focus on the identification of maternal genetic variants that may contribute to HG susceptibility. Identification of maternal genetic factors will elucidate the biology of nausea and vomiting in pregnancy and allow novel therapeutics to be developed to treat the cause of the disease rather than the symptoms.

### **Acknowledgement**

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In this study of Hyperemesis Gravidarum, severe nausea/vomiting of pregnancy, recurrence risk does not change with a change in paternity.

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**Table 1. Demographic Characteristics**

	<b>no change Mean (260)</b>	<b>Partner- changed Mean (58)</b>	<b>p-value</b>	<b>C.I</b>
Year-Born	1975	1974	0.6025	(-1.3869,2.3750)
Number of Pregnancies	2.87	3.38	0.0112	(-0.8940,-0.1185)
Race (Caucasian)	245(94%)	50(86%)	0.0986	(-0.0154,0.1758)
Weight (pounds)	143.41	132.6607	0.0072	(2.9748,18.5254)
Height (inches)	65.23	64.6909	0.2772	(-0.4447, 1.5298)
Living children	2(1.98)	2(1.8)	0.3920	(-0.1735, 0.4377)
Voluntary Termination (No change:171 Partner change: 54)	29(12%)	32(59%)	<0.001	(-0.6139, -0.3316)
Pregnancy Losses (No change:244 Partner change:55)	101(41%)	22(16%)	0.8507	(-0.1329, 0.1607)
Country (USA)	250(96%)	54(93%)	0.3947	(-0.0405, 0.1015)
Partner's race (Caucasian)	234(90%)	40(69%)	0.0016	(0.0825, 0.3382)
Race of Mother and partner (Different)	45(17%)	23(39%)	0.003	(-0.3508, -0.0750)
Delivery method (Cesarean) (No change:168, Partner change:19)	25(15%)	1(5%)	0.0931	(-0.0175, 0.2151)
Baby's sex Male (No change: 167, Partner change: 19)	67(40%)	6(32%)	0.4691	(-0.1548, 0.3158)
<b>Percentage of HG pregnancies</b> = number of HG pregnancies/ Total number of pregnancies	<b>78%</b>	<b>71%</b>	<b>0.0743</b>	<b>(-0.7206,15.0832)</b>

**Table 2. Comparison of first and second pregnancies**

<b>1 &amp; 2nd pregnancy</b>	<b>no change Average (255)</b>	<b>Partner-changed Average (40)</b>	<b>p-value</b>	<b>C.I</b>
Year Born	1975	1975	0.9586	(-2.17, 2.2857)
Birth age at 1st pregnancy	27	21	<0.001	(4.8965, 7.6207)
Birth age at 2 <sup>nd</sup> pregnancy	29	28	0.0850	(-0.2399, 3.5863)
Number of Pregnancies	3	3	0.2811	(-0.6381, 0.1891)
Race (Caucasian)	240(94%)	33(83%)	0.0703	(-0.01, 0.2424)
1st Partner's race (Caucasian)	230(90%)	24(60%)	<0.01	(0.1394, 0.4645)
Different races of women & 1st partner	28(11%)	16(40%)	<0.01	(-0.4532, -0.1272)
2nd Partner's race (Caucasian)	228(89%)	33(83%)	0.2844	(-0.0593, 0.1975)
Different races of mother & 2nd partner	29(11%)	11(28%)	0.0351	(-0.3107, -0.0118)
Different races of 1st partner & 2nd partner	0	14(35%)	<0.001	(-0.5045, -0.1955)
Delivery Method (Cesarean)	13(8%)	4(13%)	0.3933	(-0.1919, 0.1333)
1 <sup>st</sup> Baby's sex (Male)	78(41%)	5(36%)	0.7261	(-0.2442, 0.3425)
2nd Baby's sex (Male)	98(49%)	13(42%)	0.4398	(-0.1202, 0.2714)
Living children	2.02	1.7	0.0612	(-0.0156, 0.6548)
Voluntary Termination	29(11%)	24(60%)	<0.01	(-0.6494, -0.3232)
<b>HG in 2<sup>nd</sup> pregnancy</b>	<b>193 (74%)</b>	<b>39 (67%)</b>	<b>0.306</b>	<b>(-0.0651, 0.6724)</b>

Table 3. Treatment for HG in second pregnancy

	Control Group Number	Partner-changed Number	p-value	C.I
Second Pregnancy	273	45		
Intravenous Fluids	154(60%)	27(68%)	0.3844	(-0.2336, 0.0915)
Phenergan	117(46%)	18(45%)	0.9183	(-0.1629, 0.1806)
Reglan	84(33%)	18(45%)	0.1619	(-0.2912, 0.05)
Total Parenteral Nutrition	36(14%)	4(10%)	0.4385	(-0.0645, 0.1469)
Zofran	146(57%)	21(53%)	0.5818	(-0.1246, 0.2197)

Table 4

	Control Group (No change ) Average	Partner-changed Group Average	P-value	C.I
1st pregnancy HG Rate	4.1	3.8	0.095	(-0.0683, 0.8267)
2nd Pregnancy HG Rate	4.4	4.5	0.392	(-0.5171, 0.2058)
Rate Difference	0.9	1.3	0.1546	(-0.8047, 0.1312)