Contemporary approaches to hyperemesis during pregnancy
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Purpose of review
Nausea and vomiting of pregnancy (NVP) affects 90% of pregnant women and its impact is often underappreciated. Hyperemesis gravidarum, the most severe end of the spectrum, affects 0.5–2% of pregnancies. The pathogenesis of this condition remains obscure and its management has largely been empirical. This review aims to provide an update on advances in pregnancy hyperemesis focusing on papers published within the past 2 years.

Recent findings
The cause of hyperemesis is continuing to be elaborated. Recent data attest to the effectiveness of the oral doxylamine–pyridoxine in NVP. Follow-up data of children exposed in early pregnancy to doxylamine–pyridoxine for NVP are reassuring. Evidence is increasing for ginger as an effective herbal remedy for NVP. Metoclopramide is effective in NVP and hyperemesis gravidarum, with a good balance of efficacy and tolerability. A recent large-scale study on first trimester exposure to metoclopramide is reassuring of its safety. Evidence is emerging for the treatment of acid reflux to ameliorate NVP. The role of corticosteroids for hyperemesis gravidarum remains controversial. Transpyloric feeding may be warranted for persistent weight loss, despite optimal antiemetic therapy.

Summary
Women with significant NVP should be identified so that they can be safely and effectively treated.

Keywords
hyperemesis gravidarum, nausea, pregnancy, vomiting

Introduction
In contemporary studies, nausea and vomiting of pregnancy (NVP) affects 78–89% of pregnant women [1,2]. NVP starts in the first trimester in 99% of the affected women [1,2]. In about a third of cases, NVP causes significant distress. Excessive salivation and dry retching are frequent accompanying complaints in NVP.

When nausea and vomiting is of a severity to cause dehydration and starvation, hospital treatment is typically required. Hospitalization is often used as a practical criterion differentiating NVP from hyperemesis gravidarum [3]. Weight loss of 5% or more can be used as criterion for hyperemesis gravidarum in a research setting, but is impractical clinically as a reliable prepregnant weight is often not available for comparison.

It is not known at present whether hyperemesis gravidarum is a different disease or just the severe end of the spectrum in NVP. There is no specific diagnostic test for hyperemesis gravidarum. Given the near universal presence of nausea and vomiting in early pregnancy, it is probable that a proportion of women classified as having hyperemesis gravidarum are NVP cases whose symptoms and clinical condition are exacerbated by unrecognized intercurrent illness, preexisting ill health, or particularly excessive maladaptation to the milieu of early pregnancy changes. Diverse risk factors for hyperemesis gravidarum such as hyperthyroid disorders, psychiatric illness, pre-existing diabetes, gastrointestinal disorders, and asthma support this view. It is vital to identify and treat other causes of nausea and vomiting in pregnant women if they are present.

Natural history
Although there are regional and ethnic variations, hyperemesis gravidarum is generally accepted to affect 0.3–2% of pregnancies [4]. Hyperemesis gravidarum is the second most common indication for antenatal hospital admission among women with a live birth [5] with a typical hospital stay of 3–4 days [5,6]. Women with hyperemesis gravidarum report a median of 2 weeks of symptoms prior to hospitalization [7]. In the 2 weeks after hospital discharge, over 95% of women continue to
be symptomatic [8]. The hospital readmission rate for hyperemesis gravidarum is a significant 25% [6].

Generally, the symptoms of nausea and vomiting decrease as the pregnancy advances [1]. In NVP, the condition resolves in 60% of affected pregnancies by 12 weeks gestation and in over 90% by 16 weeks, whereas in contrast, for hyperemesis gravidarum cases typically only 25% resolve by 12 weeks and in 50%, symptoms may persist beyond 16 weeks [4].

Previously, 10% of hyperemesis gravidarum patients may die [4]. Maternal death due to hyperemesis gravidarum was as high as 159 per million births, but death is now rare following the advent of intravenous fluid therapy [3]. A proportion of current deaths may be due to complications from interventions [4].

**Pregnancy outcome**

NVP is associated with an excellent pregnancy outcome if self-limited. NVP is associated with a decreased risk of spontaneous miscarriage and this association is most marked among older women [9]. A recent comparative study of children up to 3–7 years of age shows that the NVP-exposed group scores significantly higher than the nonexposed group on a number of neurodevelopmental parameters [10].

Hyperemesis gravidarum is associated with preterm delivery, low birth weight, and low 5-min Apgar score [11]. Adverse pregnancy outcome is confined to women with hyperemesis gravidarum who failed to gain adequate weight through pregnancy of at least 7 kg and the outcome profile is related to lack of weight gain rather than hyperemesis gravidarum [12]. A recent descriptive report on hyperemesis gravidarum women with extreme weight loss (>15% body weight) from a hyperemesis gravidarum registry website highlights the high incidence of prematurity and behavioral abnormality in the child [13].

**Cause and pathogenesis**

Nausea and vomiting is postulated to have an advantage in evolutionary biology, functioning as a mechanism to reduce the ingestion of harmful substances at the time when a pregnancy is at its most vulnerable stage [4]. In the era of safe food supply, this presumably embryo protective mechanism has limited benefit and can cause distress or worse.

NVP and hyperemesis gravidarum are by definition pregnancy-related and resolve following pregnancy. The presence of an embryo or fetus is not a necessary prerequisite for the condition as nausea and vomiting is common in molar pregnancies.

**Key points**

- The problem of nausea and vomiting in pregnancy should be taken seriously and conscientiously by care providers.
- Women with troublesome symptoms should be acknowledged and supported.
- Safe and effective treatment commencing with pyr- idoxine, ginger, or acupressure on P6 point and progressing to antiemetic drugs should be offered within a stepwise approach.
- Hospital admission is indicated in the presence of dehydration and ketonuria for intravenous rehydration and antiemetic medication.

Goodwin [4] has proposed that hyperemesis gravidarum is a syndrome triggered by the placenta with the final phenotype arising from different pathways. The cause of pregnancy hyperemesis appears to be multifactorial and is still largely obscure.

**Hormones**

The confluence of human chorionic gonadotropin (hCG) level with the timing and resolution of symptoms [14] as well as the correlation of higher hCG levels with clinical severity of hyperemesis gravidarum [15] is persuasive of a central role for hCG in the pathogenesis of hyperemesis gravidarum. hCG receptors are present in area postrema of the brain stem [16], an area associated with nausea and vomiting reflexes, which is not protected by the blood–brain barrier and freely accessible to hCG. Hyperemesis gravidarum may be mediated through these receptors [17]. However, the absolute hCG level is poorly correlated to symptoms and even very high levels may not cause symptoms.

High-dose estrogen is emetogenic and a higher level of endogenous estrogen has been demonstrated in hyperemesis gravidarum. Adaptations attributable to estrogens in pregnancy may also contribute to susceptibility to nausea and vomiting. However, estrogen level progressively rises through pregnancy in contrast to natural course of NVP [3]. There is no association of higher estradiol level with clinical severity of hyperemesis gravidarum and women with a history of vomiting on the oral contraceptive pill are not more likely to develop hyperemesis gravidarum implying that estrogen sensitivity is not a major contributor [15].

Biochemical abnormalities of the thyroid axis are common in hyperemesis gravidarum, but clinical hypothy-roidism is fairly rare. It is likely that hCG structural homology to thyroid stimulating hormone (TSH) sup-presses TSH release. hCG effect at TSH receptor sites may contribute to hyperthyroidism, particularly if variant...
infection and hyperemesis gravidarum. Helicobacter pylori infection
Helicobacter pylori infection has emerged as a possible factor in the pathogenesis of hyperemesis gravidarum. A recent meta-analysis has shown a significant association between H. pylori infection and hyperemesis gravidarum. However, the association is weaker in studies with a clear definition of hyperemesis gravidarum compared to studies without this condition and in recent studies compared to earlier studies [19]. There is debate about whether subclinical H. pylori infection contributes to the pathogenesis of hyperemesis gravidarum or results as a consequence of altered susceptibility due to hyperemesis gravidarum effects on the upper gastrointestinal tract [3].

Genetic factor
A recent large population-based study from Norway has shown the importance of maternal genotype compared to fetal genotype in the development of hyperemesis gravidarum. Women exposed to hyperemesis gravidarum as fetuses were at much higher risk of having hyperemesis gravidarum when they became pregnant. However, for men exposed to hyperemesis gravidarum as fetuses, their offspring did not significantly increase the risk of having hyperemesis gravidarum when they became pregnant. However, the association is weaker in studies with a clear definition of hyperemesis gravidarum compared to studies without this condition and in recent studies compared to earlier studies [19]. There is debate about whether subclinical H. pylori infection contributes to the pathogenesis of hyperemesis gravidarum or results as a consequence of altered susceptibility due to hyperemesis gravidarum effects on the upper gastrointestinal tract [3].

Gastroesophageal reflux
The presence of heartburn and acid reflux has recently been shown to be independently associated with increased severity of NVP [23]. Sixty-nine percent of women with hyperemesis gravidarum who underwent endoscopy had esophagitis, gastritis, or diaphragmatic hernias [24]. A descriptive study on the use of acid-reducing medication has shown reduction in severity of NVP and improvement in general well being [25]. Histamine-2 receptor blockers [26] and proton pump inhibitors [27], medications that may be used to treat acid reflux, appear to be well tolerated in pregnancy. Decreasing exposure to supplementary iron may also reduce symptoms in NVP [28].

Psychological factor
Emesis in pregnancy has long been speculated to have a psychological origin with various hypotheses put forward to account for this pathogenetic pathway. Rejection, ambivalence, conflict, dependence, aversion, immaturity, conversion, and hysteria have all been expounded and sometimes in competition with one another as explanations for the development of hyperemesis gravidarum [3,4]. The signs of anxiety and depression are present in 57% women with hyperemesis gravidarum probably as a consequence rather than a cause of hyperemesis gravidarum. Affected women do not have antecedent psychological illness and do not take up offer of a psychiatry appointment for assessment [7]. Women with hyperemesis gravidarum consider hyperemesis gravidarum to have a biologic basis [29]. Qualitative research on women with hyperemesis gravidarum indicates that the condition imposed a considerable burden. Patients felt unpopular with healthcare professionals who may be skeptical about symptom severity. Women are also left with the perception that they are time wasters or somebody else’s responsibility. For women most severely affected, it appears that primary care support is often lacking [30]. Psychological consequences can be profound in hyperemesis gravidarum and learnt behavioral responses may contribute to hyperemesis gravidarum. However, there are no quality data to support a primary psychological basis for hyperemesis gravidarum.

Treatment
Given the wide range of severity of symptoms that may be present, treatment clearly has to be tailored to the individual. For most women, nausea and vomiting is an accepted part of pregnancy that is tolerated and self-limited. Apart from reassurance, no further treatment is needed for these women. However, it is important to recognize and acknowledge the third of affected women, whose NVP symptoms have become a burden in order to provide support, alleviate symptoms, and limit further deterioration to hyperemesis gravidarum.

In hyperemesis gravidarum, the mainstay of treatment is intravenous rehydration and antiemetic drugs. The ideal rehydration regime is not known. Commonly used antiemetics are discussed later. Wernicke’s encephalopathy, a potentially lethal complication arising from thiamine
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deficiency occurs after prolonged symptoms of at least 3 weeks and is fortunately rare. Thiamine supplementation is essential in hyperemesis gravidarum either orally if tolerated or intravenously. It can be triggered by thiamine consumption in response to dextrose infusion. Dextrose containing infusion fluid should not be given without first supplementing the patient with thiamine.

Another rare complication and avoidable severe complication in hyperemesis gravidarum is central pontine myelinolysis. It arises from too rapid correction of hyponatremia. Severe hyponatremia should be corrected at a rate of not faster than 10 mmol/l per 24 h.

Diet and lifestyle modification
There is no quality trial on the effect of diet or lifestyle modification in hyperemesis. Women are typically advised to avoid food that might upset them, to eat before rising, to eat small frequent meals as tolerated of dry bland food like biscuits and toasted bread and to keep hydrated [31]. Women with NVP are found to reduce their intake of meat products and thus protein, take proportionately more carbohydrate and this dietary behavior persists through pregnancy [32].

Pyridoxine
Pyridoxine at doses of up to 75 mg per day is effective in reducing NVP [33] as a standalone. Pyridoxine has a long half-life of 15–20 days and the tolerable upper intake level is up to 100 mg/day. However, a recent trial on hyperemesis gravidarum cases has shown that adding pyridoxine to a treatment regime, which included intravenous rehydration and metoclopramide, did not reduce symptom severity, length of hospital stay, or rehospitalization [8].

Ginger
Ginger extracts, a food supplement, is effective in NVP and generally of similar effectiveness to pyridoxine [33]. A recent trial of 70 women using 1 g/day of ginger compared to 40 mg/day of pyridoxine suggests that ginger might be better at relieving nausea, but not in reducing vomiting [34]. Another recent placebo-controlled trial of 250 mg ginger capsules four times a day also supports ginger’s effectiveness as a herbal remedy for NVP [35].

Antiemetic drugs
There is very limited evidence from trials to guide the choice of antiemetic drugs for hyperemesis gravidarum particularly. The American College of Obstetrics and Gynecology (ACOG) practice bulletin’s algorithm on antiemetic pharmacotherapy for NVP suggests doxylamine then promethazine or dimenhydrinate either orally or rectally for the treatment of NVP. In women hospitalized for hyperemesis gravidarum, intravenous dimenhydrinate, metoclopramide, or promethazine are recommended first-line therapies with methylprednisolone or ondansetron as second line [36]. Prochlorperazine is also commonly used in pregnancy hyperemesis. Combination therapy is also commonly employed.

Doxylamine
Doxylamine combined with pyridoxine has long been used in NVP. A recent placebo-controlled trial attests to its effectiveness [37]. There are also reassuring data on developmental outcomes from a recent study of children exposed in the first trimester to pyridoxine–doxylamine who were followed up to age 3–7 years [10]. Concerns about birth defects had led to withdrawal of a pyridoxine–doxylamine-containing preparation (Bendectin) from the US market in 1983, but follow-up studies have not supported the initial safety concerns [4].

Metoclopramide
The effectiveness of metoclopramide in NVP and hyperemesis gravidarum is fairly well described in the literature [38,39,40]. A 2010 trial comparing intravenous promethazine with metoclopramide for the treatment of hyperemesis gravidarum shows similar antiemetic and antinauseant activity for both agents. The adverse event profile strongly favors metoclopramide with less drowsiness, dystonia, and treatment curtailment [40]. A large database study reporting in 2009 of 3458 women exposed to metoclopramide in the first trimester provides quality evidence of its safety [41]. However, the USA Food and Drug Administration has in 2009 mandated a black box warning for metoclopramide due to reports of tardive dyskinesia, particularly with high dose and long-term use [42]. Metoclopramide should not be given at a dose exceeding 10 mg thrice a day or for longer than 3 months.

Promethazine
Promethazine monotherapy is less effective than combined metoclopramide and pyridoxine in NVP [39]. Promethazine is also less effective in reducing rehospitalizations in hyperemesis gravidarum compared to a tapered course of oral methylprednisolone [43].

Dimenhydrinate
A 2007 trial comparing oral dimenhydrinate with ginger in NVP shows similar antinauseant and antiemetic effect, but more drowsiness with dimenhydrinate.

Ondansetron
Ondansetron is not more effective than promethazine according to results from a pilot trial of 30 women with hyperemesis gravidarum [44]. Despite the lack of evidence of superiority and with only anecdotal literature, ondansetron is increasingly being used in hyperemesis gravidarum driven by its record of superiority in chemotherapy-induced nausea and vomiting. Pending
further development, ondansetron should be considered a second-line antiemetic but ahead of corticosteroids in recalcitrant cases of hyperemesis gravidarum.

**Corticosteroids**
The evidence for corticosteroids treatment in hyperemesis gravidarum is mixed. The largest trial to date with 126 women comparing a tapered course of intravenous methylprednisolone followed by oral prednisolone to placebo, wherein all women are also treated with metoclopramide and promethazine did not show any reduction in the primary outcome of rehospitalization [45] in contrast to a smaller study of 40 women [43]. Oral corticosteroids did not result in a more rapid resolution of symptoms [43,46,47]. Within an intensive care setting, in a trial of 40 women, intravenous hydrocortisone tapered down over a week is more effective than metoclopramide in symptom resolution and prevention of rehospitalization [48]. Corticosteroids use during embryogenesis may be associated with oral clefts. Corticosteroids should be avoided until after 10 weeks gestation in hyperemesis gravidarum. It should be reserved for severe recurrent hyperemesis gravidarum that is resistant to other antiemetics and with proven weight loss more than 5%.

**Acupressure and acupuncture**
There is limited evidence on meta-analysis that acupressure at the P6 point or the ear but not acupuncture is effective [33*], but the most recent trial report shows that auricular pressure does not reduce symptoms or use of antiemetic drugs [49].

**Psychological therapy**
A recent review on psychiatric assessment commented that there are little data in the psychosomatic medicine literature to guide diagnostic evaluations and treatment of patients with hyperemesis gravidarum [50*]. A specific recent review on hypnosis for hyperemesis gravidarum also comes to a similar conclusion that the quality of current evidence is not sufficient to establish whether hypnosis is an effective treatment for hyperemesis gravidarum [51].

**Parenteral or transpyloric feeding**
There are no defined criteria for parenteral or transpyloric feeding. The necessity and effectiveness of these types of feeding is not well established. Anecdotally they can be successful and are often employed as a last resort when all other medical therapy has failed and the only other practical option is pregnancy termination.

**Total parenteral nutrition**
Total parenteral nutrition is a complex high-risk intervention. A recent series of 97 central venous catheter placements in 85 obstetric cases shows a 25% catheter-related serious complication rate, principally infections and venous thromboses [52*]. In 33 women with hyperemesis gravidarum treated with a peripherally inserted central line for feeding, 66% had infective or thromboembolic complications [53].

**Transpyloric feeding**
Prolonged transpyloric feeding at the duodenal or jejunal level via a nasal approach is often poorly tolerated and prone to tube dislodgement. Feeding via a percutaneous endoscopic gastrojejunostomy has been described in the treatment of hyperemesis gravidarum. A recent series of five cases describes the successful management without serious complication of severe hyperemesis gravidarum through feeding via a surgical jejunostomy [54*]. Given the considerable problems with prolonged total parenteral feeding and the poor tolerability of transnasal tube feeding, transpyloric feeding via a jejunostomy may be an attractive alternative.

**Conclusion**
Nausea and vomiting in pregnancy is very common and typically benign. However, a substantial proportion of affected women suffer from significant psychological, socio-economic, and physical burdens as a consequence. Many of these women feel that their condition is under-appreciated by disinterested healthcare providers. The pathogenesis of hyperemesis gravidarum is still largely obscure and seems likely to be multifactorial. Effective treatment should be made available to women with troublesome symptoms with the reassurance that the treatment is also safe. Despite its large footprint, NVP is underresearched. There is urgent need for clinical trials of dietary interventions, antiemetics, and intravenous fluid regimes.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

6 Maternal-fetal medicine


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