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Nausea and Vomiting of Pregnancy-What's New?

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Abstract

Nausea and vomiting of pregnancy (NVP) is one of the most common disorders of pregnancy. The symptoms occur predominantly during the first trimester, although in a subgroup of patients they can continue throughout the entire pregnancy and can affect the woman's quality of life. A small percentage of women develop a severe form of NVP called hyperemesis gravidarum (HG) that if left untreated may lead to significant maternal morbidity and adverse birth outcomes. Overall, the morbidity in pregnant women with NVP is significant, although it tends to be underestimated. The pathogenesis of NVP remains unclear, but there is consensus that the disorder is multifactorial and that various genetic, endocrine and infectious factors may be involved. The treatment of NVP can be challenging as the optimal targets for therapy are not known. Currently, the therapy used depends on the severity of the disorder and it is focused on improving the symptoms while minimizing risks to mother and fetus. Therapies range from dietary changes, pharmacologic treatment or hospitalization with intravenous fluid replacement and nutrition therapy. The aims of this review are 1) to provide an overview of NVP, 2) to present possible links between the most important factors associated with the pathogenesis of NVP and 3) to discuss the effectiveness and safety of the pharmacologic and non-pharmacologic options available to treat this disorder.

Keywords

Nausea and Vomiting of Pregnancy; Hyperemesis Gravidarum; pathogenesis; therapy

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1. NAUSEA AND VOMITING OF PREGNANCY

Nausea and Vomiting of Pregnancy (NVP) is a very common disorder reported in 70 – 80% of all pregnant women (Flaxman et al., 2000; Lacroix et al., 2000; O'Brien et al., 1995; Pepper et al., 2006). Symptoms usually begin 2–4 weeks after fertilization, peak between 9 and 16 weeks of gestation and generally resolve by 22 weeks gestation (Brandes, 1967; Broussard et al., 1998; Gadsby et al., 1993; Hasler et al., 1995; Klebanoff et al., 1985; Lee et al., 2011; Zur, 2013). Up to 10% of women have a prolonged course with symptoms extending until the time of delivery (Hasler et al., 1995). NVP persists throughout the day in as many as 98% of women with NVP (Hasler et al., 1995); therefore, the popular term "morning sickness" doesn't properly reflect this condition (Lacroix et al., 2000; Zur, 2013).

Although NVP tends to be treated as a normal part of pregnancy (Brandes, 1967; Tierson et al., 1986), it can significantly reduce the quality of life of the pregnant woman. Women with NVP have significantly increased odds for high blood pressure and preeclampsia compared with symptom-free pregnant women (Chortatos et al., 2015). In addition, in 10–35% of patients the symptoms of NVP lead to increased feelings of depression, and may cause a negative impact on employment, household duties, parenting and family relationships (Attard et al., 2002; Mazzotta et al., 2000b; Mazzotta et al., 2000c; Niebyl, 2010; O'Brien et al., 1992; Smith et al., 2000). Even more concerning is the observation that women with mild NVP have also reported experiencing the same psychosocial problems as women with severe symptoms (Mazzotta et al., 2000b). These data suggest that morbidity in pregnant women with NVP is significant although these issues tend to be overlooked. In addition, NVP also exerts a large economic impact on patients, caregivers and society. In 2012 the total economic burden of NVP was estimated to be $1.77 billion in the United States (Piwko et al., 2013).

In contrast to the burden that NVP can be for the pregnant woman, most studies have found that mild NVP is associated with favorable outcomes for the fetus including reduced odds for low birth weight and small for gestational age (Brandes, 1967; Chortatos et al., 2015; Little, 1980; Medalie, 1957; Milkovich et al., 1976; Petitti, 1986; Tierson et al., 1986), reduced risk of preterm delivery (Brandes, 1967; Jarnfelt-Samsioe, 1987; Klebanoff et al., 1985; Koren et al., 2014; Medalie, 1957; Milkovich et al., 1976; Petitti, 1986; Tierson et al., 1986) and reductions in the likelihood of miscarriage (Jarnfelt-Samsioe, 1987; Klebanoff et al., 1985; Koren et al., 2014; Medalie, 1957; Milkovich et al., 1976; Petitti, 1986; Weigel et al., 1989).

Finally, the severity of symptoms for NVP range from mild to moderate nausea and vomiting to pathologic cases of women with a severe form of NVP called hyperemesis gravidarum (Lee et al., 2011).

2. HYPEREMESIS GRAVIDARUM

Hyperemesis gravidarum (HG) is characterized by severe nausea and excessive vomiting starting before the end of the 22nd week of gestation (World-Health-Organization, 2016). HG affects 0.3–2% of pregnant women and if left untreated or if treatment is unsuccessful it

may lead to significant maternal morbidity and adverse birth outcomes (Dodds et al., 2006; Lee et al., 2011; Munch, 2002; Verberg et al., 2005; Zur, 2013). In fact, women with HG have a lower health-related quality of life (Munch et al., 2011). The condition interferes with liquid and food intake and may lead to dehydration, electrolyte and acid-base imbalance, nutritional deficiency, ketonuria and loss of more than 5% of body weight (Bashiri et al., 1995; Fejzo et al., 2009; Golberg et al., 2007; Goodwin, 1998; Grooten et al., 2015a; Verberg et al., 2005). In addition, women with HG also can have excess salivation (Godsey et al., 1991), vitamin B1 and mineral deficiencies (Koch et al., 2003), gastroesophageal reflux symptoms and abnormal liver function tests (Lee et al., 2011). HG is associated with morbidity such as acute kidney injury (Machado et al., 2012), liver dysfunction (Shekhar et al., 2015), pneumomediastinum (Gorbach et al., 1997; Liang et al., 2002), ruptured esophagus (Buchanan et al., 2014), and Wernicke's encephalopathy (Berdai et al., 2016; Giugale et al., 2015). In addition, a recent case-control study found that psychological distress was a direct consequence of HG (Aksoy et al., 2015), which is in accordance with previous reports of increased risk of cognitive, behavioral, and emotional disorders in this population (Poursharif et al., 2008; Zur, 2013). Even more, the complications associated with HG can result in termination of an otherwise wanted pregnancy (Poursharif et al., 2007; Trogstad et al., 2005). The long-term consequences of HG on mothers are still undetermined, although several studies suggest increased rates of depression, post-traumatic stress disorder, and various neurological disorders (Goodwin, 2008; Grooten et al., 2015a).

HG is the most common reason for hospitalization in the first half of the pregnancy and second only to preterm labor throughout the whole of pregnancy (Gazmararian et al., 2002). In the United States over 285,000 women are admitted to the hospital and over 26,077 are admitted to the Emergency Department each year due to HG (Piwko et al., 2013; Zur, 2013). The cost of care is estimated to be $47,351 per HG patient (Piwko et al., 2013). Although uncommon in contemporary practice, several maternal deaths have also been reported secondary to HG (Daaloul et al., 2012; Kantor et al., 2014; Knight et al., 2014; MacGibbon et al., 2015). These fatalities illustrate the importance of rapid diagnosis, preventative vitamin supplementation, and electrolyte monitoring and correction (MacGibbon et al., 2015).

Some studies have also found an association of HG with poor neonatal outcomes like low birth weight, preterm birth, fetal death and small for gestational age (Dodds et al., 2006; Grooten et al., 2015a; Lee et al., 2011; Veenendaal et al., 2011; Zhang et al., 1991). HG is also associated with poor adult health for the offspring like decreased insulin sensitivity and increased risks of psychological and behavioral disorders (Mullin et al., 2011; Veenendaal et al., 2011). Besides, infants born to women with HG and low pregnancy weight gain were more likely to have low birth weight, have a 5-minute Apgar score of < 7 and have increased blood pressure (Dodds et al., 2006; Grooten et al., 2015a; Lee et al., 2011).

3. PREGNANCY UNIQUE QUANTIFICATION OF EMESIS (PUQE) SCORE

The severity of NVP has a broad spectrum therefore it is critical to have a graded scale to track the severity of symptoms as a guide to determine the appropriate treatment and response to treatment. In 2002 Ebrahimi et al. introduced the Pregnancy-Unique

Quantification of Emesis (PUQE) scoring system (Ebrahimi et al., 2009). The updated PUQUE score assesses the severity of NVP based on three physical symptoms: nausea, vomiting, and retching over the previous 24 hours (Birkeland et al., 2015; Ebrahimi et al., 2009; Koren et al., 2005). The PUQE-scoring has been validated as a robust indicator of HG with higher PUQE-score values in HG patients compared to controls (median 13; 95% CI 11–14 vs. 7; 95% CI 4–8) (Birkeland et al., 2015). The calculation of the PUQE score is simple and there are several online tools freely available for this purpose (APGO, 2016; HER-Foundation, 2016).

4. PATHOGENESIS

Although the pathogenesis of NVP and HG remain unclear, it is widely accepted that it is likely to be multifactorial and that various genetic, endocrine, and gastrointestinal factors may be involved.

GENETIC PREDISPOSITION

Maternal genetics appear to be a risk factor for NVP. For example, there is a higher use of nausea medication in pregnancy among female monozygotic twins compared to female dizygotic twins (Corey et al., 1992). A recent study on 1723 women with either monozygotic or dizygotic twins as well as twin-sister pairs demonstrated that NVP is highly heritable. In this study genetic effects accounted for 73% of the variance, 51% for duration of NVP and 53% for severity of NVP (Colodro-Conde et al., 2016). In addition, family history of HG is also a risk factor with approximately 28% of women reporting a history of HG in their mothers and 19% reporting their sisters had HG symptoms (Fejzo et al., 2008; Gadsby et al., 1997; Zhang et al., 2011). In accordance with this findings, it has been reported that the risk of HG in a pregnant woman is threefold if the woman’s mother had ever experienced hyperemesis in a pregnancy (Vikanes et al., 2010). Besides, women who experienced HG in their first pregnancy have a significant risk of recurrence when compared to women who did not experience the condition in their first pregnancy (Trogstad et al., 2005).

The incidence of NVP also appears to vary with ethnicity and ranges between 3 and 20 per 1,000 pregnancies (Bashiri et al., 1995; Lee et al., 2011). It is more commonly diagnosed in women in India, Pakistan, Asian, New Zealanders compared to European, American Indian, and Eskimo populations (Verberg et al., 2005).

PLACENTALLY MEDIATED MECHANISMS

A possible involvement of the placenta in the pathology of NVP has been suggested by Niebyl. The evidence in support of this hypothesis is based on the observation that pregnancies with no fetus (complete hydatidiform mole) are associated with clinically significant NVP indicating that the stimulus is produced by the placenta, not the fetus. According to this hypothesis, NVP is less common in older women, multiparous women, and smokers and this observation has been attributed to the smaller placental volumes in these women (Niebyl, 2010).

Some studies have found an association between HG and placental dysfunction disorders like pre-eclampsia and placental abruption in patients where the HG diagnosis was made in the second trimester of pregnancy (Bolin et al., 2013; Wood, 2014). On the other hand, Vandraas et al. found a positive association between HG and high placental weight-to-birth weight ratio limited to female offspring (Vandraas et al., 2013). Based on these reports, it is possible that changes in placenta characteristics and function in HG patients may be related to changes in the production of hormones by this organ.

An important function of the placenta is the production of reproductive hormones that have been implicated in the pathogenesis of HG (Goodwin et al., 1994; Jarnfelt-Samsioe et al., 1986; Kauppila et al., 1979; Lagiou et al., 2003; Masson et al., 1985; Soules et al., 1980). Trophoblast-derived tumor necrosis factor (TNF)-a, interleukin (IL)-1 and IL-6 regulate the production and release of human chorionic gonadotrophin (hCG) (Kaplan et al., 2003). This hormone stimulates placental prostaglandin E2 which peaks between 9 and 12 weeks of gestation (Lee et al., 2011). North et al. quantified maternal serum prostaglandin E2 and found levels to be higher during periods of nausea and vomiting (North et al., 1991).

REPRODUCTIVE HORMONES

Hormone levels change dramatically in pregnancy, especially in the first trimester. Several studies suggest that reproductive hormones (hCG, estrogen and progesterone) may be directly and indirectly responsible for the symptoms of NVP (Furneaux et al., 2001; Goodwin et al., 1994; Jarnfelt-Samsioe et al., 1986; Kauppila et al., 1979; Ladyman et al., 2004; Ladyman et al., 2011; Lagiou et al., 2003; Masson et al., 1985; Soules et al., 1980).

HUMAN CHORIONIC GONADOTROPIN (hCG)

The most commonly implicated hormone in NVP and HG pathology is the human chorionic gonadotropin (hCG). This is based largely on the temporal relationship between the peak of NVP and the peak of hCG production, both of which occur simultaneously with the most intense symptoms of NVP—weeks 9 to12 of gestation (Braunstein et al., 1976; Patil et al., 2012). Besides, hCG levels plateau or decline in a similar manner to the resolution of the HG symptoms (Sanu et al., 2011). In addition, nausea and vomiting are often worse in pregnant women with conditions associated with elevated hCG levels such as molar pregnancies, multiple gestations, Down syndrome and pregnancies of female fetuses (Davis, 2004; Niebyl, 2010; Verberg et al., 2005). In fact, an association between HG and female gender of the fetus has been found in several studies (Kallen, 1987; Schiff et al., 2004; Veenendaal et al., 2011). Furthermore, higher urinary hCG (Lee et al., 2011) and serum hCG levels have also been found in women with NVP (Masson et al., 1985). Finally, concentrations of hCG correlate positively with the severity of symptoms in women with HG (Goodwin et al., 1992).

Despite the numerous studies linking hCG to NVP and HG, the role of hCG in these pathologies is not yet clear. Research to date has offered conflicting results about the relationship between serum hCG levels and severity of symptoms of NVP (Verberg et al., 2005). For example, Soules et al. did not find relationship between serum hCG in pregnant women during the first trimester and the occurrence and severity of nausea and vomiting

(Soules et al., 1980). Jarnfelt-Samsioe et al. also reported the lack of correlation between hCG and HG and suggested instead an association of HG with steroidal hormones and liver function (Jarnfelt-Samsioe et al., 1983). In addition, a recent systematic review showed inconsistent association of hCG with HG (Niemeijer et al., 2014).

A possible explanation for the conflicting data about the role of hCG in NVP is based on reports suggesting it is the ratio of the hCG isoforms rather than the total serum hCG that may explain hCG's effect on NVP. An increased proportion of acidic hCG isoforms, appears to play a role in HG (Jordan et al., 1999). Each hCG isoform has a unique half-life and potency; for example, isoforms without the carboxy-terminal portion have shorter half-lives but are more powerful stimulants of the luteinizing hormone and thyroid-stimulating hormone. In contrast, hyperglycosylated hCG isoforms have a longer half-life and longer duration of action (Jordan et al., 1999). These different isoforms of hCG are likely the result of genetic or epigenetic factors which may thus explain the differences in HG incidence found in different populations (Lee et al., 2011). In addition to hCG isoform variation, hCG receptor mutations may also explain some of the variability in the relationship between NVP and hCG (Goodwin, 2008).

PROGESTERONE AND ESTROGEN

Estrogen and progesterone, which increase dramatically in pregnancy, have also been implicated in the pathogenesis of NVP and HG (Jarnfelt-Samsioe, 1987). In support of their causal role in NVP, studies have shown that some women experience nausea when taking oral contraceptives, which typically contain a combination of estrogen and progesterone (Huxley, 2000). In addition, women who experience nausea while taking oral contraceptives are more likely to experience NVP and HG (Jarnfelt-Samsioe et al., 1983; Jordan et al., 1999; Vandormael et al., 1987). Furthermore, states of high estrogen concentration such as low parity and high maternal body mass index have been associated with a higher incidence of HG (Depue et al., 1987; Verberg et al., 2005). Similarly, levels of total estradiol are reported to be higher in patients with HG (Depue et al., 1987; Verberg et al., 2005; Yoneyama et al., 2004), although other studies could not confirm these findings (Verberg et al., 2005).

In terms of the mechanism behind the role of estrogen and progesterone in NVP, it has been reported that stimulation with hCG increase serum concentrations of progesterone and estrogen in a mouse model (Ezoe et al., 2014). Progesterone and estrogen can alter gastric rhythms in non-pregnant women increasing gastric intestinal transit time and slowing gastric emptying which may lead to increased nausea and vomiting (Bruce et al., 1978; Lee et al., 2011; Milenov et al., 1973; Walsh et al., 1996). For example, estrogen is thought to stimulate the production of nitric oxide via nitrogen oxidase synthase, which in turn relaxes smooth muscle slowing gastric intestinal transit time and gastric emptying (Lee et al., 2011). Similar disruptions in the gastric rhythms in pregnant women may be mediated by elevations of these two hormones (Spiegel et al., 2012). In accordance with this idea, Walsh et al. showed that the same slow-wave gastric rhythm disruption found in women with NVP could be induced in non-pregnant women by progesterone alone or in combination with estradiol in doses that reproduce levels in pregnancy (Walsh et al., 1996).

GASTROINTESTINAL DYSMOTILITY

As we mentioned previously, estrogen and progesterone are the likely mediators of esophageal dysmotility in pregnancy (Richter, 2005) and changes in gastric rhythmic activity are associated with nausea (Koch et al., 2003) and may contribute to NVP (Lee et al., 2011).

In support of gastrointestinal dysmotility as part of the pathogenesis of NVP, some studies reported that individuals with normal slow wave activity were less likely to complain of nausea during pregnancy (Koch et al., 1990). In contrast, individuals with higher or lower rates were more likely to complain of nausea. In addition, pregnant women with NVP had more unstable elastogastrography activity compared with women after pregnancy termination and non-pregnant controls (Riezzo et al., 1992).

Despite data linking gastrointestinal dysmotility to the pathogenesis of NVP, its role, is controversial. Many studies have found no difference in the liquid emptying rate between pregnant women before voluntary abortion, 6 weeks after abortion, and in non-pregnant control women (Lee et al., 2011). Another study that used the C-octanoic breath test found no abnormalities in the timing of gastric emptying of women with HG, compared with those without HG (Maes et al., 1999). Similarly, studies using paracetamol showed no gastric emptying delay in the first, second, or third trimester (Macfie et al., 1991).

HELICOBACTER PYLORI

Helicobacter pylori (H. pylori) is more common identified in the stomach of women with HG than in women without HG (Lee et al., 2011; Shaban et al., 2014). Furthermore, several studies have demonstrated a positive relationship between the symptoms of HG and H. pylori seropositivity (Cardaropoli et al.; Erdem et al., 2002; Gungoren et al.; Kocak et al., 1999; Salimi-Khayati et al., 2003). For example, Frigo et al. reported that more than 90% of women with HG were positive for H. plyori compared to 46.5% of controls (Frigo et al., 1998). One study that used the gold standard of testing, histologic exam of the mucosal biopsy (Bagis et al., 2002) found that 95% of HG patients tested positive for H. pylori compared with 50% in the control group. Bagis et al. also found higher H. pylori densities in the gastric antrum and corpus in HG patients. Besides, three systematic reviews found a significant association between maternal H. pylori infection and HG (Golberg et al., 2007; Niemeijer et al., 2014; Sandven et al., 2009).

In contrast, other studies found no significant difference in infection rates between the HG group and the control group (Berker et al., 2003; Jacobson et al., 2003). Even more, infection does not necessarily correlate with symptoms of nausea, vomiting, or reflux during pregnancy (Weyermann et al., 2003; Wu et al., 2000). In fact, most infected women are asymptomatic (Verberg et al., 2005).

The conflicting data on the association of maternal H. pylori infection and HG could be explained by the following findings. Serologic testing for H. pylori cannot distinguish between active infection and past infection (Cutler et al., 1996) and active versus past infection may produce different symptoms (Lee et al., 2011). Accordingly, a case report suggests that treatment and eradication of active infection of H. pylori can decrease NVP (Mansour et al.). In addition, most studies do not differentiate between H. pylori strains,

which is important since some strains H. pylori that express the CagA protein are more aggressive and can increased the risk for peptic ulcers (Ali et al., 2005). In this context, a study that considered H. pylori strains, reported that CagA positivity is more prevalent in patients with HG (Xia et al., 2004).

In terms of the role of H. pylori on the pathogenesis of HG, it has been suggested that H. pylori may exacerbate hormone-induced changes in the nerve and electric functioning of the stomach, increasing the risk for infected women to be at the more severe end of the spectrum of nausea and vomiting (Golberg et al., 2007).

Screening for H. pylori can be done in patients with HG, especially those with prolonged conditions that are refractory to conventional management as well as cases that extend to the second trimester (Shaban et al., 2014).

SEROTONIN

Serotonin is a key factor in the regulation of some autonomic gastrointestinal functions including motility, secretion and visceral sensitivity (Browning, 2015). This neurotransmitter has also been hypothesized to contribute to NVP (Lee et al., 2011). However, a study of serotonin excretion and its association with NVP did not show any difference in serotonin levels in urine among pregnant women with HG, pregnant women without nausea and vomiting, and nongravid women (Borgeat et al., 1997). If serotonin contributes to the pathogenesis of NVP it would be expected that serotonin receptor antagonists would be superior to other medications at reducing NVP, yet the results reported in randomized control trials on the superiority of serotonin receptor antagonist over dopamine antagonists and antihistamines are still conflicting. A randomized controlled trial comparing the serotonin 5-HT3 receptor antagonist, ondansteron to promethazine (dopamine antagonists) demonstrated no benefit of ondansetron over promethazine in patients hospitalized for HG (Sullivan et al., 1996). On the other hand, a randomized controlled trial performed by Oliveira et al. showed that ondansetron is superior to the combination of pyridoxine and doxylamine (antihistamine) in the treatment of NVP (Oliveira et al., 2014). Similarly, conflicting results comparing two serotonin receptor antagonist are also reported. Abas et al. showed that ondansetron and metoclopramide (dopamine and serotonin receptor antagonist) demonstrated similar antiemetic and antinauseant effects in patients with HG (Abas et al., 2014). While another randomized trial reported that patients with HG treated with ondasetron had significantly lower vomiting scores versus the patients treated with metoclopramide (Kashifard et al., 2013). All in all, the role of serotonin in NVP and HG is still controversial.

THYROID HORMONES

Pregnancy has profound but reversible effects on the thyroid gland; it is actually a state of excessive thyroid stimulation leading to an increase in thyroid size (Nazarpour et al., 2015). The prevalence of thyroid dysfunction in pregnant women is relatively high occurring in 2–3% of pregnancies (Nazarpour et al., 2015). The most common reason for hyperthyroidism during pregnancy is the transient hyperthyroidism found in HG patients (Glinoer et al., 2010; Nazarpour et al., 2015). In fact, abnormal results in thyroid function are found in up to

70% of women with HG (Goodwin et al., 1992; Sun et al., 2014). Because hCG cross-reacts with the alpha-subunit of thyroid stimulating hormone (TSH) receptor and stimulates the thyroid gland, TSH is typically suppressed (Goodwin et al., 1992). This gestational hCG effect is characterized by suppressed TSH and slightly elevated free thyroxine (T4). In the majority of cases, these laboratory abnormalities are not clinically relevant as women with HG are generally euthyroid with no history of prior thyroid diseases, without a goiter and with negative anti-thyroid antibodies (Kuscu et al., 2002). This apparent hyperthyroid state usually resolves spontaneously and almost all women with HG have normal TSH levels by the second trimester without any intervention (Goodwin et al., 1997; Lee et al., 2011; Sun et al., 2014). Besides, treatment with propylthiouracil does not alleviate the nausea and vomiting in HG patients (Kirshon et al., 1988) and there is no relationship between thyroid dysfunction and the severity of HG symptoms (Evans et al., 1986). In addition, patients with primary hyperthyroidism rarely have vomiting (Eliakim et al., 2000) and transient gestational hyperthyroidism does not affect pregnancy outcomes (Sun et al., 2014).

Few studies have suggested that HG patients with gestational hyperthyroidism may have thyroid gland hypersensitivity to hCG. In fact, two cases of HG and gestational thyrotoxicosis caused by mutations of the thyroid stimulating hormone receptor (TSHR) have been described (Coulon et al., 2016; Rodien et al., 2004). The mutations, in the lysine 183 into asparagine or arginine, located in the extracellular domain of the TSHR resulted in increased sensitivity to hCG. These data suggest a direct relationship between hyperthyroidism and HG, since treatment of thyrotoxicosis led to disappearance of vomiting (Rodien et al., 2004). On the other hand, there are reports that suggests that some patients with gestational thyrotoxicosis secrete hCG with a higher thyrotrophic activity (Kimura et al., 1993) possible caused by different isoforms of hCG (Tsuruta et al., 1995; Yoshimura et al., 1994a; Yoshimura et al., 1994b).

5. TREATMENT

The pathogenesis of NVP and HG are still unknown therefore the treatment can be challenging as neither the optimal targets for treatment nor the full effects of potential treatments on the developing fetus are known. Currently there are no evidence based treatments for HG although a randomized controlled trial that aims to clarify whether early enteral tube feeding is more effective in treating HG than intravenous rehydration alone is being performed (Grooten et al., 2016). Therapy is focused on improving symptoms while minimizing risks to mother and fetus. Treatment modalities depend on the severity of the symptoms and range from dietary changes, intravenous fluid rehydration (including electrolytes, vitamins, and thiamin), pharmacologic treatment, and hospitalization.

5.1 NON PHARMACOLOGIC

DIETARY MODIFICATIONS—Dietary changes are basic for the initial therapy for NVP. Eating small amounts of food several times a day instead of large meals has been recommended (Bischoff et al., 2006; Jednak et al., 1999; Newman et al., 1993). The meals should be bland and low in fat as fatty foods may further delay gastric emptying and spicy foods may trigger nausea (Jednak et al., 1999). Eating meals that are high in protein and low

in carbohydrates and taking in more liquids than solids may also improve the gastric dysrhythmias associated with NVP (Jednak et al., 1999). Drinking small volumes of fluids between meals including beverages with electrolytes is also advisable (Bischoff et al., 2006; Jueckstock et al.; Newman et al., 1993). If the smell of hot foods also triggers nausea, cold foods should be used instead (Broussard et al., 1998; Jednak et al., 1999).

GINGER—The American College of Obstetrics and Gynecology (ACOG, 2004) recommends ginger as a non-pharmacologic intervention to treat NVP. Recently, a systematic review and meta-analysis of randomized trials found that ginger improved nausea compared to placebo, but did not decrease the episodes of emesis (Viljoen et al., 2014).

Several studies suggest that ginger may be effective in treating nausea and gastric hypomotility (Haniadka et al., 2013; Hu et al., 2011; Pertz et al., 2011; Yamahara et al., 1990). In this context, it has been reported that ginger contains gingerols and shogaols that inhibit cholinergic M3 receptors and serotonergic 5-HT3 receptors and acts on the gastrointestinal tract as a dopamine and serotonin antagonist enhancing gastric motility (Pertz et al., 2011; Yamahara et al., 1990). In addition, gingerols inhibit the growth of H. pylori (Mahady et al., 2003), which is now considered to play a possible role in HG pathogenesis.

Clinical trials that used the powdered root of ginger to treat women with HG have demonstrated that ginger provided a significantly greater relief of symptoms compare to placebo (Fischer-Rasmussen et al., 1991; Vutyavanich et al., 2001). Regarding the safety of ginger in pregnancy, a case-control study of pregnant women found no increase in the rate of major malformations with first trimester use (Portnoi et al., 2003). On the other hand, the use of ginger in patients on anticoagulants is not recommended because ginger may inhibit platelet function (Backon, 1991).

ACUPRESSURE/ ACUPUNCTURE—Acupressure applied to the pericardium 6 (P6 or Neiguan) has been reported by several studies to significantly decrease the occurrence of nausea, vomiting and retching in patients with nausea related to chemotherapy (Genc et al., 2015; Molassiotis et al., 2007; Taspinar et al., 2010), surgery (Vickers, 1996) and women with NVP (Vickers, 1996; Werntoft et al., 2001).

In a controlled trial, pregnant women receiving traditional acupuncture or pericardium 6 acupuncture reported less nausea and less dry retching compared to controls (Smith et al., 2002). Similarly, a randomized study of women with HG comparing treatment with metoclopramide and cyanocobalamin versus acupuncture sessions demonstrated that HG symptoms were equally relieved in both groups (Neri et al., 2005). These data suggest that acupressure and acupuncture therapy may be helpful for NVP treatment, although the benefits of these therapies are still inconclusive. In a systematic review of randomized trials, P6 acupuncture or an acupressure wristband was not significantly more effective than placebo (Matthews et al., 2015).

THIAMINE SUPPLEMENTATION—Of importance is the initiation of thiamine supplementation in pregnant women with HG. Thiamine pyrophosphate is the biological

active form of vitamin B1; it is an essential coenzyme in many biochemical pathways in the brain (Sechi et al., 2007). The daily requirement of thiamine is around 1.1 mg/day for females, and it increases to 1.5 mg/day, particularly during pregnancy (Chiossi et al., 2006) and even more by the impaired absorption due to HG. Early thiamine replacement will reduce maternal morbidity, especially Wernicke's encephalopathy (Berdai et al., 2016).

INTRAVENOUS FLUID REHYDRATION—In HG patients with more severe dehydration or ketonuria, inpatient admission is commonly suggested. Prompt maternal hydration will commonly relieve many of the symptoms on HG. In addition to hydration, parenteral nutrition and vitamin and mineral replacement/supplementation will help correct any electrolyte imbalance. Adding glucose to an infusion will provide a much needed energy source (Jueckstock et al., 2010).

5.2 PHARMACOLOGIC TREATMENT

ANTIHISTAMINES—Antihistamines, are commonly used during early pregnancy for the treatment of nausea and vomiting (Gilboa et al., 2014). First generation H1-receptor antagonists diphenhydramine (Benadryl), dimenhydrinate (Dramamine), meclizine (anitvert) and doxylamine indirectly affect the vestibular system, decreasing stimulation of the vomiting center (Badell et al., 2006). These antihistamines are pregnancy category B and have been shown to be effective in controlling NVP symptoms (Leathem, 1986; Mazzotta et al., 2000a). The majority of 31 cohort studies and 23 case-control studies that aimed at identifying positive associations between antihistamines and birth defects demonstrated a lack of association between prenatal antihistamine exposure and birth defects (Gilboa et al., 2014; Milkovich et al., 1976; Seto et al., 1997).

Of special interest is the use of doxylamine with or without pyridoxine to treat NVP. The American College of Obstetricians and Gynecologists (ACOG, 2004) currently recommends that these agents singly or in combination be used as first line treatment for NVP.

Pyridoxine (vitamin B6, pregnancy category A) is a water soluble vitamin that is involved in the metabolism of amino acids, lipids, and carbohydrates (Spiegel et al., 2012). Randomized, placebo controlled trials have shown effectiveness of vitamin B6 in the treatment of NVP (Sahakian et al., 1991; Vutyavanich et al., 1995; Zur, 2013). Doxylamine (pregnancy category B) directly inhibits the action of histamine at the H1-receptor, acts indirectly at the vestibular system, and exhibits some inhibition of muscarinic receptors to decrease stimulation of the vomiting center (Spiegel et al., 2012).

In April 2013, the FDA approved the sale of Diclegis, an identical combination to the original Bendectin and its Canadian equivalent Diclectin, after a randomized blinded placebo controlled trial demonstrated its effectiveness to treat NVP (Koren et al., 2010). The delayed-release tablet contains doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg (Koren et al., 2010). This drug combination has been widely used in different countries around the world (Zur, 2013) and several studies and meta-analyses over the last 3 decades support its efficacy (2004; Niebyl et al., 2002) as well as its fetal and maternal safety (Einarson et al., 1988; Holmes, 1983; Koren et al., 2015; Madjunkova et al., 2014; McKeigue et al., 1994). Drowsiness is the most common side effect reported for this drug

(Sanu et al., 2011). A factor that may affect the utility of this and other oral medications is the inability of some women with NVP or HG to swallow any oral medication (Zur, 2013).

ANTIEMETICS—The central and peripheral dopamine antagonists chlorpromazine (Thorazine) and prochlorperazine maleate (Compazine) have been shown to reduce symptoms in NVP and HG (Leathem, 1986). They are antiemetics that fall in the pregnancy category C and their use in the first trimester of pregnancy has been associated with a slightly increased risk of birth defects (Lee et al., 2011; Rumeau-Rouquette et al., 1977). Promethazine (Phenergan), another member of the phenothiazine family, is widely used to treat NVP in many countries, despite its classification of pregnancy category C (Zur, 2013). In several studies promethazine use during pregnancy was not found to be associated with teratogenic effects (Anderka et al.; Bartfai et al., 2008; Witter et al., 1981), although it has anticholinergic side effects including dry mouth, drowsiness, and sedation (Zur, 2013). For this reason it is considered as a second line treatment for NVP (Zur, 2013) specially as a substitute for doxylamine (Niebyl, 2010; Zur, 2013).

BENZAMIDES—Metoclopramide is a dopamine and serotonin receptor antagonist (Milkovich et al., 1976), widely used for the treatment of NVP (Tan et al., 2010). This benzamide increases gastric transit and corrects gastric dysrhythmias by stimulating antral contractions and promoting antroduodenal contractions (Lee et al., 2011). Metoclopramide is pregnancy category B and its use during pregnancy has shown to be free of any increased risk of congenital malformations, low birth weight, preterm delivery, or perinatal death (Matok et al., 2009; Milkovich et al., 1976; Sanu et al., 2011; Sorensen et al., 2000). Despite its efficacy, metoclopramide use is limited by its side effects which includes drowsiness, dizziness, dystonia and the risk of tardive dyskinesia with chronic use (Lee et al., 2011; Tan et al., 2010). Despite its side effects, metoclopramide is considered as a third-line therapy for NVP (Zur, 2013).

SEROTONIN RECEPTOR ANTAGONISTS—Serotonin receptor antagonists are the most effective antiemetic drugs available in the market (Goodwin, 2008) and are also the most commonly prescribed antiemetics (Rubenstein et al., 2006). Ondansetron (Zofran) works both centrally and peripherally by blocking serotonin receptors in the small bowel and medullary vomiting center (Badell et al., 2006). Ondansetron is classified as pregnancy category B (Lee et al., 2011) and In the United States, it is used more often for the treatment of HG than in other countries (Goodwin, 2008). Its safety in pregnancy is controversial. Some studies have shown no significant increase of adverse fetal outcomes when ondansetron was taken during early pregnancy (Einarson et al., 2004; Pasternak et al., 2013). In contrast, other studies including a systematic review of women who had taken ondansetron in early pregnancy found that the teratogenic risk with ondansetron is low but an increased risk for a cardiac septum defect is likely (Carstairs, 2016; Danielsson et al., 2014). Finally, a recent review about ondansetron safety during pregnancy concluded that there is insufficient evidence of harm to preclude its use in pregnancy (Siminerio et al., 2016).

Several randomized controlled trials comparing ondansetron to other medications have been published. Some trials reported that patients with HG treated with ondansetron had

significantly lower vomiting scores versus the patients treated with metoclopramide (Kashifard et al., 2013). Similarly, ondansetron is reported to be superior to the combination of pyridoxine and doxylamine in the treatment of NVP (Oliveira et al., 2014). On the contrary, other studies in HG patients demonstrated no benefit of ondansetron over promethazine (Sullivan et al., 1996) and similar antiemetic and antinauseant effects of ondansetron and metoclopramide (Abas et al., 2014). Considering the equal effectiveness of ondansetron compared with promethazine, and no sedative effect (Sullivan et al., 1996), ondansetron has been suggested to be the preferred medication in women who have responded to antiemetics but experience significant sedation (Sanu et al., 2011).

Many pregnant women can't swallow oral medications because of the severe sensitivity of the upper gastrointestinal tract in the first trimester. For these patients the transdermal route as a simple method to deliver drug has a significant added value and can improve patient's compliance (Zur, 2013). In this context our group has recently evaluated the pharmacodynamics of granisetron (category B), administered with a transdermal patch to women with NVP (Caritis et al., 2016). The study demonstrated that granisetron significantly improved symptoms of NVP. The granisetron patch also provided another option for treating NVP and may be particularly useful in women who cannot tolerate oral medications. Although the results of granisetron administered as a transdermal patch for treating NVP are promising, further studies evaluating this treatment option are necessary.

ACID-REDUCING AGENTS—Heartburn and acid reflux during pregnancy should be treated, as some studies report that symptoms of gastroesophageal reflux disease have been associated with an increased severity of NVP (Gill et al., 2009b; Law et al., 2010). Furthermore, treatment of heartburn and reflux results in improved PUQE scores and quality of life scores (Gill et al., 2009a). Antacids containing aluminum or calcium are recommended as first-line of treatment during pregnancy for acid reflux and heartburn and can be used to treat women with NVP considering that these drugs were not found to be teratogenic (Law et al., 2010; Mahadevan, 2007; Zielinski et al., 2015). Histamine-2 receptor antagonists such as ranitidine (Zantac) or famotidine (Pepcid) are another treatment option if antacids are no longer working. These drugs are considered safe (category B) to treat acid reflux and/or heartburn in women with NVP (Gill et al., 2009c; Gill et al., 2009d; Zielinski et al., 2015). Several studies to date indicate that proton pump inhibitors are most likely safe in pregnancy, although omeprazole (Prilosec) is classified as a category C drug because its use in early pregnancy may increase the risk of birth defects (Zielinski et al., 2015).

On the other hand, high-dose and prolonged use of magnesium trisilicate-containing antacids are not recommended during pregnancy because they are associated with nephrolithiasis, hypotonia, and respiratory distress in the fetus. In addition, bicarbonate-containing antacids can also cause maternal and fetal metabolic acidosis and fluid overload and are not recommended during pregnancy (Law et al., 2010; Mahadevan, 2007).

CORTICOSTEROIDS—Corticosteroids seem to exert an antiemetic effect on the chemoreceptor trigger zone in the brainstem (Lee et al., 2011) and have been used to treat refractory cases of HG demonstrating conflicting results. Two randomized controlled trials

of women with HG treated with methylprednisolone or promethazine demonstrated that methylprednisolone had a lower rate of re-hospitalization (Safari et al., 1998) and at least the same effects than promethazine on reducing the symptoms of HG with fewer drug side-effects (Ziaei et al., 2004). In addition, a double-blind study demonstrated a significant reduction in vomiting episodes in patients receiving intravenous hydrocortisone (Bondok et al., 2006). On the other hand, a double-blind, placebo-controlled trial demonstrated an improved sense of wellbeing, appetite and increased weight gain in HG patients treated with corticosteroids, although this treatment did not lead to rapid and complete remission of nausea and vomiting (Nelson-Piercy et al., 2001). In addition, a randomized, double-blind, placebo-controlled trial found that addition of parenteral and oral corticosteroids to promethazine-metoclopramide treatment for HG did not reduce the need for re-hospitalization later in pregnancy (Yost et al., 2003). Finally, a meta-analysis that considered five trials evaluating the effectiveness of oral prednisolone, oral methylprednisolone, intravenous methylprednisolone, or intravenous hydrocortisone found no significant effect of corticosteroids on readmission rates for HG (Grooten et al., 2015b).

The use of corticosteroids during the first trimester of pregnancy demonstrated a slight increase in major malformations and an increase in orofacial cleft in infants exposed to this drugs (Park-Wyllie et al., 2000; Pradat et al., 2003). In contrast, data from the National Birth Defect Prevention Study show no association between maternal corticosteroid use and cleft lip and palate in the offspring (Skuladottir et al., 2014). Currently, there are no established guidelines for the use of corticosteroids for NVP or HG and its use remains controversial.

6. HOSPITALIZATION

INTRAVENOUS FLUID REHYDRATION

In HG patients with more severe dehydration or ketonuria, inpatient admission is required. Maintaining hydration or, in the case of severe dehydration achieving quick and sufficient rehydration, is the most important intervention. Volume and electrolyte replacement (at least 3 L/day), correction of potential electrolyte imbalance, administration of vitamins and parenteral administration of carbohydrate and amino acid solutions (about 8400 to 10,500 kJ/d) are recommended. Rehydration is most easily and quickly accomplished intravenously and this reduces adverse symptoms very effectively.

7. FUTURE DIRECTIONS

Since HG is the most common reason for hospitalization in the first half of the pregnancy it is of concern that currently there are no evidence-based treatments for HG. In this context, it is critical to increase the number of randomized clinical trials that assess the effectiveness of different potential treatments for HG. Further advancements will not occur without a better understanding of the pathophysiologic antecedents of NVP and HG. In this regard, it would be important to perform genome-wide association studies (GWAS) and SNPs studies of genes likely involve in NVP and HG pathogenesis (hCG, hCG receptor, TSHR, etc).

8. CONCLUSIONS

NVP is probably the most common disorder in pregnancy; it ranges in spectrum from mild to its pathologic form HG. NVP significantly reduce the quality of life of the pregnant woman and has a large economic impact on patients, caregivers and society, yet this disorder is very often underestimated.

Although the pathogenesis of NVP remains unclear, it is widely accepted that it is likely to be multifactorial, with a genetic predisposition and a placentally-mediated mechanism characterized by the production of reproductive hormones. In this context hCG, progesterone and estrogen seem to play a role in the induction of gastrointestinal dismotility, that may contribute to the development of NVP. On the other hand, the bacteria H. pylori may be an important factor for the development of HG possibly by the exacerbation of the hormone-induced changes in the nerve and electric functioning of the stomach.

Currently, the therapy for NVP depends on the severity of the disorder and it is focused to improve symptoms while minimizing risks to mother and fetus. The therapy ranges from dietary changes, intravenous fluid rehydration (including electrolytes, vitamins including thiamin), pharmacologic treatment, and hospitalization.

The American College of Obstetrics and Gynecology recommends ginger as a nonpharmacologic intervention to treat NVP and a combination of oral pyridoxine hydrochloride and doxylamine succinate as the first line of pharmacologic treatment for NVP.

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Abbreviations

NVP	Nausea and vomiting of pregnancy
HG	Hyperemesis gravidarum
PUQE	Pregnancy-Unique Quantification of Emesis scoring
TNF-a	Tumor necrosis factor alpha
IL-1	Interleukin 1
IL-6	Interleukin 6
hCG	Human chorionic gonadotrophin
H. pylori	Helicobacter pylori

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