Hyperemesis Gravidarum: A Review

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SUMMARY

Vomiting in pregnancy is a very common phenomenon, though not well understood. The extreme form, hyperemesis gravidarum can lead to severe complications. Articles published in the last decade in this field were searched and studied. Various aetiological factors were identified, the recent ones being the association of *Helicobacter. pylori* with hyperemesis, as well as the presence of cell free fetal DNA. The management of the condition involves symptomatic treatment along with antiemetic, pyridoxine and thiamine. Important role of alternative therapies like ginger and P6 acupoint stimulation in the treatment of hyperemesis has been identified .

KEY WORDS:
Nausea and vomiting of pregnancy, Hyperemesis gravidarum, Morning sickness, Pyridoxine, Antiemetics

INTRODUCTION

Nausea and vomiting of pregnancy has been a very common age old phenomenon. Though not well understood, it occurs in almost 70 percent of pregnant women. While "morning sickness" remains common, it is usually more troublesome when it is serious. As the aetiology remains obscure, the treatment lacks effectiveness. The traditional practice of giving the symptomatic anti-emetic treatment without much knowledge and confidence, has not changed over the years. The severe end of the continuum, hyperemesis gravidarum, may complicate up to 0.3 - 2 percent of pregnancies, causing physiological changes that may affect the mother and fetus. There have not been many novel discoveries in this field and we mostly rely on personal experiences. In most cases, affected individuals progress from mild or moderate nausea and vomiting to hyperemesis gravidarum which can be 'complicated' or 'uncomplicated', the former referring to acetonuria, fluid electrolyte imbalance and Wernicke's encephalopathy. Prematurity, low birth weight, small for gestational age and a 5-minute apgar score of less than 7, have been reported in fetuses of mothers affected with hyperemesis gravidarum (Level of Evidence-II-2)[10], more so in women with poor maternal weight gain associated with it.

Aetiology

The cause of hyperemesis is still not well understood. The associated risk factors and the significance of these associations are depicted in Table I.

It is seen more commonly in singleton female pregnancies, pregnancies with multiple male fetuses as well as male and female combinations than in singleton male pregnancies. The factors associated with hyperemesis are primarily medical and fetal factors that are not easily modifiable, but their identification may be useful in determining those women at high risk for developing hyperemesis. High risk for recurrence is observed in women with hyperemesis in the first pregnancy. The risk is reduced by a change in paternity. For women with no previous hyperemesis, a long interval between births slightly increases the risk of hyperemesis in the second pregnancy. So, relative impact of genetic and environmental factors and their possible interactions in seen in hyperemesis[3]. A low prepregnancy weight : height ratio may predispose women to the development of hyperemesis[2]. Low maternal age and parity more than one independently increases the risk for nausea and vomiting in pregnancy. Smoking before pregnancy and using vitamins in early pregnancy are associated with a decreased risk for nausea and vomiting (Level of Evidence – II-2)[4]. Women working outside the home have a lower rate of nausea and vomiting than housewives and women out of work[5].

Hormonal factors are known to play an important role in the aetiology. The cause seems to be associated with higher levels of selected forms of human Chorionic Gonadotropin (variations in glycosylation) with the greatest thyroid stimulating capacity. Chorionic gonadotropin, especially isoforms with relatively diminished amounts of sialic acid, act via the thyroid – stimulating hormone receptor to accelerate iodine uptake. Also low levels of prolactin and high levels of estradiol can contribute to nausea in pregnancy[6]. Researchers theorized that during human evolution, sickness during pregnancy protected the fetus by making the mother too nauseous to eat foods that were most likely to be toxic in the early pregnancy. Support for this idea comes from the fact that many of the foods that tend to repulse pregnant women contain potentially harmful substances. Also, women who have virtually no nausea or vomiting appear to be more likely to miscarry than those who experience some sickness. Psychological and social factors influence this disease, such as unwanted pregnancies. Young unwed mothers are common sufferers of this syndrome. Remarkable improvement with hospitalization is often noted in such cases, with rapid relapse once released to the home environment. Hysterical and immature personalities can predispose one to this condition.

This article was accepted: 6 August 2008
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RECENT DEVELOPMENTS

Role of Helicobacter pylori

Recently, association between *Helicobacter pylori (H. pylori)* and hyperemesis gravidarum has been found and serologically positive *H. pylori* infection has been demonstrated in the hyperemesis group[7]. In this study, Karaca *et al*. compared 56 pregnant women with hyperemesis gravidarum to 90 pregnant women without hyperemesis and detected specific serum immunoglobulin G for *H. pylori* by fluorescent enzyme immunoassay method in 82 percent subjects of the hyperemesis gravidarum group as compared to 64 percent in the controls, the difference being statistically significant. Supporting this, agents active against *H. pylori* have been found to be very effective for the treatment of hyperemesis[8,9]. The elevated human Chorionic Gonadotropin (hCG)) causing a shift in pH along with pregnancy – induced gastrointestinal dysmotility and altered humoral as well as cell – mediated immunity in pregnancy are believed to be the reasons for infection. Lower socio-economic status may also be an important risk factor for infection with *H. Pylori* in pregnant women with hyperemesis gravidarum[7].

Immunological Factors

Recent reports also significantly correlate the severity of hyperemesis with increased concentrations of cell-free fetal deoxyribonucleic acid (DNA)[10]. Yumi *et al*. studied 202 pregnant women between 6 – 16 weeks bearing a single male fetus. They classified forty – five women with hyperemesis into three groups based on the severity of the condition and matched for gestational age with 157 controls and analyzed them blindly without knowledge of case – control status. They plotted both gestational age and hyperemesis severity vs $\log_{10}$ fetal DNA and found that these were associated with a direct proportional increase. The fetal DNA concentration in the plasma of pregnant women in the control group gradually increased as the pregnancy progressed and the clinical severity of hyperemesis was directly associated with the increase in fetal DNA.

The fetal DNA comes from the destruction of villous trophoblasts which border the intervillous space filled with maternal blood[11,12]. These are destroyed by the hyperactivated maternal immune system. The functional activation of natural killer and cytotoxic T-cells is found to be more prominent in hyperemesis than in women with an uncomplicated pregnancy[13]. The clinical severity of hyperemesis is directly associated with the increase in fetal DNA. If the maternal immune system completely tolerates the fetus, the myometrium might be invaded by growing trophoblasts, but in the presence of anomalies of the immune interaction between the mother and the fetus, invasion of trophoblasts into the myometrium would lead to increased concentrations of fetal DNA in the maternal plasma. In hyperemesis, a similar situation can occur. Thus hyperactivation of the maternal immune system may be responsible for the onset of hyperemesis, probably while maternal immune tolerance to the semiallograft is being established.

This could explain why fetal DNA and hyperemesis are related and proportionally correlated. Because, the majority of cell free fetal DNA likely originates from placental trophoblasts,[11,12] trophoblasts might be more damaged in severe hyperemesis than in uncomplicated pregnancies or in cases of mild hyperemesis occuring during formation of the placenta.

Furthermore, levels of tumor necrosis factor – alpha are found to be significantly high in patients with hyperemesis, and could be involved in the etiology[14]. Similarly, high levels of interleukin – 6 are reported to enhance secretion of beta-hCG from trophoblastic cell line[15]. Various hormonal and immunological factors associated with hyperemesis are depicted in Table II.

Diagnosis

Though, nausea and vomiting are very common symptoms of pregnancy, hyperemesis gravidarum is considered when all other causes of persistent nausea and vomiting like pyelonephritis, pancreatitis, cholecystitis, hepatitis, appendicitis, gastroenteritis, peptic ulcer disease, thyrotoxicosis, and hyperthyroidism are ruled out, the main reason being that these are treatable conditions and can also present with intractable nausea and vomiting.

The diagnostic work-up must always start with confirmation of a viable, intrauterine pregnancy. Electrolytes, liver function tests, thyroid function tests, creatinine, blood urea nitrogen, urinalysis and a complete blood count are some of the investigations that need consideration in the work-up of severe hyperemesis gravidarum where starvation and fluid imbalance can be encountered .

Management

According to American College of Obstetricians and Gynecologists (ACOG) [18], taking multivitamins at the time of conception decreases the severity of symptoms.

Psychological Support

As the psychological factors are known to play an important role, it is crucial to expand the circle of support from family to health care professionals involved in looking after sufferers. Reassurance and emotional support is must to these patients and counseling should be initiated once symptoms have abated. Though isolation practice existed since 1914 based on the belief that these women were simulating pain in order to obtain abortion, but now it does not appear that patients have to be isolated to reveal their desire for abortion. A psychological interview allows better understanding of the ambivalent attitudes of pregnant women.

Conventional Therapy

There was no proven pharmacological treatment until now. The therapies and drugs which have been studied for their efficacy are shown in Table III and Table IV respectively.

Women who have experienced severe nausea and vomiting in previous pregnancy, have been shown to

Table I: Risk factors for hyperemesis gravidarum

Risk Factor	Significance	Study Design	Numbers in the study
Prepregnancy underweight	Increased risk (P < 0.01)	Retrospective Chart Review[2]	38
Change inpaternity	Decreased risk-10.9%vs16 % OR=0.60;95% CI=0.39–0.92	Cohort Study3 in logistic regression model	
Second pregnancy	15.2% increased risk OR=26.4;95% CI=24.2–28.7	Cohort Study3 in logistic regression model	547,238
Previous Molar Pregnancy	Increased risk (RR= 3.3) 95% CI =1.6–6.8	Population based Cohort with logistic regression[4]	547,238
Maternal Age > 30	Decreased risk	Population based Cohort[4]	157,922
Hyperthyroid disorders	Increased risk (RR = 4.5) 95% CI=1.8–11.1 38% increased incidence	Population based Cohort with logistic regression[4] (Level of evidence II –2)	157,922
Preexisting Diabetes	Increased risk (RR = 2.6) 95% CI=1.5–4.7	Population based Cohort[4] (Level of evidence II –2)	157,922
Psychiatric illness	Increased risk (RR = 4.1) 95 % CI=3.0–5.7	Population based Cohort with logistic regression[4]	157,922
Gastrointestinal Disorders	Increased risk (RR = 1.5) 95% CI=1.8–3.6	Population based Cohort with logistic regression[4]	157,922
Asthma	Increased risk (RR = 1.5) 95% CI=1.2–1.9	Population based Cohort with logistic regression[4]	157,922

Table II: Factors associated with hyperemesis gravidarum

Association	Significance	Study Design	Numbers in the study
Low Prolactin Levels	P < 0.01	Prospective Cohort Study[6]	262
Higher levels of estradiol	P = 0.06	Prospective Cohort Study[6]	262
Estriol, progesterone, or sex hormone binding globulin	No association	Prospective Cohort Study[6]	262
Increased plasma TNF – alpha concentration	P < 0.05	Case Control Study[14]	90
Interleukin – 2 receptor	No association	Case Control Study[14]	90
Interleukin – 8	No association	Case Control Study[14]	90
High Interleukin – 6 levels	P = 0.13	Case Control Study[14,15]	90
Lower socio-economic status and association with H. Pylori	P = 0.013	Case Control Study7	146
Increased plasma Fetal DNA concentration	P <0.001	Double blind Case Control Study[10]	202
Increased TSH Level	P<0.05	Case Control Study[16]	84
High Plasma adenosine Level	P < 0.05		84
Serum anti – *H. Pylori* IgG antibodies	No significant association	Prospective Case Control Study[17]	160

Table III: Treatment modalities for hyperemesis gravidarum

Treatment	Efficacy	Study Design	Numbers in the study
Pre- emptive treatment better than treatment after symptoms appear	P = 0.01	Prospective Case Control Study[19]	60
Anti – emetic medication effective	OR = 0.16 95%CI =0.08– 0.33	Cochrane Review[20] (Metaanalysis)	12 trials
Pyridoxine	Evidence of beneficial effects	Randomized trials[20,21]	10 Randomized trials ACOG 18 recommendation
Combination of pyridoxine & metoclopromide superior to either monotherapy	P<0.05	Prospective randomized controlled trial[22]	174
Ginger	1. Inhibits growth of H. Pylori CagA+ strains9 2. Evidence of beneficial effects	Randomized trials by Alkins *et al*[21]	10 Randomized trials ACOG 18 recommendation
P6 acupressure	Equivocal	Metaanalysis Randomized trials[20,21]	28 trials Recommended by NICE
Nerve stimulation	1. Symptoms improved (P=0.02) 2. Weight gain (P=0.003)	Randomised Controlled Trial[23]	230

Table IV: Drugs studied for treatment of hyperemesis gravidarum

Drug	Efficacy	Study Design	Numbers in the study
Levomepromazine 6.25 mg tds	Effective in resistant cases	Prospective Trial[24]	6
Ondansetron	No advantage over Promathazine	Randomized Prospective Double Blind Study[25]	30
Erythromycin	Marked rapid improvement	Clinical Study[9]	2
Diazepam	1. Greater reduction in symptoms (P<0.05) 2. Shorter Hospital Stay (P<0.05) with no teratogenicity	Case – Control Study[26]	50
Corticosteroids	No reduction in rehospitalization	Randomised, double blind placebo–control study[27]	126
Cannabis	92% found as effective or extremely effective	Survey[28]	84

benefit from taking antiemetics before, as prophylaxis, or immediately at the start of symptoms in a subsequent pregnancy, so called "pre-emptive therapy"[19]. Pharmacotherapy with antiemetics and pyridoxine is found to be effective[22]. Pyridoxine is marketed in combination formulations with Doxylamine. Though the combination, Benedectin was taken off the market in the United States in the 1980s because of liability issues, the ACOG Guidelines 2004 recommend 10mg of pyridoxine plus one half of 25mg of doxylamine (antihistamine) administered orally every 8 hours as first line pharmacotherapy. If it is not available over the counter, it recommends to take sleep medications that contain doxylamine. Pyridoxine is a class A drug and can be given safely in pregnancy. Conventional antiemetics such as H1 receptor blockers, phenothiazines and benzamines are found to be efficacious and safe. Antiemetics like Prochlorperazine, Promethazine, Chlorpromazine may relieve nausea and vomiting by blocking postsynaptic mesolimbic dopamine receptors through anticholinergic effects and depressing reticular activating system. These are Class C drugs with safety not established for use during pregnancy. There is very little information on effects of anti-emetic therapy on fetal outcomes from randomized controlled trials though no association could be demonstrated between metoclopramide and adverse effects like malformations, low birth weight and preterm delivery[29]. Combination therapy with pyridoxine and metoclopromide is found to be superior to either monotherapy in the treatment[22]. Prophylactic thiamine supplementation can be given to prevent Wernicke's encephalopathy which can be seen as a complication of hyperemesis. While this life – threatening complication is rare, it is important for all who care for obstetric patients to be aware of it and alert to its development. If a pregnant woman has symptoms of severe vomiting along with ocular findings such as retinal hemorrhage or restricted extraocular movement, one must suspect the diagnosis of Wernicke-Korsakoff Syndrome.

Role of Alternative Therapies

Other alternative therapies have been studied and are found to be very effective. Ginger root (Zingiber officinale Roscoe) is reported to have chemoprotective activity in animal models. The gingerols are a group of structurally related polyphenolic compounds isolated from ginger and are known to be the active constituents. The methanol extract of ginger rhizome has been seen to inhibit the growth of 19 strains of *H.pylori* by Mahady *et al.*[8]. The fraction containing the gingerols is found to be active and inhibits the growth of all *H. pylori* strains with significant activity against the Cytotoxin associated gene (Cag) A+ strains, one of the important strains causing infection. A randomized, double – blind, crossover trial of a ginger extract was shown to be more beneficial for reducing symptoms than placebo. They are not approved by the United States Food and Drug Administration (US FDA) with concerns of potential effect on testosterone binding and thromboxane synthetase activity, but are remedies believed to improve symptoms and strongly recommended by ACOG 2004[19]. The dose to be given is 250 mg of powdered ginger root administered orally every 6 hours.

Acupressure bands and acupuncture have been tried. The Systematic Cochrane Review supports the use of P6 acupoint stimulation in patients without antiemetic prophylaxis. P6 acupoint stimulation seems to reduce the risk of nausea[24]. National Evidence-based Clinical (NICE) Guidelines October 2003 on antenatal care recommend ginger, P6 acupressure and antihistamines for the treatment of nausea and vomiting in pregnancy showing level I evidence. Low level nerve stimulation therapy over the volar aspect of the wrist has shown to reduce nausea and vomiting and promote weight gain in pregnancy[24].

Role of adenosine is now identified in counteracting progression of hyperemesis gravidarum associated with gestational thyrotoxicosis[16]. Adenosine is an established suppressor of excessive sympathetic nerves activation and cytokine production, so the increase in plasma adenosine in hyperemesis might serve to counteract further progression of hyperemesis gravidarum[30]. American College of Obstetricians and Gynecologists[18] recommends the use of corticosteroids such as methylprednisolone as a last resort, due to the potential risks to the fetus.

The age old therapy of antiemetic medication which was used without much proven benefit, can now be used with confidence. All other alternative therapies like ginger root extract, P6 acupoint stimulation, low level nerve stimulation, cannabis, erythromycin and diazepam have been found to be effective though many of them are not approved by US FDA. Extensive studies and drug trials on a large scale are needed to get these medications in the market for treatment. Even though they do not belong to our conventional mode of therapy, they remain important.

Supporting the NICE Guidelines, we should inform about all forms of self- help and non- pharmacological treatments available for pregnant women who have nausea and vomiting(Good Practice Point).

With all these proven effective medications available, the sourness of hyperemesis gravidarum has definitely decreased over the last few years.

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Multiple Choice Questions:

1. Which of the following microorganism is associated with hyperemesis gravidarum?
   A. Human papilloma virus
   B. Helicobacter pylori
   C. Escherichia coli
   D. Gardenella vaginosis

2. Which of the following statement is true regarding the aetiology of hyperemesis gravidarum?
   A. Low maternal age
   B. Maternal smoking
   C. Women working outside their homes
   D. High prolactin levels

3. Which of the following statement is true?
   A. Severity of hyperemesis is associated with increased concentrations of cell free DNA.
   B. Levels of tumor necrosis factor –alpha is found to be low in patients with hyperemesis.
   C. Taking multivitamin at the time of conception increases the severity of hyperemesis.
   D. Antiemetics are not effective in the treatment of hyperemesis.

4. Which of the following statement is true regarding the treatment of hyperemesis gravidarum?
   A. Combination therapy is superior to monotherapy.
   B. Psychological support has no role.
   C. Prophylactic thiamine supplementation is given to prevent pellagra.
   D. Non – pharmacological treatment is not available.

5. Which of the following statement is true regarding the treatment of hyperemesis gravidarum?
   A. Ginger root extract is beneficial for reducing symptoms
   B. Cochrane Review does not support P6 Acupoint stimulation.
   C. Corticosteroids should be routinely used for the treatment of hyperemesis gravidarum.
   D. Different forms of self – help and non- pharmacological treatments should not be informed to the patient.