

Dysmenorrhea as a Risk Factor for Hyperemesis Gravidarum

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Abstract

Background: The aims of the study were to assess the association of dysmenorrhea and hyperemesis gravidarum (HG) and to determine other factors that may influence its onset and severity.

Methods: This is a prospective case-control IRB approved study of 344 consecutive singleton pregnant women with and without hyperemesis gravidarum in pregnancy from February 2011 to April 2012. The association between HG and dysmenorrhea in adolescent and adult was examined using Pearson's Chi-square with Yates correlation, Student's *t*-test and Mann-Whitney U test. Bivariate analysis and odd ratios (ORs) were calculated to evaluate the strength of their association, and multivariate logistic regression analysis while correcting for confounders. P-value of 0.05 was considered statistically significant.

Results: A total of 344 consecutive singleton pregnant women were recruited. Significant association was found between HG and adolescent dysmenorrhea: 77.8% versus 43.4% of controls ($P < 0.0001$, OR: 4.6, 95% CI: 2.3 - 8.9). Also, there was a significant association between HG and adult dysmenorrhea: 76.4% versus 38.1% controls ($P < 0.0001$, OR: 5.3, 95% CI: 2.7 - 10.2). The association of severe adolescent and adult dysmenorrhea with HG was stronger ($P < 0.0001$, OR: 8.8, 95% CI: 3.9 - 19.9 and $P < 0.0001$, OR: 12.2, 95% CI: 5.0 - 29.7 respectively). There was a modest association with moderate dysmenorrhea ($P = 0.004$, OR: 3.1, 95% CI: 1.4 - 6.9) which was not

sustained but no associations were found between HG and all mild dysmenorrhea of both adolescent and adult.

Conclusion: This study found an association between adolescent and adult dysmenorrhea and HG. These associations were stronger with severe dysmenorrhea.

Keywords: Dysmenorrhea; Hyperemesis gravidarum; Adolescent; Adult; Onset; Severity

Introduction

Nausea and vomiting are common in pregnancy and affect 70-85% of pregnant women [1]. Hyperemesis gravidarum (HG) is an extreme of the spectrum of nausea and vomiting in pregnancy that affects approximately 0.5-2% of pregnancies [2]. This is characterized by persistent vomiting not related to other causes resulting in dehydration, acute starvation evidence by ketonemia and large ketonuria, weight loss of at least 5% of pre-pregnancy weight and electrolytes disorders. There may also be thyroid and liver abnormalities [3, 4]. Nausea and vomiting symptoms usually manifest before 9 weeks of gestation and it is the commonest indication for hospital admission in the first trimester of pregnancy. HG causes significant maternal and fetal morbidity and possibly mortality.

Though the etiology of HG is unknown, various theories have been adduced to HG including psychological predisposition [5], evolutionary adaptation [6], and hormonal stimulus [5, 6]. Hormonal stimuli such as human chorionic gonadotrophin (hCG) and estrogen have been established to have varying influences on nausea and vomiting [7, 8]. Other hormones such as progesterone, adrenal and pituitary hormones may also trigger HG. However, the links between these hormones and hyperemesis are not straightforward because patients with hyperemesis may either have elevated or lower level of progesterone [9-11]. Other researchers found no association between hyperemesis and progesterone concentration because progesterone treatment does not improve complaints [12, 13]. Risk factors include an increase in placenta mass such as advance molar pregnancy and multiple gestation, genetic and family history, first pregnancy, overweight, history of HG in previous pregnancies, carrying of a female fetus, daughters and sisters

Manuscript accepted for publication October 02, 2015

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doi: <http://dx.doi.org/10.14740/jcgo356w>

Table 1. Relationship Between Adolescent Dysmenorrhea and Hyperemesis Gravidarum

Nausea and vomiting	Presence dysmenorrhea	Absence dysmenorrhea	Total
Absence	49 (43.3%)	64 (56.7%)	113
Mild	37 (67.3%)	18 (32.7%)	55
Moderate	73 (70.0%)	31 (30.0%)	104
Severe	56 (77.8%)	16 (22.2%)	72
Total	215	129	344

P < 0.0001 (OR: 4.57, 95% CI: 2.34 - 8.92).

of women with HG, motion sickness and migraines [14, 15].

The association between increased maternal serum concentration of hCG and nausea and vomiting of pregnancy has been studied for more than half a century. Shoeneck et al and other researchers have demonstrated a positive correlation between maternal serum level of hCG and nausea and vomiting of pregnancy. Their findings were based on the fact that the peak maternal serum and urinary hCG levels are from 6 to 14 weeks of pregnancy which corresponds to when nausea and vomiting of pregnancy is usually encountered [16-19]. However, Soules et al and Bagshawe did not find this correlation based on the fact that there is no nausea and vomiting in chorio-carcinoma where there is extremely high maternal serum and cerebrospinal fluid concentration of hCG. This leads to the suspicion that other factors which increase the synthesis and release of hCG may be responsible for nausea and vomiting of pregnancy [20, 21].

Primary dysmenorrhea is defined as pain during menses in the absence of an identifiable pathologic lesion which usually begins during adolescence. The prevalence of dysmenorrhea is highest in adolescents ranging 20-90% with the severe form reported to be as high as 15% in the age group of 13 - 19 years [22-24]. It is characterized by cramping lower abdominal pain and may be associated with nausea, vomiting, headaches, diarrhea, and myalgia. The actual cause of primary dysmenorrhea is unknown, but several studies have proven that primary dysmenorrhea is as a result of inflammatory responses mediated by prostaglandin and leukotrienes which cause myometrial contraction and vasoconstriction. This will invariably generate cramps and systemic symptoms such as nausea, vomiting, bloating, diarrhea and headaches [25, 26]. Dawood et al in their study demonstrated that the intensity of menstrual cramps and the associated symptoms are directly proportional to the amount of PGF₂ α and PGE₂ levels measured in menstrual fluid [27]. Symptoms of dysmenorrhea such as nausea, vomiting, and diarrhea occur in approximately 60% of patients. These symptoms are similar to those experienced when exogenous prostaglandins are used as abortifacient drugs [28].

Cunningham and Muneyyirci-Delale hypothesized that there is an association between dysmenorrhea and HG [29]. This is based on the hypothesis that the prostaglandin stimulated symptoms of nausea and vomiting experienced in dysmenorrhea are affiliated with excessive nausea and vomiting during pregnancy and/or HG. Hence, the objectives of this study were to assess the association of dysmenorrhea and HG and to assess other factors that may influence onset of HG and

Table 2. Relationship Between Adult Dysmenorrhea and Hyperemesis Gravidarum

Nausea and vomiting	Presence dysmenorrhea	Absence dysmenorrhea	Total
Absence	43 (38.1%)	70 (61.9%)	113
Mild	31 (56.4%)	24 (43.6%)	55
Moderate	60 (57.7%)	44 (42.2%)	104
Severe	55 (76.4%)	17 (23.6%)	72
Total	189	155	344

P < 0.0001 (OR: 5.30, 95% CI: 2.74 - 10.22).

its severity.

Methodology

Study design

This is a prospective case-control IRB approved study of 72 consecutive singleton pregnant women admitted for HG in their index pregnancy from February 2011 to April 2012 at the State University of New York (SUNY) Downstate Medical Center and King's County Hospital Center. Also recruited were participants with various spectrum of nausea and vomiting in pregnancy and a control group without any symptoms of nausea and vomiting during the study period.

Study population

The study population consists of a total of 344 participants: 72 with HG, 104 moderate and 55 with mild nausea and vomiting and 113 as controls without nausea and vomiting. They were recruited from the prenatal clinics or on admission to State University of New York (SUNY) Downstate Medical Center and King's County Hospital Center. The emesis gravidarum and dysmenorrhea in adolescent and adulthood were classified into three categories: 1) mild emesis gravidarum: nausea only without vomiting; 2) moderate emesis gravidarum: nausea and vomiting but not requiring hospital admission; and 3) severe emesis gravidarum (HG): nausea and vomiting requiring hospital admission due to dehydration and electrolytes imbalance, and others.

The three categories of dysmenorrhea were based on pain intensity using visual analogue scale (VAS): 1) mild dysmenorrhea: pain intensity of 1 - 3; 2) moderate dysmenorrhea: pain intensity of 4 - 7; and 3) severe dysmenorrhea: pain intensity of 8 - 10.

Sample size

The sample size was determined based on the prevalence of emesis gravidarum of 70-85%; a total of 300 participants were required in addition to 10% calculated attrition rate and a mar-

Table 3. Nausea and Vomiting and Intensity and Hyperemesis Gravidarum

Nausea and vomiting	Absence dysmenorrhea	Mild dysmenorrhea	Moderate dysmenorrhea	Severe dysmenorrhea	Total
Absence	62 (55%)	5 (4%)	31 (28%)	15 (13%)	113
Mild	18 (33%)	3 (5%)	24 (44%)	10 (18%)	55
Moderate	31 (30%)	3 (3%)	33 (32%)	37 (35%)	104
Severe	16 (22%)	5 (7%)	17 (24%)	34 (47%)	72
Total	127	16	105	96	344

$P < 0.0001$ (OR: 9.38, 95% CI: 3.97 - 22.18).

gin of error of 5% at a confidence level of 95% and a power of 80%.

Data collection

Written informed consent was obtained from individual participant and they were interviewed with structured IRB approved self-administered questionnaire about dysmenorrhea in adolescent and adulthood and emesis gravidarum symptoms. The questionnaires were distributed by two research assistants who were not privy to the objectives of the study. The research assistants were trained to guide participants to respond to questions that they needed more clarifications. Some of pertinent data collected were socio-demographic data, parity, history of nausea and vomiting in the index pregnancy, severity of the symptoms, gestational age of onset of symptoms, history of hospital admission for nausea and vomiting, gestational age at admission, number of fetuses, medical, psychiatric and surgical history, gynecologic and obstetric history, medications, pre-pregnancy weight and weight at admission, laboratory results at presentation such as complete blood count, comprehensive chemistry panel, TSH, serum β -hCG, duration of admission and history of nausea and vomiting in previous pregnancies. Information in regards to adolescent and adulthood dysmenorrhea, severity of dysmenorrhea using VAS for pain assessment, the age of onset of dysmenorrhea, history of chronic pelvic pain, dyspareunia, history of dysmenorrhea and HG in first degree relatives were collected.

Data management

Data obtained were entered into a computer running Statistical Package for Social Sciences version 20 (SPSS 20) software. Descriptive statistics of the baseline characteristics of participants were displayed in frequency tables. Participants were classified into four categories: HG, moderate nausea and vomiting in pregnancy not requiring hospitalization, nausea only and absent of nausea and vomiting in pregnancy used as control group. Comparisons of the baseline characteristics of each of the individual group with the control group were done using Chi-square for categorical variables and Student's *t*-test for normally distributed continuous variables. Continuous variables that were not normally distributed were examined using Mann-Whitney U test. The proportions of primary dysmenor-

rhea were calculated for each group and compared, and tested for statistical significance using McNemar's Chi-square test of 2×2 contingency table with Yates correlation for continuity. The odds ratio (OR) and 95% confidence interval (CI) were calculated to determine the strength of association between primary dysmenorrhea and nausea and vomiting, and HG. Multiple logistic regression analysis was used to determine the association between primary dysmenorrhea and HG while correcting for confounding variables.

Results

A total of 344 consecutive sonogram proven singleton pregnant women were recruited with a mean age of 27.9 years, parity ranging from 0 to 7 with a mean parity of 1.07, and mean weight of 176.5 lbs. In the participants, 76.3% were African American, 14.2% were Hispanic and 9.5% were Caucasian. Seventy-two participants were hospitalized for HG, 104 had nausea and vomiting but not hospitalized, 55 had only nausea and 113 who neither experienced nausea nor vomiting served as controls. A significant association was found between HG and adolescent dysmenorrhea; 77.8% of participants with HG gave history of adolescent dysmenorrhea versus 43.4% of controls ($P < 0.0001$, OR: 4.6, 95% CI: 2.3 - 8.9), as shown in Table 1. Similarly, there was a significant association between HG and adult dysmenorrhea; 76.4% of participants with HG had adulthood dysmenorrhea versus 38.1% controls ($P < 0.0001$, OR: 5.3, 95% CI: 2.7 - 10.2) as shown in Table 2.

The impacts of the severity of dysmenorrhea on HG were examined using a VAS classified into mild, moderate and severe (scores 1 - 3, 4 - 7 and 8 - 10 respectively). Examining only those with severe dysmenorrhea, the association with HG was stronger for both adolescent and adult dysmenorrhea ($P < 0.0001$, OR: 8.8, 95% CI: 3.9 - 19.9 and $P < 0.0001$, OR: 12.2, 95% CI: 5.0 - 29.7) respectively (Tables 3 and 4). A modest association between moderate adult dysmenorrhea with HG was also found ($P = 0.004$, OR: 3.1, 95% CI: 1.4 - 6.9) as shown in Table 4. There was no significant association between HG with mild and moderate adolescent dysmenorrhea and mild adult dysmenorrhea ($P = 0.08$, 0.076 and 0.12 respectively). The adjusted ORs for adolescent and adult dysmenorrhea after controlling for confounders were 6.93 and 8.34 respectively ($P < 0.0001$).

Further bivariate analysis showed statistically significant associations between nausea and vomiting in pregnancy and

Table 4. Nausea and Vomiting and Intensity of Adult Dysmenorrhea

Nausea and vomiting	Absence dysmenorrhea	Mild dysmenorrhea	Moderate dysmenorrhea	Severe dysmenorrhea	Total
Absence	69 (61%)	8 (7%)	26 (23%)	10 (8%)	113
Mild	24 (44%)	3 (5%)	21 (38%)	7 (13%)	55
Moderate	44 (42%)	6 (6%)	36 (35%)	18 (17%)	104
Severe	17 (24%)	5 (6%)	20 (28%)	30 (42%)	72
Total	154	22	103	65	344

$P < 0.0001$ (OR: 11.56, 95% CI: 4.53 - 29.44).

family history of nausea and vomiting in first degree relatives, personal history of nausea and vomiting in previous pregnancies ($P < 0.0001$), and past surgical history such as cesarean section and laparotomies for any indication ($P = 0.011$). There were no statistically significant associations between nausea and vomiting and medical history such as diabetics, hypertension, GERD, etc. ($P = 0.357$), marital status ($P = 0.457$), new father of baby as different from previous pregnancies ($P = 0.161$), contraceptive usage of any form ($P = 0.356$) and dyspareunia ($P = 0.451$). Multivariate logistic regression analyses using personal and family histories of nausea and vomiting of pregnancy and surgical history as cofounders showed persistent statistically significant association between nausea and vomiting of pregnancy and adult and adolescent dysmenorrhea. The adjusted ORs for adolescent and adult dysmenorrhea after controlling for cofounders were 6.93 and 8.35 respectively ($P < 0.0001$).

Discussion

Our study shows that there is a positive association between nausea and vomiting in pregnancy and history of dysmenorrhea as adult and adolescent. This association remains consistent even when controlled for cofounders. There is also a linear relationship between the severity of emesis and the severity

of dysmenorrhea in adolescent and adult (Fig. 1, 2).

Dysmenorrhea and hyperemesis are two disease entities that the overall etiologies are both unknown. The positive correlation between these diseases in our study may be due to an increase in prostaglandins, hormones and other factors [29]. The association between HG and increase level of hCG still remains debatable. An isoform of hCG that has genetic connotation has been proposed [2, 30, 31]. However, conditions that are associated with high level of hCG such as chorio-carcinoma, do not typically result in nausea and vomiting, and many pregnant women with high hCG levels do not suffer from HG. In addition, there are a significant number of women with HG whose symptoms go beyond first trimester when hCG levels are falling. The use of hCG as luteal support or to trigger oocyte maturation has not been found to cause symptoms of HG. Hence, other hormones and factors that have been linked to HG include progesterone, estrogen, thyroid hormones, leptin, adrenal cortex hormones, prolactin, growth hormone, placenta serum markers, immunology, gastro-intestinal infection and intestinal motility, change in lower esophageal sphincter pressure, increased fluid secretion in the gastro-intestinal tract, liver enzymes, amylase, vitamin 6 and trace element deficiency [32].

Many hormones, hormone releasing factors, cytokines and prostaglandins have been found to stimulate the synthesis and

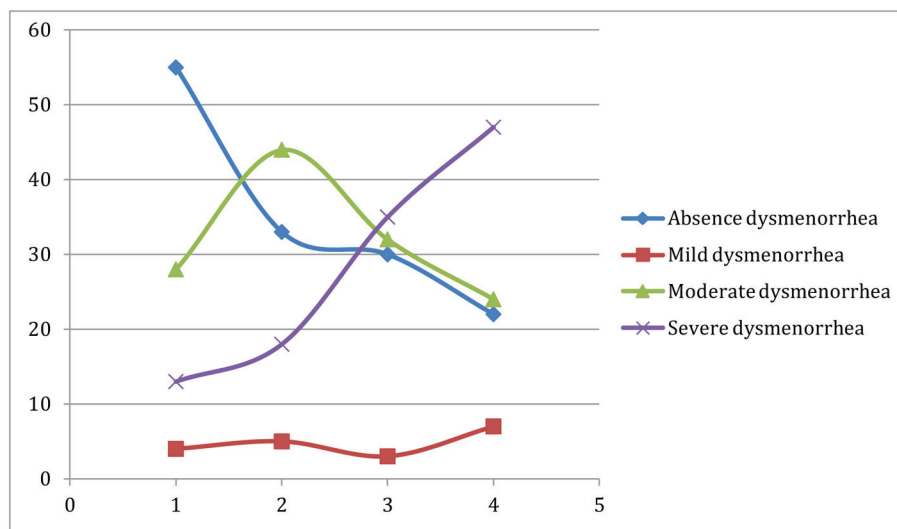


Figure 1. The relationship between intensity of adolescent dysmenorrhea and severity of nausea and vomiting.

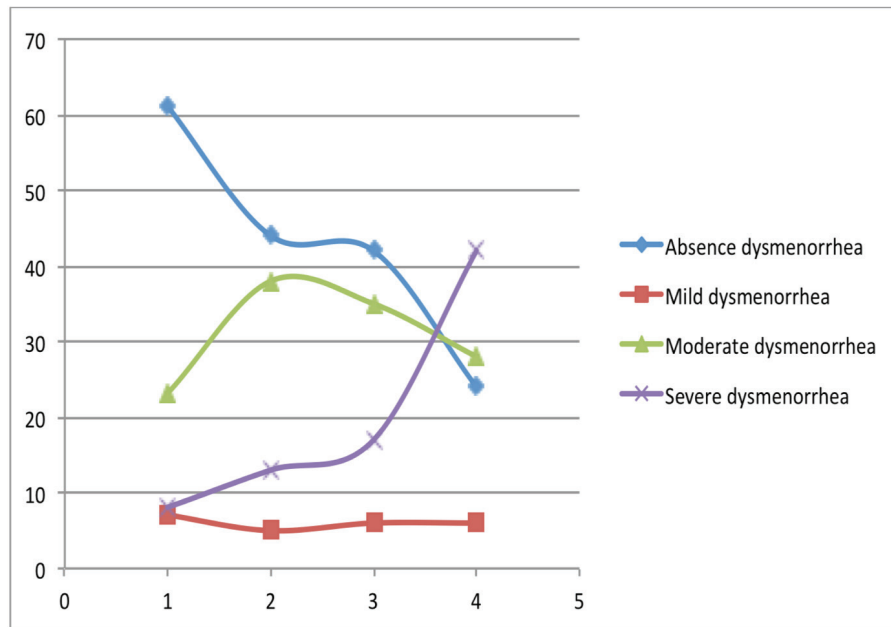


Figure 2. The relationship between intensity of adult dysmenorrhea and severity of nausea and vomiting.

release of hCG from syncytiotrophoblast cells in early pregnancy. Of all these factors, only prostaglandin E₂ (PGE₂) and prostaglandin F_{2α} (PGF_{2α}) are known to cause nausea and vomiting of pregnancy when these prostaglandins are given to procure legal termination of early pregnancy. PGE₂ is produced by the syncytiotrophoblast cells of human trophoblast at 7 - 11 weeks of gestation. The production of PGE₂ is stimulated by several hormones and cytokines such as interleukin-1 and hCG itself. The production and release of PGE₂ is controlled by prostaglandin dehydrogenase (PGDH) which is found in early trophoblast and convert PGE₂ to its inactive metabolite 5-ketoprostaglandin E₂ [33]. The syncytiotrophoblasts which are in direct contact with maternal blood are devoid of PGDH but it is present in cytotrophoblast and the decidual cells. This results in increased maternal serum level of PGE₂ disproportionate to the decidual tissues and small blood vessels [34]. The activities of PGDH are regulated by progesterone, and increased production of progesterone is directly proportional to synthesis of PGDH especially in the decidual tissues which prevent miscarriage. The natural reduction of progesterone between 5 and 9 weeks of pregnancy results in low activities of PGDH which invariably increase maternal level of PGE₂ [35]. Increased maternal serum level of PGE₂ causes nausea and vomiting of pregnancy.

After reviewing PubMed, Cochrane library, Medline using MeSH search, there is no study till date that shows that there is an association between dysmenorrhea and HG. The major link between the two disease entities is prostaglandin as proposed by Cunningham and Muneyyirci-Delale in their hypothesis [29]. It is established that prostaglandin is the main etiology of primary dysmenorrhea in both adolescents and adults [25, 26]. Our study shows that women with history of adolescent and adult dysmenorrhea have five-fold increased risk of develop-

ing HG. This risk further increased by about 10-fold when they have severe dysmenorrhea. There is a modest increased risk of HG with moderately severe adolescent and adult dysmenorrhea. Mild adolescent and adult dysmenorrhea was not found to increase the risk of nausea and vomiting of pregnancy and HG in this study.

Conclusion

While it is possible to ameliorate the effects of HG, the scourge of intractable condition remained a huge challenge. Many of the prior interventions such as thalidomide and diethylstilbestrol (DES) ended up causing more harm than good. The reduction in prostaglandin and leukotriene synthesis can both have synergistic effects in reducing the syntheses and release of hCG which will invariably decrease the occurrence and severity of nausea and vomiting in pregnancy. There is speculation that pre-pregnancy aggressive treatment of dysmenorrhea with NSAID to reduce the level and effect of prostaglandin until pregnancy may reduce the severity of HG. Corticosteroids such as methylprednisolone or dexamethasone which inhibit synthesis of prostaglandin and leukotrienes are used for treatment of refractory HG [36]. Early treatment of severe nausea and vomiting with corticosteroids in patients with history of severe dysmenorrhea may reduce the morbidity associated with HG. However, corticosteroids especially dexamethasone which crosses the placenta should be used with precautions because of its potential teratogenic effects. When required, they should be used after 8 - 10 weeks gestation when lip fusion has been completed. However, further research is needed to establish causal relationship between dysmenorrhea and HG.

Support

No support was received for this work.

Conflict of Interest

The authors declare no conflict of interest.

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