SOMANZ

SOCIETY OF OBSTETRIC MEDICINE OF AUSTRALIA AND NEW ZEALAND

GUIDELINE FOR THE MANAGEMENT OF NAUSEA AND VOMITING IN PREGNANCY AND HYPEREMESIS GRAVIDARUM

2019

Lowe SA, Bowyer L, Beech A, Robinson H, Armstrong G,

Marnoch C, Grzeskowiak L.

These are the recommendations of a multidisciplinary working party convened by the Society of Obstetric Medicine of Australia and New Zealand. They reflect current medical literature and the clinical experience of members of the working party. The accompanying Executive Summary and Treatment Algorithms (1 and 2) summarise the key recommendations. These should be read in conjunction with this complete guideline which also includes a Patient Information Leaflet and a template for an Individual Patient Management Plan.

The authors declare there are no conflicts of interest.

This guideline has been endorsed by the following organisations:

- *Royal Australian and New Zealand College of Obstetrics and Gynaecology (RANZCOG)*
- *Royal Australasian College of Physicians (RACP)*
- *Australasian College for Emergency Medicine (ACEM)*
- *The Society of Hospital Pharmacists of Australia (SHPA)*
- *New Zealand Hospital Pharmacists' Association (NZHPA)*

This guideline has been officially recognised as an Accepted Clinical Resource by The Royal Australian College of General Practitioners.

CONTENTS

Introduction

The approach to the management of nausea and vomiting in pregnancy (NVP) and hyperemesis gravidarum (HG) in the current era is strongly reminiscent of the cultural attitudes towards the management of pain in labour prior to the introduction of epidural anaesthesia in the 1970s.

Women and their families have been appropriately concerned about medication use in early pregnancy and doctors have been reticent to offer women therapy, being mindful of the impact of the thalidomide tragedy of the 1950-60s. Women have been expected to tolerate significant symptoms both physical and psychological because NVP is a normal and expected part of pregnancy. In a recent Norwegian study, focus groups indicated that women felt their distress due to NVP was trivialized by their doctors whilst the doctors appeared uncertain with respect to appropriate medical treatment of NVP (1). Compounding this problem, the women themselves were sceptical towards the use of medicines while pregnant, and avoidance was sought despite being ill.

Just as society adjusted to the medical advances that have allowed women to manage pain in labour, it is only appropriate that we change our attitudes through research, education and evidence based guidance to ensure women have access to appropriate, safe and timely management for NVP and HG.

Methods

Evidence was sought from MEDLINE, EMBASE and PUBMED searches and based on an extensive review of this literature, a fully referenced guideline was written. The quality of evidence was evaluated and the recommendations made according to NHMRC principles and described as per Table 1 (2). Where there was insufficient evidence, the expert opinion of the guideline group was sought and agreement reached by majority opinion.

The recommendation terms include the terms “should” or “must” (where benefits of the recommendation exceed the harms), “consider” (where the quality of evidence was limited or the available studies demonstrated little clear advantage of one approach over another, or the balance of benefits to harm was unclear) and “should not” or “do not” or “avoid” (where there is either a lack of appropriate evidence, or the harms outweigh the benefits).

The authors were selected by the Council of the Society of the Obstetric Medicine Group of Australia and New Zealand and represent a diverse group of physicians, obstetricians and a clinical pharmacist with expertise in these conditions. The Guideline was also reviewed by midwives, general practitioners and other clinicians as well as consumers with an interest in NVP and HG. This included women with current or previous NVP or HG.

From this, the critical recommendations were derived along with a series of potentially auditable outcomes to create the accompanying Executive Summary. These were then summarised and published as a SOMANZ Position Paper in the Australian and New Zealand Journal of Obstetrics & Gynaecology

Table 1: Definition of recommendations and simplified levels of evidence (2)

RECOMMENDATION	DESCRIPTION
Evidence based (EBR)	Where sufficient evidence was available
Consensus recommendations (CBR)	Where there was insufficient evidence, the expert guideline development group made clinical consensus recommendations
Clinical practice points (CPP)	Important implementation and other issues (such as safety, side effects or risks) arose from discussion of evidence based or clinical consensus recommendations
LEVELS OF EVIDENCE	DESCRIPTION
I	A systematic review of Level II studies
II	A randomised controlled trial
III	Any non-randomised study(ies) including comparative study with concurrent controls, cohort, case-control, historical controls
IV	Case series

Abbreviations

5HT	Five hydroxy tryptamine receptor inhibitors
aOR	Adjusted odds ratio
BD	Two times a day
CI	95% Confidence interval: [ ]
CNS	Central nervous system
CVC	Central venous catheter
CYP	Cytochrome P450
EN	Enteral nutrition
EUC	Electrolytes, urea, creatinine
FBC	Full blood count
GER	Gastroesophageal reflux
GHT	Gestational hyperthyroxinemia/Gestational hyperthyroidism
GP	General practitioner
HCG	Human Chorionic Gonadotrophin
HG	Hyperemesis gravidarum
H. Pylori	Helicobacter Pylori
hypoK	Hypokalemia
hypoMg	Hypomagnesemia
IM	Intramuscular
IQR	Interquartile range
IV	Intravenous
LFT	Liver function tests
M	Muscarinic
mcg	Microgram
NP	Nausea in pregnancy without vomiting
NV	Nausea and vomiting
NVP	Nausea and vomiting in pregnancy
OD/BD/TDS/QID	Once /twice/three times/four times: per day
OR	Odds ratio
PICC	Peripherally inserted central catheter
PO	Oral

PUQE-24	Pregnancy-Unique Quantification of Emesis and Nausea scored over 24 hours
QID	Four times a day
RCT	Randomised controlled trial
RR	Relative risk
SC	Subcutaneous
SGA	Small for gestational age
TDS	Three times a day
TFT	Thyroid function tests
TPN	Total Parenteral Nutrition
TPOAb/TRAb/TgAb	Thyroid peroxidase/Thyroid receptor/Thyroglobulin: Antibody
TSH	Thyroid stimulating hormone

What are the definitions of NVP and HG?

There is no accepted definition for NVP nor for the more severe disorder, HG. NVP is generally defined as symptoms of nausea, vomiting and/or dry-retching commencing in the first trimester without another cause.

A recent publication (3) has summarised all definitions for HG used in the literature and an international collaborative is being developed to define HG as per the CoRe Outcomes in Women and Newborn health initiative (CROWN). The most commonly cited criteria for diagnosis of HG include: persistent vomiting with weight loss not related to other causes along with an objective measure of acute starvation such as carbohydrate depletion, electrolyte abnormalities and/or acid-base disturbance (4). The ICD-10 criteria are similar but specify onset before 22 weeks of gestation (5). The degree of weight loss required to meet the criteria for HG is often defined as at least 5% of pre-pregnancy weight (6, 7). Ketonuria is often cited as a measure of dehydration or starvation in HG, however, in a systematic review and meta-analysis, ketonuria was not found to be reliably associated with either the diagnosis or severity of HG (8). Although there may be a continuum between these two conditions, it is critical to distinguish HG from NVP as the management and potential maternal and fetal complications differ.

Several scoring systems exist for quantitating nausea and vomiting including the Rhodes Score (9) (originally designed for chemotherapy patients) and the Motherisk **P**regnancy-**U**nique **Q**uantification of **E**mesis and Nausea (PUQE) scoring index (Table 2) which has been validated and proven simpler and equally reliable as the Rhodes score (10). The PUQE system assesses the severity of nausea and vomiting with three questions relating to duration of nausea, and frequency of vomiting and dry retching symptoms. The PUQE-24 scored over 24 hours (Table 2), has more recently been established to correlate closely with the woman's own estimate of overall physical and mental well-being ($P < 0.001$) as well as important practical indicators of severity such as rates of hospitalization and emergency room visits (11).

Table 2. Motherisk PUQE-24 scoring system

Total score: mild ≤6; moderate 7 to 12; severe ≥13 (Scores in brackets)

1. In the last 24 hours, for how long have you felt nauseated or sick to your stomach?				
Not at all (1)	1 hour or less (2)	2-3 hours (3)	4 to 6 hours (4)	More than 6 hours (5)
2. In the last 24 hours, have you vomited or thrown up?				
I did not throw up (1)	1 to 2 (2)	3 to 4 (3)	5 to 6 (4)	7 or more times (5)
3. In the last 24 hours, how many times have you had retching or dry heaves without throwing up?				
None (1)	1 to 2 (2)	3 to 4 (3)	5 to 6 (4)	7 or more times (5)

SOMANZ proposed definitions:

Nausea and vomiting of pregnancy:

Nausea, vomiting and/or dry retching caused by pregnancy, with symptoms commencing in the first trimester without an alternate diagnosis. Severity is based on the PUQE-24 Score (11) [LOE-I].

- Mild: PUQE-24 = 4-6
- Moderate: PUQE-24 = 7-12
- Severe: PUQE-24 ≥ 13

Hyperemesis Gravidarum:

Nausea and/or vomiting caused by pregnancy leading to significant reduction of oral intake and weight loss of at least 5% compared with pre-pregnancy, with or without dehydration and/or electrolyte abnormalities. By definition this condition is considered severe.

All women should be asked about NVP at each visit between 4 and 16 weeks and if present, severity should be assessed by PUQE-24 score, measurement of weight and hydration status.

What is the incidence and natural history of NVP and HG?

Nausea and vomiting are common symptoms of pregnancy with prevalence varying in different parts of the world. A recent meta-analyses of the global prevalence estimated a risk of any NVP of 69% [95% Confidence Interval 67-72%] (12). The average rate of nausea alone was 33% [22-44%] with the majority of women rating their nausea as moderate to severe. In a recent Australian observational study 72% of women reported NVP of which 42% had mild symptoms, 55% moderate and 1% severe (13). Retching has been recognised as a significant and distinct symptom with independent impact on well-being (14).

The incidence of hyperemesis gravidarum (HG) is much lower than NVP at 1.1% [0.8-1.3%], depending on the definitions used (12). There were geographical differences with most high income countries having similar rates. Much higher rates were seen in East Asia and low rates in India and Netherlands. Even within a country, ethnicity seems to influence the prevalence, with Pacific Islanders in New Zealand having a significantly increased incidence of HG compared with controls (15).

Both NVP and HG typically have their onset between the 4th and the 10th week of gestation, with the majority experiencing resolution by 20 weeks gestation. In the global meta-analysis, 24% [13-34%] of women described NVP even in late pregnancy and in approximately 10% of HG patients, symptoms persisted throughout pregnancy (12, 16). In another prospective recent study, only 50% of women reported relief of their symptoms by 14 weeks' gestation although 90% had relief by week twenty two (17).

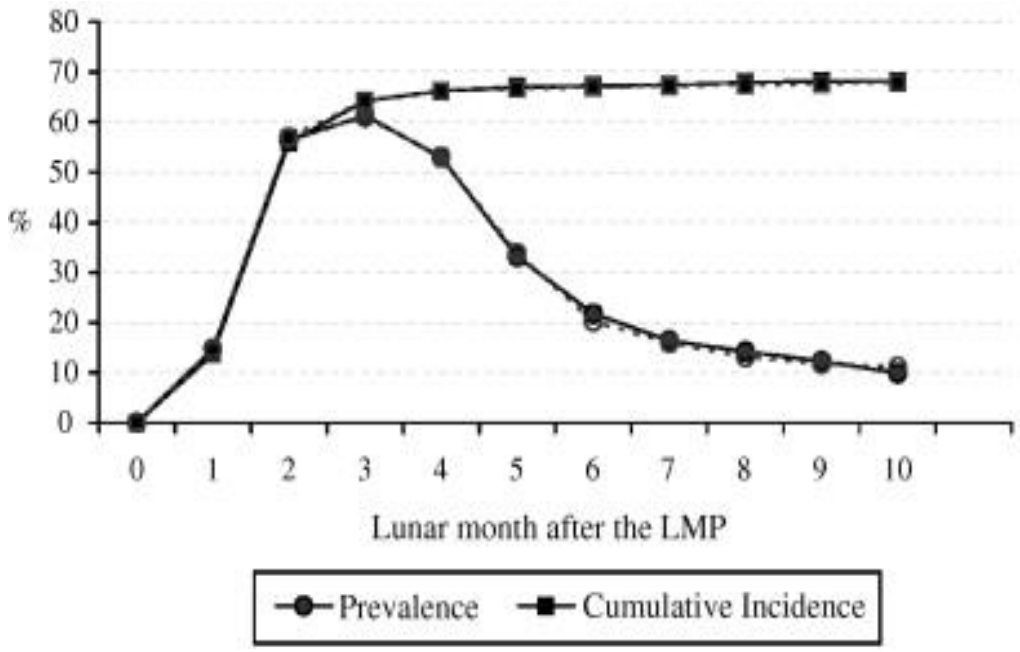


Figure 1: Incidence and prevalence of NVP (Reprinted with permission) (18)

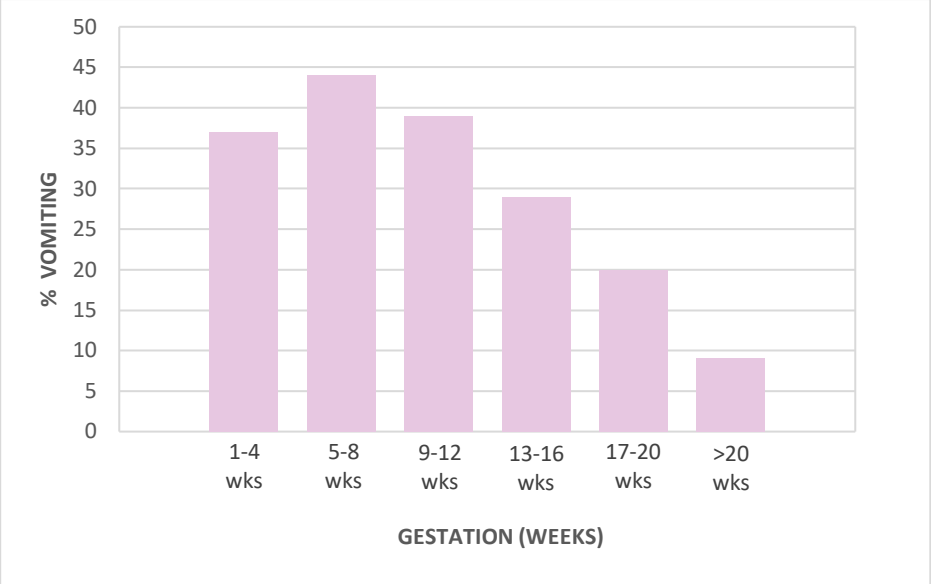


Figure 2. Incidence of vomiting by gestation (based on data from 19)

What is the cause of NVP and HG?

The etiology of NVP and HG remains unclear but is likely to be multifactorial as discussed in a recent review by Bustos et al (20). Numerous factors have been implicated, particularly the effect of high levels of Human Chorionic Gonadotrophin (HCG) or specific isoforms of HCG (21). Conditions with higher HCG levels, such as trophoblastic disease and multiple pregnancy, have been associated with increased severity of NVP. Although numerous conditions have been associated with NVP, they are not necessarily causal.

In a recent meta-analysis, Helicobacter pylori (H. Pylori) infection was associated with an increased likelihood of HG during pregnancy, with a pooled OR of 1.3 (1.2-1.5 $p < .001$) although the literature in this area does show mixed results, almost certainly reflecting differing background prevalence in the populations studied (22, 23). Other associations including deficiency of trace elements, excess thyroid hormones, gravidity, multiple pregnancy, fetal female sex, psychiatric and dietary factors have all been suggested as part of the etiology but the methodology to support these hypotheses has been criticised (24). In one study, maternal smoking and having the support of three or more persons were protective for NVP (25).

Several lines of evidence support a genetic predisposition to NVP and HG. A multinational NVP Genetics Consortium has been created (including Australian participants) to add knowledge to the characterization of the genetic as well as environmental risk factors for HG and NVP (26). The Consortium has already published data suggesting heritability estimates of 73% [57–84%] for occurrence, 51% [36–63%] for duration and 53% [38–65%] for severity of NVP (27). In this study, the genetic correlation between duration and severity was almost perfect. In women with HG or severe

NVP, several studies have suggested a higher incidence amongst first degree relatives (28-30). In a recent study, an association has been demonstrated with variants in the ryanodine receptor (RyR2) gene which encodes an intracellular calcium release channel involved in vomiting and cyclic-vomiting syndrome. It is also a thyroid hormone target gene which is consistent with the association of thyroid dysfunction and HG (31). Propranolol blocks RyR2 phosphorylation and lowers its expression and has been used with significant success (92% effective) to treat cyclic vomiting syndrome in children (32). A Genome Wide Association Scan has identified several genes in women with a history of HG which appear to be encode proteins of potential interest (33). These proteins include GDF15 and IGFBP7 which are produced by trophoblast cells and have been shown to be regulators of physiological body weight and appetite via central mechanisms as well as being significant mediators of cancer anorexia and cachexia. Subsequent studies have demonstrated significantly increased levels of GDF15 and IGFBP7 at 12 weeks' gestation in women with HG, compared with women with NVP or no NVP. By 24 weeks, when symptoms had largely resolved, the levels were similar (33a). These are very early studies and require further research although the prospect of testing for a marker protein for HG is of significant interest. The recurrence risk in subsequent pregnancies is also suggestive of a genetic etiology.

Studies examining demographic factors such as work status, income and education associated with the presence and severity of nausea and vomiting, have produced inconsistent results (17-19, 34). Using a database search strategy of more than 8 million pregnancies, women admitted to hospital with HG were younger, of lower socioeconomic status, were more likely to be of Asian or Black ethnicity, were more likely to be carrying a female fetus and were more likely to be having a multiple pregnancy (35).

What investigations are required for women with NVP?

Patients with mild-moderate nausea and vomiting of pregnancy (PUQE-24 ≤12), where symptoms are not suspicious for HG or another diagnosis, do not need investigation [LOE-III]. History and physical examination should be directed towards identification of alternate diagnoses. Physical examination should include assessment of temperature, weight, palpation of the abdomen for abdominal tenderness and signs of peritonism, and an assessment for neck stiffness and signs of raised intracranial pressure if the history is suggestive of a central nervous system cause for the symptoms. Signs to support a diagnosis of dehydration include decreased skin turgor, dry mucous membranes, decreased urine output, concentrated urine, and postural drop in blood pressure.

Women with severe NVP (PUQE-24 scores ≥13 or suspected HG should have the following investigations performed at first presentation:

1. Sodium, potassium, chloride, bicarbonate, magnesium, urea and creatinine

2. Bilirubin, Alanine Transaminase (ALT), Aspartate Aminotransferase (AST), Albumin
3. Obstetric ultrasound to exclude multi-fetal or gestational trophoblastic disease
4. Tests to exclude alternate diagnoses where indicated
5. Thyroid stimulating hormone (TSH) where indicated (see below)

Electrolytes and renal function:

Women with HG frequently have hyponatremia, hypokalemia, hypochloremia, hypomagnesaemia, and low serum urea with a metabolic hypochloremic alkalosis. If severe, a metabolic acidaemia may develop (6, 36, 37). An elevation in serum creatinine (>70umol/L) will suggest significant dehydration. Rarely, starvation ketoacidosis may occur resulting in significant metabolic derangement.

- For patients not requiring admission to hospital or treatment with IV fluids, electrolytes should be remeasured only if their condition deteriorates.
- For women requiring repeated IV fluids or admission to hospital, electrolytes should be measured daily or less frequently if stable after commencement of therapy.
- More frequent monitoring of electrolytes (at least daily) is required for women with diabetes or other significant underlying conditions.

Liver function tests:

- Liver enzymes are elevated in 15-50% of patients with hyperemesis but are generally less than four times the upper limit of normal (38, 39).
- Liver dysfunction most commonly includes mild-moderate rises in transaminase levels (>2-3x local reference range for pregnancy), however, elevated bilirubin can also be seen although it is less common (39).
- Liver dysfunction typically resolves rapidly with improvement in HG symptoms (40).
- Further investigation should be considered if liver enzyme dysfunction is greater than 4 times the upper limit of normal for pregnancy.

Thyroid Function tests: See “How to manage gestational hyperthyroxinemia” (below)

- Women with NVP who do not meet diagnostic criteria for HG do not require TFT measurement.
- TSH should be measured in women with HG or NVP refractory to treatment or in those with more mild symptoms who have signs and/or symptoms of thyrotoxicosis.

Obstetric ultrasound

- Should be performed to assess for multiple gestation and gestational trophoblastic disease if not done already (41).

Tests to exclude alternate diagnoses where indicated

In the patient who has atypical symptoms, signs or relevant history, further investigations may be required. The differential diagnosis for nausea and vomiting in pregnancy is varied and includes any disorder that can cause these symptoms (see Textbox)). Symptoms such as abdominal pain, fever, headache and neck stiffness are not features of NVP or HG and suggest an alternate diagnosis. In addition the vomitus of nausea and vomiting of pregnancy is usually non-bilious and non-bloody, although hematemesis may occur in the context of Mallory-Weiss tears (42). In women with refractory HG, consider investigation for H. Pylori with fecal antigen testing or serology for IgM.

Differential diagnosis of NVP in pregnancy [more common causes in bold]

Gastrointestinal
- **Infectious gastroenteritis**
- **Gastro-oesophageal reflux disease-Helicobacter Pylori**
- Infectious hepatitis
- Pancreatitis
- Biliary tract disease
- Peptic ulcer disease
- Bowel obstruction
- Gastroparesis
- Appendicitis
- Peritonitis

Genitourinary
- **Urinary tract infection including pyelonephritis**
- Ovarian Torsion
- Nephrolithiasis

Metabolic/Toxic
- **Drugs-including pregnancy vitamins**
- Use and/or withdrawal of cannabinoids or other illicit drugs
- Diabetic ketoacidosis
- Addison's disease
- Thyrotoxicosis
- Non-infectious hepatitis
- Hypercalcemia
- Eating Disorders

Central-nervous system disease
- **Migraine**
- Infection
- Tumours
- Raised intracranial pressure
- Vestibular system pathology: labyrinthitis, Meniere's

Who should care for women with NVP?

NVP is such a common problem in early pregnancy that all maternity caregivers including midwives, general practitioners (GPs) as well as obstetricians should be well placed to care for most women with mild-moderate symptoms (PUQE-24 score ≤ 12). Women often consult their community pharmacists and they may be an important source of information and advice regarding treatment. One study of the value of professional support (including individualised health education through provision of an information booklet and supportive phone calls) for women with NVP demonstrated a reduction in the severity of symptoms and distress and a significant improvement in quality of life ($p < 0.05$) (43). Even though there was no significant difference between the two groups in body weight gain at week 4, attentive empathetic care is an important aspect of holistic management.

Clinical assessment and care of women with severe NVP or HG (PUQE-24 score ≥13) should be undertaken by clinicians with experience in recognising the signs and symptoms of HG, and with expertise in managing this condition effectively (LOE- III). These clinicians should be identified within each maternity care setting and depending on local resourcing, this may be an obstetrician, physician (either a general physician, obstetric physician, emergency physician or gastroenterologist) or a general practitioner (GP). This clinician should be designated as the lead clinician for this aspect of the woman's care. We recommend consultation with a dietitian for all women requiring inpatient care and for women with protracted symptoms of severe NVP, especially where there is evidence of malnutrition.

Due to resource availability, access to an experienced clinician may be limited, and consideration should be given to contacting experienced practitioners via an appropriate referral pathway (e.g. to a tertiary maternity hospital) or via telemedicine.

Where should management for NVP and HG take place?

The majority of women with a PUQE-24 score <13 can be managed in the community (LOE-I). In women with severe NVP or HG (PUQE-24 score ≥13), community care alone may be inadequate. Women with Type 1 diabetes and other high risk conditions (eg short bowel syndrome) or those requiring continuity of essential oral medications (eg severe epilepsy, transplant recipients) should be admitted to hospital at least for initial management and until they are stable (LOE- III) (6).

Where available, Ambulatory Day Stay facilities and Hospital in the Home services should be utilised for women who require parenteral fluid resuscitation and parenteral anti-emetic administration if they are unable to tolerate these orally in the community setting (LOE-II) (44). Outpatient services to manage NVP and HG provide rapid and simple access to symptomatic women

and have the potential advantage of self-referral (45). Being able to access outpatient services rather than requiring inpatient admission is beneficial for minimising disruption and maintaining family units.

One study demonstrated ambulatory care enrolment was associated with improvement of symptoms in 89% of women. Characteristics of those who failed outpatient care in this study included a higher mean PUQE-24 score at the start of outpatient management, an earlier gestational age at the start of the NVP, and the need for additional adjunctive parenteral fluid during their outpatient management (44). A randomized controlled trial of 98 women with NVP demonstrated that ambulatory day care management with protocols escalating to intravenous fluid and anti-emetic therapy, reduced admission rates to hospital and was satisfactory to women enrolled in the program (46). A subsequent cost utility analysis confirmed the cost effectiveness of day care management compared to inpatient management (47).

In the absence of access to hospital-based ambulatory day stay facilities and Hospital in the Home, alternative options for provision of care need to be considered. This may include provision of parenteral rehydration therapy and/or antiemetics in:

- the emergency department of the local hospital
- general practice/family practice/community health centres with suitable facilities
- private infusion centres
- non-pregnancy day stay services

All of these sites should seek to provide management in a comprehensive, empathetic environment with advice from a clinician with expertise in treating NVP and HG.

During outpatient management, women require regular review, at least every 1 to 2 weeks, by their lead clinician to ensure appropriate titration of therapy.

InPatient Care

In women with severe NVP, community-based care may be insufficient and admission to hospital may be required (LOE-II). HG is the main cause for hospitalisation of pregnant women in the first half of pregnancy. In addition, one recent study documented 38% of women being readmitted after a mean of 11.2 days (48). Three factors were identified that predicted readmission: gestational age < 9 weeks, length of hospitalisation more than 2 days and HG during a previous pregnancy.

Inpatient management is required for women with:

- Severe electrolyte disturbance eg potassium < 3.0mmol/L
- Significant renal impairment or acute kidney injury: creatinine > 90 mmol/L
- Concurrent significant co-morbidity eg Type 1 diabetes, poorly controlled epilepsy, transplant recipients, or those requiring essential immunosuppression

- Malnutrition/continuing significant weight loss despite therapy or starvation ketoacidosis
- Associated conditions requiring inpatient management eg infection, hematemesis

Discharge will be indicated when:

- Appropriate oral (or rectal pharmacotherapy when available) has been tolerated
- Adequate oral nutrition and hydration has been tolerated
- Management of concurrent conditions is completed

In all cases, the lead clinician needs to communicate a clearly documented plan for ongoing management to the patient (See Individual Patient Management Plan below) and the treating team members including: details of therapy, arrangements for clinical re-assessment and arrangements for ongoing antenatal care.

What is the best treatment for NVP and HG?

Although NVP is common, not all women seek help. In a subset of respondents in the Australian Longitudinal Study on Women's Health, 42.2% of women reporting nausea sought help from a health care practitioner whilst of the 201 women reporting repeated vomiting, 78.6% sought help (49). A recent cross-sectional study from a web-based questionnaire received responses from 9113 women from throughout Europe, North America and Australia regarding rates of nausea and factors related to the treatment of NVP during pregnancy (50). Amongst these women, 17.9% used "conventional medicines" and 8.3% used herbal medicines. Amongst Australian respondents, the rates were 24 and 21.7% respectively. In a more recent Australian study, only 39% of women used any NVP treatment of which 15% used pharmacotherapy, with most using non-prescription treatments such as vitamin B6, ginger and "natural remedies" (13). The majority (65%) reported they were not offered and did not ask for NVP treatment.

Numerous systematic reviews have attempted to assess the heterogeneous and limited high level evidence for the efficacy and safety of treatments for NVP and HG (51-54). In assessing the response to treatment, the fluctuant nature of NVP and the impact of progressive gestation must be considered, as spontaneous resolution is the norm. Similarly, a number of symptoms of normal pregnancy could be misinterpreted as adverse responses to treatment including bowel disturbance, gastroesophageal reflux, sedation, urinary symptoms as well as vaginal bleeding, abdominal/pelvic pain and miscarriage.

Non-pharmacological treatments

Since nausea and vomiting are very common in pregnancy (NVP), many non-pharmacological remedies have been proposed by different cultures. This section is confined to those which have published data associated with their use.

Rest

The first trimester of pregnancy is frequently associated with fatigue, at a time when pregnancy has often not been declared in public. In a prospective study of more than 7,000 Dutch woman, 44% described daily fatigue and this has been associated with a worsening of pregnancy nausea (55-58). Interventions to improve nausea and fatigue include modification of working patterns, exercise, day time sleeps and an earlier bedtime, however the data around the efficacy of these interventions is weak (59-62) [LOE-III].

Diet

Although large observational studies have demonstrated a change in quantity and quality of women's diets with NVP, there is no data on whether this is an effective treatment or merely avoidance (63, 64). An ecological study across 21 countries reported higher rates of nausea and vomiting with higher intake of meat, milk and eggs, and low intake of cereal and pulses (64, 65). However none of these studies had a pre-pregnancy diet measurement to make a comparison.

Prior to pregnancy, a diet with a higher daily intake of saturated fat increased rates of hospitalisation for hyperemesis in an American population (66). Vitamin use, smoking and alcohol consumption have all been linked to a reduced risk of NVP, the latter two remedies would of course be inadvisable in pregnancy (67, 68).

Women will tend to alter their diets to minimise their symptoms and they should be encouraged to eat whatever and whenever they can to maintain nutrition and hydration. Standard recommendations include eating small, more frequent meals that are low in fat (69, 70). One study has demonstrated that protein meals may selectively reduce nausea and gastric slow wave dysrhythmias in first trimester pregnancy (71).

Acupuncture/Acupressure

Very few studies are available in English language journals of the use of traditional acupuncture for the treatment of NVP. Only two trials compared acupuncture to sham or placebo treatment, neither found clinically significant improvement in symptoms (72, 73) [LOE-II]. No serious adverse outcomes from the use of acupuncture were reported.

Stimulation of the P6 (Nei guan) point on the wrist has been used for thousands of years by acupuncturists to treat nausea and vomiting from a variety of causes. Acupressure wrist bands are commonly used by women experiencing nausea in early pregnancy. However the Cochrane review

published in 2015 of 6 studies comparing acupressure with placebo found no overall significant reduction in women's symptoms (53). More recently a Malaysian study compared two groups of 60 women admitted to hospital for moderately severe hyperemesis who were randomised to wear either acupressure bands or placebo wrist bands for a minimum of 12 hours per day for three days (74). This study did show a significant improvement in the PUQE-24 score on day 3 in those randomised to the treatment arm (mean ± standard deviation: 4.40±0.63 versus 7.10±1.61, p< 0.001). The authors emphasised the importance of wearing the acupressure band for a minimum of 12 hours per day. Interestingly a greater percentage of the placebo group were satisfied with their treatment (85%) than the treatment group (72%, p <0.8).

Hypnosis

A review of 45 studies of the use of hypnosis for NVP found no good quality clinical evidence for its' efficacy (75) [LOE-I].

Pharmacological treatments

The principles of holistic management of NVP and HG must include:

- Interventions to reduce nausea, retching and vomiting (Tables 3a,b,c, 4, 5)
- Management of associated gastric dysmotility ie gastroesophageal reflux and constipation (Table 6)
- Maintenance of hydration, fluid and electrolyte replacement (Table 7)
- Maintenance of adequate nutrition including provision of vitamin supplements where required
- Psychosocial support
- Monitoring and prevention of side effects and adverse pregnancy and fetal outcomes

Considerations for treatment choices in NVP and HG

- Establish targets for symptom relief:
  - the ability to eat and drink adequately without necessarily complete resolution of NVP
- Discontinue prenatal multivitamins if they are contributing to NVP (LOE- III):
  - two-thirds of women reported an improvement in NVP symptoms after discontinuation of iron-containing prenatal multivitamins in a prospective cohort from Canada (76)
  - The two critical micronutrients which should be continued if possible are iodine (150 mcg per day) and folate (at least 400 mcg per day)
- The timing of administration of pharmacological therapy should reflect the woman's symptom pattern:

    - symptoms often fluctuate during the day and night and therapy should reflect these individual differences.
- The choice of antiemetic should be individualised, based on the woman's symptoms, previous response to treatment and potential side effects (Table 3a,b,c 4,5) (LOE- I):
    - if an antiemetic is ineffective at maximal dose, discontinue before commencing an alternate agent
    - if an antiemetic is partially effective, optimise dosage and timing, and only add additional agents after maximal doses of the first agent have been trialled
- Oral therapy is usually commenced first and parenteral or subcutaneous treatment reserved for refractory cases (LOE- III). Rectal therapy may have a role but no options are currently available in Australia and New Zealand.
- Written instructions should be given regarding titrating therapy (up and down) as symptoms fluctuate, deteriorate or improve (see Individual Patient Management Plan).
- Regular review of therapy is required in all cases:
    - the natural history of NVP and HG is for spontaneous resolution

Medications for treatment of NVP and HG

Treatment of NVP and HG may require a range of agents including:

- Antiemetics: herbal/vitamin and prescribed
- Acid suppression
- Laxatives
- Steroids
- Other-supplements

The most significant factor in prescribing pharmacological treatment for NVP and HG is the potential risk of teratogenicity. These therapies are generally commenced during the first trimester whilst embryogenesis is proceeding. Any potential increase in the risk of congenital malformation needs to be compared with the background rate of congenital malformations which was 3.1% in 2002–2003 (77).

Pharmacological treatment for NVP and HG should be used as part of a holistic approach to management including where appropriate, non-drug measures, psychosocial support and ongoing obstetric/midwifery care. Almost all pharmacological treatment is "off license" and based on historical experience with the limited amount of high quality research data described in small trials or systematic reviews or meta-analyses. In all cases, a rational assessment of maternal and fetal risk, particularly teratogenesis, needs to be determined based on the woman's circumstances.

Commencement and titration of pharmacological treatment for NVP or HG:

- Mild-moderate NVP:
  - start with ginger ±B6
  - add oral antihistamine or dopamine antagonist if needed
- Moderate-severe NVP or inadequate response to initial treatment:
  - consider IV/IM antihistamine or dopamine antagonist.
  - excessive sedation or inadequate response: add /substitute oral or IV serotonin antagonist at least during daytime
  - add acid suppression therapy
- Refractory NVP or HG:
  - consider corticosteroids in addition to other antiemetics
  - intensify acid suppression
- Manage/prevent constipation with laxatives.

Antiemetics

A number of systematic reviews and expert reviews of the efficacy and safety of routinely used pharmacological treatments for NVP and HG have been published (20, 51, 52, 78-83) [LOE-I]. Those medications have been included as options in Tables 3a, b, c. Table 4 describes the use of serotonin receptor antagonists and corticosteroids, and these are discussed in detail below.

In a recent systematic review, McParlin et al concluded that all routinely prescribed antiemetics including antihistamines, metoclopramide (for mild symptoms), pyridoxine-doxylamine, and ondansetron (for moderate symptoms) were more effective than placebo (54) [LOE-I]. In a study of women presenting to an Emergency Room, when comparing 4 commonly used antiemetics (ondansetron versus metoclopramide versus promethazine or prochlorperazine), there was no difference in response in terms of time from administration to discharge (84) [LOE-III]. Other trials have evaluated alternative antiemetics and there was no convincing evidence of superiority of any particular drug (LOE- I) (85). Intravenous metoclopramide and promethazine appear to be equally effective at least in the first 24 hours of use (83) [LOE-II]. The EMPOWER study (EMesis in Pregnancy – Ondansetron With mEtoclopRamide) commencing in 2018 will be comparing metoclopramide with ondansetron for severe NVP in a double dummy, double masked controlled factorial trial in the UK.

Serotonin receptor antagonists are the most effective antiemetic drugs available outside of pregnancy, but there remains controversy about their use in pregnancy. In women with HG, one RCT concluded that ondansetron was superior to metoclopramide in reducing vomiting (p=0.04) but not nausea (86), whilst another RCT found the antiemetic and antinauseant effects were equivalent but

there were less adverse effects (drowsiness and dry mouth) with ondansetron (87) [LOE-II]. The safety data for ondansetron has been reviewed by Carstairs (88) and he described the three largest studies up to 2015 showing no overall increased risk of birth defects, however, two of these studies demonstrated a slightly increased risk of cardiac defects (OR 2.0 [1.3–3.1] and 1.62 [1.04–2.14]) (89, 90) [LOE-I]. This was not replicated in all studies. Subsequent to this meta-analysis, two databases were reviewed for a study by Parker et al: the National Birth Defects Prevention Study (NBDP 1997–2011) and the Slone Birth Defects Study (SBD 1997–2014) (91). These 2 databases have a total of 253 (NBDP) and 375 (SBD) cases of mothers exposed to ondansetron in the first trimester compared with mothers with NVP who were untreated, and a secondary control group of women who took other antiemetics. Ondansetron use was not associated with an increased risk for most of the 51 defect groups analysed, including cardiac defects [LOE-II]. There was a modest increase in cleft palate but not cleft lip in the NBDP Study (AOR 1.6 [1.1–2.3]), similar to the data from an earlier period from the same registry (92) whilst all other studies have shown either no increase or a decrease in cleft palate [LOE-II] (90, 93-96)). In the SBD Study there was a slightly increased incidence of renal agenesis–dysgenesis (AOR 1.8 [1.1–3.0]) but this has not been reported in any other study.

Most recently, two retrospective cohort studies have given conflicting results (97, 98). A nested case control study from a large US administrative claims database (2000-2014) analysed 76,330 (8.8%) exposed pregnancies ascertained by filling of an ondansetron prescription in the first trimester and a subgroup of 5557 mother-child pairs (0.64%) claiming for medical administration of ondansetron. (97). They demonstrated an increased risk of cardiac defects, predominantly septal defects (AOR 1.04 [1.00-1.08]) with a non-significant increase in oro-facial clefts (AOR 1.12 [0.95-1.33]). Over a similar period (2000-2013), Huybrechts et al analysed Medicaid data from more than 1.8 million pregnancies which covers more than 50% of pregnancies in the United States of America (98). They specifically looked for an association between ondansetron use and overall congenital malformations, cardiac anomalies or oral clefts. Exposure was assumed if the woman filled a prescription for ondansetron in the first 90 days of pregnancy. There were 88,467 exposed infants in this study and no increase in overall congenital malformations (adjusted relative risk (RR) 1.01 [0.98 to 1.05]). The adjusted RR for cardiac malformations was not significant (0.99 [0.93 to 1.06]) but there was a slight increase in oral clefts, specifically cleft palate not lip (adjusted RR 1.24 [1.03 -1.48]. This would equate to an additional 2.7 [0.2 to 5.2] oral clefts per 10,000 births. An updated meta-analysis of ondansetron use, including these studies, demonstrated no significant increase in either major/severe malformation (combined OR 1.01 [0.98 to 1.05]) or cardiovascular malformation (1.03 [0.98 to 1.07]) (98a).

In the absence of consistent evidence of harm, the use of ondansetron has increased rapidly since 2006, with an associated decline in the use of promethazine and metoclopramide since 2014 (97, 99). In this study (99), the prevalence of ondansetron, promethazine, metoclopramide, or doxylamine/ pyridoxine use anytime in pregnancy was 15.2%, 10.3%, 4.0%, and 0.4%, respectively. A single pilot study has suggested that maternal genotype for serotonin receptor gene SNPs may determine the responsiveness of an individual to serotonin receptor antagonists and allow more individualised prescribing (100).

Corticosteroids are used for a variety of indications in pregnancy. In women with HG, the usual corticosteroids used have been hydrocortisone and prednisolone. Prednisolone is lipophilic so it can cross the placenta, but fetal uptake is limited by active retrograde transport by P-glycoprotein, and its conversion to inactive metabolites by placental 11β-HSD2 (101). Six randomised studies have assessed the efficacy and safety of corticosteroids for management of severe NVP or HG (102-107). Three compared corticosteroids with placebo or promethazine or metoclopramide in women with severe symptoms. Improvements were seen in all corticosteroid groups, but the only statistically significant difference was reduced vomiting in 2 of these studies, particularly prior to 10 weeks (103, 107) (LOE-I). No safety concerns were reported in these trials.

Older data from the National Birth Defect Prevention Study in the USA (1995-2001, 1997-2002) has reported an association between maternal corticosteroid use in early pregnancy with cleft lip, with or without cleft palate, in the offspring (OR 1.7 [1.1–2.6]), but not cleft palate alone (108, 109). However, in these studies, there were very few women treated with systemic corticosteroids. Further studies from the same registry (2003-2009) found no association between maternal corticosteroid use and cleft lip and palate in 12 women exposed to systemic corticosteroids (110). Over a similar period (1995-2001), Källén studied the drug associations with cleft lip and/or palate in Sweden and found no significant association (OR 1.94 [0.78–3.99]) (111). Pradat et al used data from 9 malformation registries (n=11,150 cases) collected over 13 years and found no increased risk of cleft palate or lip overall (OR 1.25 [0.72–2.15]) although there was a slight increase in the offspring of women who received corticosteroids in combination with another agent (n=61 exposures, OR 2.59 [1.18-5.6] (112).

A prospective cohort study and meta-analysis of cohort and case-control studies of corticosteroid use in pregnancy found no significant increase in major malformations (1.45 (95% CI: 0.80-2.60) although in case-control studies only (n=4), there was an increased risk of oral cleft (OR 3.35 [1.97-5.69]) (113). No significant effect was seen when the 6 cohort studies were also included in the meta-analysis. In a surveillance study of Michigan Medicaid recipients involving 229,101 completed pregnancies conducted between 1985 and 1992, 143, 236, and 222 newborns had been

exposed to prednisolone, prednisone, and methylprednisolone, respectively, during the first trimester. There was no association between exposure to these agents and congenital defects (82).

Accepting the background risk for oral cleft is 1.7 per 1000, based on the very small amount of gestation specific data for corticosteroid exposure during the relevant period of embryogenesis (starting during the 5th week of gestation, completed by the 10^{th} (114)) there is no apparent increased risk of oral cleft or other congenital malformation (LOE- I) (110, 115). Although most teratologists counsel that systemic steroids given in the first trimester may increase the risk of oral clefts, the data remains conflicted, and even the most conservative estimates would quantitate the risk to be only one or two additional cases per 1,000 treated women (116). Corticosteroids should be considered third line treatment after non-pharmacological agents and antiemetics and reserved for more severe NVP or HG (LOE- III).

Tables 3a, 3b, 3c: Oral antiemetic medications for mild-moderate NVP (117).

Dosing: BD- twice a day, TDS-three times per day, QID-four times per day, max-maximum recommended total daily dose.

Note: *Do not combine these agents with similar mechanism of action and side effects [S]-sedating, preferably use nocte only.

Table 3a HERBAL/VITAMIN	GINGER	VITAMIN B6 (PYRIDOXINE)
Mechanism of action	Improvement in gastrointestinal motility: weak effect on cholinergic M3 receptors and serotonergic 5-HT3 and 5-HT4 receptors in the gut	Water soluble vitamin, inhibits H1 receptor, acts indirectly on vestibular system, some inhibition of muscarinic receptors to decrease stimulation of vomiting centre
Evidence for efficacy	↓N but not V Superior to placebo Equal to Vitamin B6, dimenhydrinate, metoclopramide, doxylamine, P6 (LOE- II)	↓N but not V Less effective than dimenhydrinate (LOE- I)
Recommended/max dose	Use standardised products rather than foods: up to 1200 mg/day split doses eg 250 mg QID	10 to 25 mg PO 3-4x/day Up to 200 mg/day Or 37.5 mg combined with ginger 600 mg up to 2x/day
Side effects	Inability to tolerate treatment, sedation and heartburn	Sensory neuropathy has been reported with chronic intake of pyridoxine at doses >500 mg/day
Risk of teratogenesis	No increase	No increase
Practice points	Theoretical but unproven risk of bleeding risk by decreasing platelet-aggregation. May inhibit growth of Helicobacter Pylori	More effective when used in combination eg with doxylamine or dicyclomine (equivalent to metoclopramide)

Table 3b HISTAMINE/DOPAMINE ANTAGONISTS	DOXYLAMINE[S]/DIMENHYDRINATE[S] DIPHENHYDRAMINE[S]/CYCLIZINE[S]/ PROMETHAZINE[S]	METOCLOPRAMIDE
Mechanism of action	Indirectly affect the vestibular system, decreasing stimulation of the vomiting centre	Dopamine and serotonin receptor antagonist which stimulates upper gastrointestinal motility and acts on CNS vomiting centre
Evidence for efficacy	DOXYLAMINE: ↓N compared with placebo, with or without pyridoxine (LOE II) DIMENHYDRINATE/DIPHENHYDRAMINE/ CYCLIZINE: (LOE-III)	Equal to ondansetron for N but less effective for V (LOE-II)
Recommended/max dose	DOXYLAMINE*: 6.25-25 mg TDS po, max 50 mg/day DIPHENHYDRAMINE*: 25-50 mg TDS, max 150 mg/day DIMENHYDRINATE*: 25 to 50 mg TDS, max 100 mg/day CYCLIZINE*: 12.5-50 mg TDS, max 150 mg/day PROMETHAZINE*: 25 mg TDS, max 75 mg/day	10 mg TDS, max 30 mg/day
Side effects	Sedation, anticholinergic effects	Less sedation, akathisia, depression. Rare: tardive dyskinesia with chronic use
Risk of teratogenesis	No increase	No increase
Practice points	Doxylamine and dimenhydrinate are available as non-prescription sleeping tablets or travel sickness tablets. Dimenhydrinate is often combined with caffeine and hyoscine. Safety data on combination indicates no concerns. Best reserved for evening dosing	

Table 3c PHENOTHIAZINES*	PROCHLORPERAZINE[S]	CHLORPROMAZINE[S]
Mechanism of action	Central and peripheral dopamine antagonists	
Evidence for efficacy	Superior to placebo for NVP (LOE-I)	(LOE-III)
Recommended dose	5-10 mg TDS, max 30 mg/day	10-25 mg TDS
Side effects	Sedation, akathisia, anticholinergic effects, hypotension Rare: dystonias, tardive dyskinesia with chronic use	
Risk of teratogenesis	No increase	
Practice points	Best reserved for evening dosing	

Table 4: Oral antiemetic medications for severe NVP and HG [see discussion above pages 20-23].

	ONDANSETRON	CORTICOSTEROIDS
Mechanism of action	Central (medullary vomiting centre) and peripheral (small bowel) serotonin receptor blocker	Antiemetic effect on the chemoreceptor trigger zone in the brainstem
Evidence for efficacy	Superior to combination doxylamine/B6 for reduction in N and V Superior to metoclopramide for reduction of V but not N in HG	Improved sense of wellbeing, appetite and increased weight gain in HG patients No difference in days of hospital admission or readmission rates compared to placebo Equal to promethazine with fewer side-effects (LOE-I) Superior to IV metoclopramide (LOE-I)
Recommended dose	4-8 mg up to TDS	Prednisone 40-50 mg/day. (May be commenced as hydrocortisone 100 mg IV BD)
Side effects	Constipation, headache, dizziness	Potential Cushing's syndrome, mood disturbance, hypertension, hyperglycemia
Risk of teratogenesis	Conflicting data but does not appear to increase overall risk of birth defects	Possible increased risk of oral clefts when used < 10 week's gestation, but data are weak
Practice Points	No sedation Expensive Available as tablets, wafers and oral dispersible formulations Ensure concurrent management of constipation-bowel obstruction has been reported Recommended as second line agents	Consider withholding until after 10 weeks gestation if alternate therapy an option Restrict to refractory cases

Mode of administration of pharmacological therapy:

Depending on the severity of NVP, oral therapy is usually commenced first and parenteral or subcutaneous treatment reserved for refractory cases (Table 5). Oral dispersible formulations are available for some medications, eg ondansteron but these are not absorbed sublingually and need to be swallowed like tablets. Outpatient continuous subcutaneous antiemetic management has been described in a number of observational studies (118, 119). If available, subcutaneous ondansetron appears to be more effective than subcutaneous metoclopramide although both significantly reduced the risk of rehospitalisation (LOE-III). However, almost half the women still required intravenous hydration during the treatment period and patients remained on therapy for a mean of 22.3 +/– 20.2 days (118).

At present, subcutaneous microinfusion pumps of these antiemetic therapies do not appear to be cost effective when compared with conventional treatment alternatives, including periodic hospitalisation (LOE- II) (118, 119).

Table 5: Parenteral/subcutaneous antiemetics (118, 120) - for additional information see Tables 3a, 3b, 3c and 4.

	Dosage (Max daily dose)	Comments
METOCLOPRAMIDE	10 mg IV TDS (0.5 mg/kg to max 30 mg/day) Or 1.2 to 1.8 mg/hour intravenously by infusion Or Subcutaneous infusion 20-40 mg/day	Slow IV over 2-20 min Sedation
CYCLIZINE	50 mg slow IV BD-TDS	Severe sedation
DROPERIDOL	0.5 to 1 mg/hour (25 mg/day)	Sedation
PROMETHAZINE	25 mg IM or IV TDS-QID (100 mg/day)	Sedation
PROCHLORPERAZINE	5 to 10 mg IV TDS-QID	Sedation
ONDANSETRON	4-16 mg IV TDS SC infusion 16-28 mg/day	Avoid in women with pre-existing QT prolongation
METHYLPREDNISOLONE	16 mg TDS for 48 to 72 hours	
HYDROCORTISONE	100 mg IV BD	

What other pharmacological therapies are being trialled/considered for women with NVP and HG?

A number of other agents have been used for treatment of NVP and HG in small studies but are not yet in routine use or are not available in Australia and New Zealand. None of these agents are recommended by this guideline.

- A delayed-release combination of doxylamine succinate and pyridoxine hydrochloride has completed Phase 3 Trial with demonstrated efficacy but is not currently available in Australia or New Zealand (121).
- Transdermal granisetron: In a small pilot study, women with NVP received a single dose of IV granisetron followed by application of a 34.3 mg granisetron patch. This was left on for 7 days and produced persistent, relief equal to the initial IV dose for up to 3 days after patch removal (122). In the future, transdermal agents may be a valuable addition for management of NVP and HG.
- Transdermal clonidine :One small study of 12 women with treatment resistant HG used a 5 mg clonidine patch in a sequential placebo controlled study (123). Clonidine is a centrally acting, alpha-2 adrenergic agonist which has been used in pregnancy for management of hypertension but has also been effective for prevention of postoperative nausea and vomiting. The mechanism underlying the antiemetic effect is as yet unknown: it may involve a direct effect on nausea and vomiting trigger zones in the midbrain or a secondary effect with reduction of the level of noradrenergic activation. In this trial, clonidine led to a significantly greater improvement in NVP associated with a small reduction of blood pressure: systolic 6 mmHg and diastolic 3 mmHg.
- Mirtazapine, a tetracyclic antidepressant with central alpha-2 and 5HT-3 receptor blocking ability has been used for both depression and HG (124-127). It reduced both NVP and depression at a dose of 7.5-45 mg per day with the only side effects being dry mouth and sedation. Limited data suggests no increased risk of congenital malformation when used in pregnancy (127). However, the number of women treated with mirtazapine for HG remains small and it is not considered a standard drug for nausea and vomiting in pregnancy.
- Gabapentin: A single pilot study of gabapentin in HG suggested some benefit but only limited data is available about first trimester exposures although results did not suggest any increased risk of malformations (128, 129). Gabapentin has been useful in reducing postoperative nausea and vomiting and the postulated mechanisms include a reduction in calcium signalling in the area postrema as well as a decreased tachykinin neurotransmission. Further studies of this agent may be indicated.
- Diazepam: Benzodiazepines such as diazepam are thought to be helpful in HG, presumably through alleviating psychosomatic symptoms such as anxiety. However, the safety of these medications in pregnancy is still controversial with some studies demonstrating a positive

association between neonatal exposure to diazepam and prematurity and low birth weight (52). Several observational studies have reported using intravenous diazepam as an adjunct for women with HG. In one study, 74 women with refractory HG were given IV fluids with or without IV diazepam (mean dose 62.8 +/- 24.5 mg (range 40-160) (130). The number of hospitalisation was significantly lower, and patient satisfaction was significantly higher in the diazepam group. In a second randomised study, 50 women with HG were treated with IV fluids and vitamins plus or minus diazepam. The mean stay in hospital was shorter in the diazepam group (4.5 +/- 1.9 vs. 6 +/- 1.6 days $p < 0.05$) and readmission to the hospital was 4% in the diazepam group versus 27% in the control group ($p < 0.05$). There was a significant reduction in nausea in the diazepam group ($p < 0.05$) and a significant reduction in vomiting was observed in both groups (131).

Acid suppression

Many women with vomiting in pregnancy experience symptoms of gastroesophageal reflux (GER) as well, and the presence of such symptoms is associated with more severe NVP (132). The treatment of GER along with anti-emetic therapy has been associated with reduced PUQE-24 scores (9.6 ± 3.0 to 6.5 ± 2.5, $P < .0001$) and improved quality of life scores (4.0 ± 2.0 to 6.8 ± 1.6, $p < .0001$) (Table 6) (LOE- I) (133). The mechanism of this association is primarily related to gastroesophageal motility. Neuromuscular abnormalities of the stomach associated with symptomatic nausea in pregnancy include gastric dysrhythmias, both brady- and tachy (134). In HG, the gastric myoelectrical pattern is a flatline or arrhythmic pattern. The mechanisms underlying this gastric dysrhythmia are poorly understood. Estrogen and progesterone administered to healthy women induced gastric dysrhythmias, particularly bradygastrias (135). Thyroid dysfunction may also disrupt intestinal pacemaker activity and changes in intravascular volume status that affect vasopressin secretion may also disrupt gastric dysrhythmia (134).

Concerns have been raised regarding an increased risk of childhood asthma in the offspring of women treated with acid suppressive agents (136), however, none of the studies adjusted for the full panel of known confounders and the true risk has not been determined.

Table 6: Acid suppression for symptoms of gastroesophageal reflux (137-140).

Therapy	Dose	Risk	Comment
First line: Antacids containing magnesium, calcium, or aluminium	As required for mild symptoms	No increase in congenital malformations	Constipation or diarrhoea in high doses.
Second line: H2 antagonists	RANITIDINE 150-300 mg BD FAMOTIDINE 20 mg OD or BD	No increase in congenital malformations	Well tolerated
Third line: Proton-pump inhibitors	OMEPRAZOLE 20 mg OD-BD LANSOPRAZOLE 15 mg OD-BD RABEPRAZOLE 20 mg OD-BD ESOMEPRAZOLE 40 mg OD-BD PANTOPRAZOLE 40 mg OD-BD	No increase in congenital malformations	Well tolerated

Laxatives and stool softeners

Dehydration, gastric dysrhythmia and other drugs used for treatment of NVP, particularly ondansetron, can contribute to significant and symptomatic constipation in women with NVP and HG. Increasing dietary fibre and fluids is the preferred treatment of constipation during pregnancy, although this can be difficult in women with restricted diet due to NVP. In a systematic review of treatments for constipation in pregnancy, stimulant laxatives produced significantly more improvement in constipation but also significantly more abdominal discomfort and diarrhoea whilst fibre supplementation increased frequency of stools [LOE- II] (141). Non-absorbed stool softeners such as docusate sodium may be effective with or without laxatives.

For refractory cases, occasional use of magnesium salts or lactulose is considered suitable for use in pregnancy [LOE- II]. Castor oil can stimulate uterine contractions and excessive use of mineral oil can interfere with absorption of fat soluble vitamins, so these agents are generally avoided. Stimulant laxatives such as senna or bisacodyl are effective but are associated with abdominal discomfort and should be used with caution in pregnancy although they are not associated with any increase in congenital malformations [LOE- III]. In general, the short-term use of stimulant laxatives is considered safe in pregnancy. Osmotic laxatives such as lactulose, sorbitol or macrogol may be required although the large fluid volume required for ingestion may be poorly tolerated. As with the general population, long-term use of laxatives should be avoided.

Fibre-containing bulking agents are probably the safest laxatives to be used in pregnancy, as they are not systemically absorbed. These agents take several days to exert their effects and are therefore not suitable for acute symptom relief. They are also contraindicated in faecal impaction. Adverse events related to bulking agents include excessive gas, crampy pain and abdominal bloating.

Rectal treatments including bisacodyl, sodium phosphate and sodium citrate/lauryl sulfoaceteate/sorbitol enemas or glycerol suppositories may also be required. An excellent guide to laxatives and enemas has been previously published in Australia (142) .

Additional Treatments

Treatment for ptyalism

Ptyalism, or excess salivation, is a common accompaniment to HG. The incidence is greater in more severe cases (59% versus 9%), in those with persistent vomiting for greater than 24 hours after admission (69% versus 23%) and in women who were admitted repeatedly for treatment compared with those admitted only once ($p<0.05$) (143). Among the subset of women presenting with nausea and vomiting to a hospital clinic in Quebec, Canada, 26% complained of excess salivation at their first prenatal visit (144).

One approach to treatment is to use drugs with anticholinergic properties eg amitriptyline in small doses eg 10-25 mg once or twice a day [LOE- III]. In a small study of palliative care patients, transdermal clonidine was used to control ptyalism with a good clinical response observed. This therapy has also been trialled for HG (see Section 10). This therapy has not been studied other than in small, pilot groups and remains untested but of interest (145).

Treatment for H. Pylori

Dual or triple eradication therapy for H. Pylori has been used in a small number of case control and one randomised study (146). In a study of 156 women with HG and a positive fecal stool antigen test for H. Pylori, all were given standard antiemetic treatment and half received dual eradication therapy with lansoprazole and amoxicillin for 2 weeks. There was a significantly improved complete response rate in the treatment arm, 81% versus 59% (p .003) although they did not report evidence of eradication as the cause for improvement and the use of a proton pump inhibitor alone may have been the active agent. Further trials are required in this area. In refractory cases of HG, investigation for H. Pylori infection and eradication may be considered (6) [LOE-III].

When should intravenous fluid and parental feeding be used for management of NVP and HG?

Fluid management

Intravenous (IV) fluid and electrolyte replacement is an important part of symptomatic management of nausea and vomiting, as well as for correction of dehydration in women with NVP or HG. IV fluids have been shown to reduce vomiting (131) and are therefore valuable for both outpatient and inpatient management of the symptoms of HG and severe NVP as well as associated dehydration and electrolyte disorders [LOE- I]. Women in the placebo arm of controlled trials for NVP demonstrated a significant improvement in nausea with supportive treatment including IV fluids without antiemetics [LOE-1] (85).

The prescription of IV fluid therapy should take into account the degree of dehydration and any electrolyte disturbances (Table 7). Care needs to be taken using any dextrose based solution as Wernicke's encephalopathy may be precipitated in women with thiamine deficiency (147). In addition, in the setting of severe hyponatremia, serum sodium should not be corrected faster than 10mmol/L per 24 hours to prevent central pontine myelinolysis (148).

Only one study has compared 5% dextrose–0.9% sodium chloride with 0.9% sodium chloride with no significant difference in episodes of vomiting, duration of IV antiemetic use, length of hospital stay, or persistence of ketonuria but nausea improved faster in the dextrose group, an effect that had dissipated by 24 hours (149). Should ongoing fluid administration be required, fluid balance (input and output) should be monitored for the duration of the treatment cycle. IV fluid resuscitation with or without electrolyte (potassium, magnesium and phosphate) replacement should be prescribed as required [LOE- I].

IV fluid therapy should preferably be administered in an outpatient setting where available, as this has been associated with equivalent patient satisfaction outcomes and lower total hospitalisation days in small studies [LOE- II] (78, 150). In one study, women with HG randomised to either Day Care or inpatient treatment required only a total of 1-2 visits for outpatient fluids with a significant reduction in symptoms and high satisfaction (46). The inpatient group received slightly higher volumes of fluid overall at 5.5 L [IQR 4–13L] compared with 4L [2–8L] in the Day Stay women, ($p < .01$). Twenty eight of 42 women randomised to Day Care did not require admission for further treatment. In a second study, rapid fluid therapy as part of outpatient care has been demonstrated to improve patient experience and was safe and efficacious with 60% of women being discharged after one treatment cycle in a Day Stay Facility (45). A number of options may be available for outpatient IV fluid therapy depending on the patient's location.

Clear pathways for access to outpatient fluid therapy can give women a sense of control over their symptoms which can be very helpful.

Table 7: Recommendations for parenteral replacement of IV fluids and electrolytes K: potassium, Mg: magnesium (151)

Type of fluid	Quantity/Rate	Comments
0.9% sodium chloride	1-2 L. Initial rate 1L/hour	Further IV fluids should be given at a rate of 1L/1-2 hours or slower to correct dehydration and electrolytes (see below)
4% dextrose and 0.18% sodium chloride or 5% dextrose	1 L. Initial rate 1L/2 hours.	Consider as an option if minimal oral intake, starvation or uncontrolled nausea and only after correction of thiamine deficiency and exclusion of hyponatremia
Add electrolytes as required		
Potassium chloride	30-40 mmol/L. Maximum infusion rate 10mmol over 1 hour	Administer with caution as per local protocol. Preferred product is premixed 30mmol potassium chloride in 1 L bags of 0.9% sodium chloride. Use large peripheral vein or central venous access only.
Magnesium sulphate	10-20 mmol/day over 20-40 minutes	Dilute with 100ml 0.9% sodium chloride. Use large peripheral vein or central venous access only.

Enteral and parenteral nutrition

HG leads to dehydration, fluid and electrolyte abnormalities, and inadequate nutrition. In severe cases, if antiemetic and steroid therapy has failed, nutritional support via enteral or parenteral routes may be required to adequately restore hydration, correct electrolyte imbalances and maintain nutrition. The parameters surrounding this escalation in therapy have not been defined, but typically are considered if there is ongoing sustained weight loss or failure to achieve appropriate weight gain, or ongoing inability to tolerate oral feeding despite antiemetic therapy.

A multidisciplinary approach to these alternative forms of therapy is essential including physician, obstetrician, dietitian and psycho-social support as indicated (6). Enteral feeding may be administered via naso-gastric or naso-jejunal tube, or via percutaneous endoscopic gastrostomy or jejunostomy. Care should be taken to ensure an experienced operator places a suitable naso-enteral feeding tube. Although a number of case reports have supported its role, a recent randomised controlled trial demonstrated that early enteral tube feeding did not improve maternal weight gain,

duration of hospital stay, NVP symptoms, perinatal outcomes or birth weight. Dissatisfaction with the therapy was high, and compliance poor (152).

In a large retrospective cohort study, women receiving enteral nutrition achieved similar maternal weight gain and pregnancy outcomes compared to those on other fluid or nutrition regimens despite having lost significantly more weight prior to commencing therapy. Enteral feeding was associated with a greater length of hospital stay and was complicated by tube clogging and inadvertent tube expulsion whilst vomiting in 54% (153). Other studies have demonstrated expulsion rates between 11 and 75% (152-155).

Percutaneous endoscopic placement of gastro-jejunal feeding tubes is feasible and can be undertaken successfully in the second trimester. This reduces the risk of early dislodgement and the need for multiple tube replacements and their associated radiation exposure. A small case series confirmed adequate maternal weight gain and no adverse perinatal outcomes, but no significant improvement in the symptoms of nausea. Of note here is the longer duration of use of feeding tube and the low rates of dislodgement compared with naso-gastric placement. However, there is a significant cost burden associated with prolonged nutritional support (156-159). Enteral solutions are considered more comprehensive in their nutrient composition although there remains a risk of refeeding syndrome (160).

Although rarely required, enteral nutrition is a therapy of last resort, and can be associated with both complications and compliance issues [LOE- II]. Patient education and involvement in the clinical decision making is essential to improve the chance of success.

Total Parenteral Nutrition (TPN) is administered via a peripherally inserted central catheter (PICC) or via a central venous catheter (CVC). TPN has been shown to be an effective method of nutritional support in women with HG with a single non-randomised study reporting a decrease in perinatal mortality (161). However, TPN is expensive, often requiring admission for the duration of therapy, and is associated with complications including pneumothorax, venous thromboembolism and sepsis (153, 162). One series of 85 pregnancies associated with CVC placement demonstrated a 25% rate of catheter-associated complications, principally infection and venous thrombosis (163). Retrospective studies of pregnancies affected by NVP and managed with PICC line insertion describe complication rates between 17 and 66%. These complications include line sepsis, cellulitis, mechanical line failure, pain, and both superficial and deep vein thromboses (153, 163-166). This complication rate is higher than those of non-pregnant individuals (20-26%) and may well be associated with the altered immune function and hypercoagulable state of pregnancy (164). TPN administration is also associated with refeeding syndrome leading to further derangements in electrolyte status.

As TPN is a high risk intervention, it should be used a last resort in cases refractory to all other attempts at caloric supplementation and enteral nutrition is recommended as first line in supplemental feeding. Maternal admission throughout the duration of TPN therapy is necessary whilst those who are enterally fed are able to continue their treatment at home. Multidisciplinary team involvement and the use of strict protocols with careful monitoring in the care of these women is important (6).

Refeeding syndrome refers to abnormalities in electrolytes and micronutrients that occur shortly after recommencement of feeding in patients who are malnourished. Hypophosphatemia is the predominant feature, but hypokalemia and hypomagnesemia can occur in response to increased cellular uptake of these nutrients. This can result in multi-organ effects including cardiac, neurological and musculoskeletal dysfunction. Thiamine deficiency can result in Wernicke-Korsakoff syndrome precipitated by refeeding (167). Patients commencing enteral or parenteral nutrition are at high risk of refeeding syndrome and need to be monitored closely, with a slow introduction of supplementation.

Due to their associated complications, cost burden and high rates of patient dissatisfaction, the use of enteral and parenteral nutrition should be a last resort, and trialled only if women are failing to respond to oral feeding and antiemetic therapy. Enteral nutrition would preferentially be recommended over TPN [LOE- III].

When should termination of pregnancy be considered for NVP or HG?

For some women, termination of pregnancy is an appropriate therapy. Occasionally, failure of response to comprehensive treatment of HG may be life threatening, and in this instance, termination of pregnancy may be the only option for prolongation of the woman's life. In less severe cases, a decision for termination of pregnancy may be made after comprehensive management, including anti-emetics and corticosteroids have been trialled and the option of enteral or parenteral feeding has been considered. This management should include appropriate psychiatric and psychological care and support in a multidisciplinary environment. Failure of therapy should be clearly documented prior to consideration of medically-indicated termination of pregnancy (168, 169).

In a recent Study based on Registry linkage studies in a large Finnish cohort, HG sufferers gave birth to fewer children than unaffected women: 1.6 births/woman versus 1.8 births/ ($p < 0.0001$) and pregnancy terminations were more 0.15 versus 0.11/woman ($p < 0.0001$) (169a). As discussed below, HG and its treatment has significant impacts on quality of life. The ability to maintain day to day activities, work capacity, and the desire to have future pregnancies is impacted. The more severe

the symptoms, the greater the impact on health-related quality of life, and the higher the risk of depression (170). Elective terminations of pregnancy have been reported in the literature in women who report severe vomiting and weight loss, depressive symptoms, family strain and lack of support from partners, and who feel they have been undertreated by their medical team (171).

A recent cross-sectional population-based study measuring severity of NVP using the PUQE-24 score and assessing global quality of life using the Quality of Life Scale (QOLS) demonstrated a significant association of severe NVP with impaired ability to engage domestically, occupationally and socially. Seventy five per cent of women with severe symptoms considered not getting pregnant again, and 27% considered termination of their pregnancy due to HG (1).

A Canadian retrospective review of women with NVP who had terminated pregnancies due to HG reported unplanned pregnancy, multiparity and feelings of depression as independent factors associated with termination of pregnancy (172). In addition, severity of symptoms and adverse effects on the relationship to the partner were risk factors for consideration of termination. Similarly, a review of 808 women, 123 of whom underwent termination of pregnancy cited inability to care for the family and self, and fear of fetal death or abnormality. Of concern, 52% reported their health care providers were uncaring, and 24% reported them to underestimate how sick these women were (168).

The physical and psychological burden of HG on women must not be underestimated, and further education within the health care community is essential. Comprehensive management, including anti-emetics, corticosteroids, nutritional support, and both psychiatric and psychological support in a multidisciplinary environment should be undertaken prior to consideration of termination of pregnancy (168, 169) [LOE- III].

What role does psychosocial assessment and support play in the management of NVP?

It comes as no surprise that constant nausea or vomiting in pregnancy is depressing, and reduces a woman's quality of life (58, 173, 174). It impairs her ability to function normally on a daily basis, impacts upon her relationships and can be impoverishing if the woman is unable to work. The more severe the vomiting, the greater the impact upon her quality of life (58).

Reluctance of health professionals to recognise and treat NVP and HG can worsen a woman's physical and mental health (175-177). Erroneous beliefs around the dangers of treatment can delay necessary and occasionally life-saving treatment for women with hyperemesis.

Historical beliefs of a psychogenic etiology for NVP (171) have been disputed (6). There is no prospective study of women with a mental health appraisal prior to and then in pregnancy. All

studies analysing mental health and NVP have been conducted once women were pregnant and symptomatic, so rely upon retrospective reporting of mental health (178).

It is however, clear that like many other studies reported below, women with severe NVP had greater levels of depression whilst experiencing those symptoms. In a cohort study of 648 Canadian women interviewed at a median of 17 and 30 weeks of gestation, NVP was prevalent at both gestations (25). Using the Cambridge worry scale and the Edinburgh depression scale worsening symptoms were associated with worsening depression and anxiety. In this study a self-reported history of pre-pregnancy depression (not necessarily medicated) was not associated with a higher risk of severe NVP. The importance of social support was outlined, having the support of at least three different people was protective against NVP.

Women who experience HG become more frequently depressed than those who do not experience HG (178). The longer and the more severe the HG, the longer the depression. In the Norwegian mother and child cohort of 92,947 women studied, 851 women (0.9%) experienced hyperemesis and these women were more likely to report emotional distress (174). However, by 18 months post-partum their levels of emotional distress matched those of the general population. The Dutch generation R study of approximately 7,000 women followed through pregnancy and analysed with a Health Related Quality of Life questionnaire, found those who suffered with worse NVP had a poorer quality of life (58). A Turkish study excluding all women with a prior history of mental illness, found 54% of 78 women with HG suffered from a moderate or severe depressive disorder compared with 6% of pregnant women without NVP (179).

In most maternity units in Australia and New Zealand routine mental health screening is undertaken with a minimum of an Edinburgh depression scale and for the majority of pregnant women this may be sufficient. Due to the high reported rates of mental ill-health women with HG or severe NVP should be screened at first presentation and this should be repeated as indicated, particularly if symptoms are severe and prolonged [LOE- III]. Social isolation is a major risk factor, social work review and support should be assessed in each case and whether daily responsibilities can be delegated to another member of the family (175).

A large population study in the UK assessed more than 8 million pregnancies and examined the hospital records of more than 180,000 hospital admissions for HG, contrary to other studies on NVP, socioeconomic deprivation as measured by the Index of Multiple Deprivation was found to be inversely related to admission for HG (180).

HG has a substantial financial impact upon the individual and upon the economy (181). In a UK study hyperemesis gravidarum was noted to account for 25,000 hospital admissions per year (182).

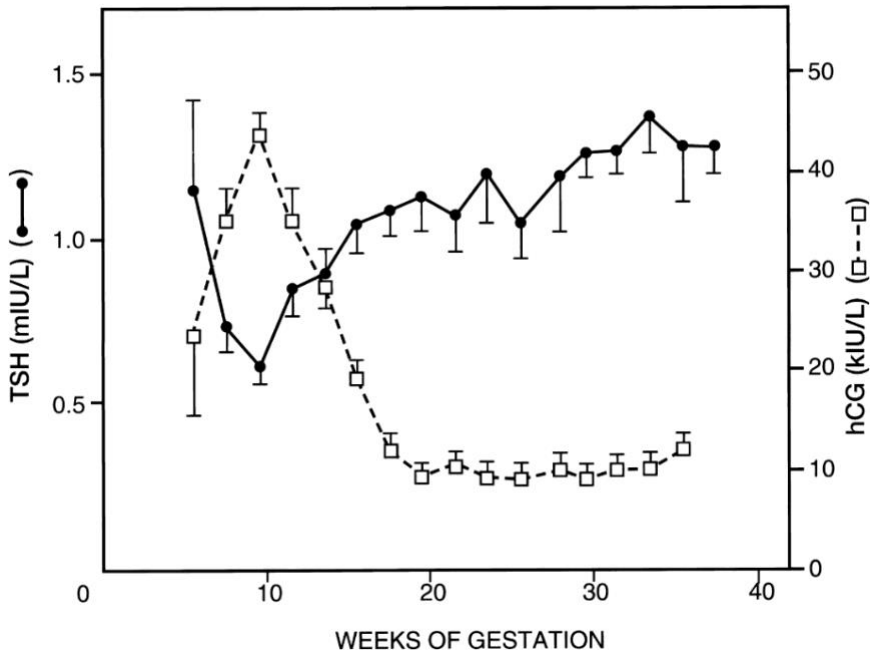
How should NVP/HG-associated gestational hyperthyroxinemia be managed?

Gestational hyperthyroxinemia (GHT), gestational transient thyrotoxicosis or gestational hyperthyroidism is a transient biochemical thyrotoxicosis, which develops in early pregnancy and resolves before 20 weeks gestation. Women do not always have overt signs of hyperthyroidism, and by definition have negative thyroid receptor antibodies. It occurs in approximately 1-3% of women in early pregnancy because placental human chorionic gonadotropin (hCG) is structurally similar to Thyroid Stimulating Hormone (TSH) and can directly stimulate the TSH receptor, increasing thyroid hormone production and suppressing serum TSH (183, 184). In ~50% of cases, gestational hyperthyroidism occurs with HG (185). This stimulatory effect of hCG is usually mild and short lived.

In the majority of prospective comparative studies, women with HG were more likely to have an elevated free thyroxine (T4) (9 of 13 studies) and lower TSH (8 of 15 studies) but the incidence of GHT has been highly variable between studies (21). Goldman and Mestman described an incidence of GHT of between 30 and 73% and related the risk to the severity of HG, ethnicity (with South Asian women having a greater risk) and a history of Graves' disease (186). The increased incidence of GHT seen in women with HG may be due to higher levels of circulating hCG, the production of altered forms of hCG with increased potency to stimulate the TSH receptor and/or hypersensitive TSH receptors more easily stimulated by hCG (21, 186-188). Some, but not all studies, have shown a positive correlation between hCG levels, the severity of vomiting and the degree of thyroid stimulation but in general, hyperthyroidism resolves as hCG and vomiting decline, usually in the early second trimester (Figure 3) (21, 187, 189-191).

Other conditions with elevated hCG levels and hyperthyroxinemia include multiple gestation, hydatidiform mole and choriocarcinoma. These are also characterized by an increased risk of HG (186, 192, 193) .

Figure 3: TSH and hCG levels as pregnancy progresses (Reproduced under CC-BY NC) (194) .



There is disagreement as to which thyroid function tests (TFTs), if any, should be measured in women with HG or NVP. Some guidelines suggest all women with HG should have TFTs (195), whilst others recommend just checking TSH (183), or only testing when clinical features of overt hyperthyroidism are also present (69) or if women are refractory to treatment for HG (6, 69, 70). If clinical features of thyrotoxicosis are present, the rationale for testing thyroid function is to distinguish GHT from other causes of overt hyperthyroidism, which may require specific treatment and fetal monitoring due to potential adverse maternal and fetal outcomes (196). Autoimmune Graves' disease is the most common alternative cause of hyperthyroidism in women with HG, diagnosed in 11% in one study (197).

In pregnancy, measurement of TSH varies slightly but not significantly with different methods of analysis (183). Measurement of TSH only, with reference to trimester specific normal ranges, is a highly sensitive and reproducible screening test for potential thyrotoxicosis (198). Any subnormal serum TSH value should be evaluated in conjunction with serum free T4 and T3 values. If abnormal thyroid function is detected, further thyroid assessment should be guided by clinical consideration of alternate causes. Table 8 outlines clinical and diagnostic features which distinguish between GHT and the most common other causes of hyperthyroidism.

Table 8. Clinical and diagnostic features, which distinguish between GHT and the most common other causes of hyperthyroidism.

	Gestational hyper-thyroxinemia	Graves' disease	Thyroiditis: autoimmune or viral	Toxic goiter: multinodular or adenoma	Iatrogenic or factitious use of thyroxine
Distinguishing Symptoms					
Associated vomiting	Yes				
History of prior thyroid disease		Variable		Goitre or known nodule may predate pregnancy	Possible history of indication for thyroxine
Clinical symptoms of hyperthyroidism prior to pregnancy		Yes	Variable	Variable	Variable
Distinguishing Signs					
Goitre	No	Variable	Variable	Yes with nodularity	No
Ophthalmopathy	Rarely lid lag, stare	Lid lag , stare proptosis and/or periorbital edema	Rarely lid lag, stare	Rarely lid lag, stare	Rarely lid lag, stare
Dermopathy	No	Rarely	No	No	No
Investigations					
TSH receptor antibody positive	No	Yes	No	No	No
Thyroid peroxidase antibody (TPOAb)*	Usually negative	Variable	Majority	No	Variable
Other investigations†				Thyroid ultrasound	
Duration of TSH suppression	< 20 weeks gestation	Variable but may also improve by 16 weeks	Variable	Variable	Variable

Management of GHT associated with HG is supportive only, with appropriate treatment of the HG (183, 195). All current guidelines agree that anti-thyroid medication is not indicated as GHT is self-limiting and does not impact specifically on maternal or pregnancy/fetal outcomes (6, 69, 70, 183, 195, 196). TFTs can be rechecked after resolution of the HG or around 16-20 weeks gestation, to confirm that TSH has returned to normal. TSH suppression persisting beyond 20 weeks gestation may indicate another cause of hyperthyroidism, which will require investigation.

Based on this information, this Guideline recommends the following:

- Do not measure TFTs in women with nausea and vomiting of pregnancy and no diagnostic criteria for HG.
- TSH should be measured in women with HG or NVP refractory to treatment, or in women with signs and/or symptoms of thyrotoxicosis.
    - If TSH is below the normal gestational corrected reference range, the following additional investigations should be performed to exclude an alternate cause:
        - Repeat TSH, free T4, free T3
        - Thyroid antibodies including thyroid peroxidase and thyroid receptor
        - Thyroid Ultrasound if there is goitre, particularly with nodularity
- If an alternative cause for hyperthyroidism is suspected/confirmed, the woman should be referred to the appropriate specialists eg physician or endocrinologist, as well as a specialist obstetrician for ongoing assessment and management of thyroid disease during pregnancy and post-partum. Appropriate management of associated HG should continue.
- Management of women who have GHT is supportive with appropriate treatment of the HG; anti thyroid medications are not required. Specialist referral is not required.

What impact does NVP and HG have on pregnancy and neonatal outcome?

Pregnancy Outcomes

HG was once associated with increased maternal mortality, however, with improved access to parenteral and enteral nutrition this is now uncommon. From 2012-2016, there were six internationally reported maternal deaths related to complications from HG (199). The reported sequelae of HG are now rare but included Wernicke's encephalopathy (vitamin B1 deficiency), bleeding diathesis (vitamin K deficiency), acute kidney injury, splenic avulsion, oesophageal rupture, pneumo-mediastinum and rhabdomyolysis (200-202). With current practice, severe cases of HG are more commonly associated with nutritional and electrolyte disturbance requiring intravenous

hydration and electrolyte replacement, enteral feeding or total parental nutrition. The debilitating nature of the symptoms and the intensive therapies required have significant personal and economic impacts for expectant mothers and therefore significantly influence emotional and psychological wellbeing (41). This is highlighted by the fact that in an international survey of women with a history of HG (168), 15% reported having at least one elective termination of pregnancy because of the condition, with the most common reasoning being 'no hope of relief'.

Post-partum and future health

One study of women with HG, recruited from an internet website, assessed post partum outcomes (203). They described high levels of post traumatic stress syndrome, assessed by questionnaire, with a number of associated negative outcomes including inability to breastfeed, marital problems, financial problems, and inability to self care. A recent prospective cohort study examining risk factors for breast cancer has demonstrated that a history of HG increases the risk of HER-2 enriched breast cancers (HR 1.76 [1.07–2.87]) (204). A single case-control study has suggested having ever been treated for NVP was associated with an increased risk of breast cancer, especially in women experiencing recent pregnancies (OR 2.03 [1.05-3.92]) (205).

Neonatal Outcomes

A recent systematic review demonstrated that NVP is associated with a favourable effect on the rate of miscarriage, congenital malformations, prematurity and childhood performance intelligence quotient (IQ) (206). In a recent prospective study of women with previous early pregnancy loss, there was a reduced risk of clinical pregnancy loss for women with nausea alone (OR 0.20 [0.09-0.44]) or NVP (OR 0.44 [0.26-0.74]), even after adjustment for the covariates of age, parity, smoking status and karyotype (207). The Norwegian Mother and Child Cohort has shown adverse pregnancy outcomes in women with NVP or nausea without vomiting (NP) including increased odds for pelvic girdle pain and proteinuria, whilst women with NVP also had increased risk of high blood pressure and preeclampsia although the authors themselves stressed that in most cases the hypertension was borderline only (208). However, the women with NVP had significantly higher rates of these complications in previous pregnancies as well. Conversely, in the same study, the women with nausea in pregnancy had a lower incidence of preterm births, birth via emergency caesarean delivery, low birth weight or a small for gestational age (SGA) newborn and had lower odds of an Apgar score <7 at birth. A more recent cohort study specifically investigated the relationship between vomiting, not treated with anti-emetics, and birth weight. In contrast to the Norwegian Mother and Child Cohort study that included women who obtained treatment for NP and NVP, this study

demonstrated a significant association between low birth weight and untreated vomiting in pregnancy (OR 3.5, p = 0.03) (209).

HG, in contrast, has been associated with placental dysfunction. A 2011 meta-analysis concluded that women with HG were more likely to have a small baby (low birth weight OR 1.42 [1.27–1.58], SGA OR 1.28 [1.02–1.60]) or a baby born preterm (OR 1.32 [1.04–1.68]) (210). A more recent study has revealed that women admitted with HG in the second trimester have twice the risk of preterm preeclampsia (OR 2.09 [1.38–3.16]), a threefold increased risk of placental abruption (OR 3.07 [1.88–5.00]) and an increased risk of an SGA newborn (1.39 [1.06–1.83]) (211). It is unclear whether HG is associated with an increased risk of stillbirth (210, 212). There are limited long term follow-up studies of the offspring of pregnancies with HG but newer evidence suggests they may have an increased risk of impaired insulin sensitivity in childhood (p=0.01) which may translate into an increased risk of type 2 diabetes, hypertension and heart disease in later life (213). One long term neurodevelopment study compared the cognitive abilities of children born to mothers hospitalised with severe HG with those managed as outpatients for milder NVP. Children of hospitalised mothers had significantly lower median scores on verbal (p = 0.04), performance (p = 0.03) and full scale IQ (p = 0.05). Duration of hospitalization, maternal depression, and maternal IQ were significant predictors of these outcomes emphasising the potential benefit of appropriate management with holistic care including psychosocial support (214).

What is the recurrence risk of NVP and HG?

As NVP is such a common symptom, the risk of recurrence is very high. Klebanoff et al reported recurrence rates of 54-83% (19). The risk of recurrent HG is more difficult to quantify. In a large cohort study based on data from the Medical Birth Registry of Norway, 1967–1998, the risk of hyperemesis was 15% in the second pregnancy in women with and 0.7% in women without previous HG (OR 26.4 [24.2, 28.7]) (215). In the UK study of Fiaschi, of those women admitted to hospital with HG in one pregnancy, 26% had an admission for HG in their subsequent pregnancy (35). However, admitted patients may not reflect the broad spectrum of women with HG.

The risk of recurrent HG is impacted by the unwillingness of some women to consider another pregnancy as demonstrated by the survey results of 100 women with one pregnancy affected by HG, recruited from a website sponsored by the Hyperemesis Education and Research Foundation (216). Although potentially a selected group of women, 37% responded that they were unwilling to become pregnant because of their experience of HG, whilst 57% had a further pregnancy. Of these, 81% had recurrent severe NVP and only 11% had no NVP.

A systematic review of recurrence risk has been proposed but has not yet been published (217).

What is the role of preconceptual counselling for NVP and HG?

In cases of subsequent pregnancy, early or even pre-emptive commencement of antiemetic therapy gives both physical and emotional relief for women who have previously experienced severe NVP or HG (218) [LOE-II]. One older study has suggested that a periconceptual multivitamin and mineral preparation commenced one month prior to planned conception, resulted in a reduced incidence of NVP (3.4 v 7.4% $p<0.01$) (219) [LOE-II].

Although there is no trial data to inform this area of practice, preconceptual counselling can provide information and reassurance to a woman previously affected by NVP or HG. It also allows planning for early, effective management if symptoms of NVP or HG occur.

References

1. Heitmann K, Svendsen HC, Sporsheim AH et al. Nausea in pregnancy: attitudes among pregnant women and general practitioners on treatment and pregnancy care. Scand J Prim Health Care. 2016;34(1):13-20.
2. Merlin T, Weston A, Tooher R et al. NHMRC levels of evidence and grades for recommendations for developers of guidelines. National Health and Medical Research Council (NHRMC) Canberra, ACT: Australian Government. 2009.
3. Koot M, Boelig R, Hooft J et al. Variation in hyperemesis gravidarum definition and outcome reporting in randomised clinical trials: a systematic review. BJOG. 2018;125:1514-21.
4. London V, Grube S, Sherer DM et al. Hyperemesis Gravidarum: A Review of Recent Literature. Pharmacology. 2017;100(3-4):161-71.
5. WHO. International statistical classification of diseases and related health problems: tenth revision. ISBN. 2004;92(4).
6. RCOG. The Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum 2016; Green Top Guideline No. 69 [Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg69-hyperemesis.pdf.
7. McCarthy FP, Lutomski JE, Greene RA. Hyperemesis gravidarum: current perspectives. Int J Women's Health. 2014;6:719.
8. Niemeijer MN, Grooten IJ, Vos N et al. Diagnostic markers for hyperemesis gravidarum: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014;211(2):150 e1-15.
9. Rhodes VA, McDaniel RW, editors. The Index of Nausea, Vomiting, and Retching: a new format of the lndex of Nausea and Vomiting. Oncol Nurs Forum. 1999;26(5):889-94.
10. Koren G, Magee L, Attard C et al. A novel method for the evaluation of the severity of nausea and vomiting of pregnancy. Eur J Obstet Gynecol ReprodBiol. 2001;94(1):31-6.
11. Ebrahimi N, Maltepe C, Bournissen FG et al. Nausea and vomiting of pregnancy: using the 24-hour Pregnancy-Unique Quantification of Emesis (PUQE-24) scale. JOGC. 2009;31(9):803-7.
12. Einarson TR, Piwko C, Koren G. Quantifying the global rates of nausea and vomiting of pregnancy: a meta analysis. J Pop Ther Clin Pharmacol. 2013;20(2):e171-83.
13. Tan A, Lowe S, Henry A. Nausea and vomiting of pregnancy: Effects on quality of life and day-to-day function. Aust N Z J Obstet Gynaecol. 2017;58:278-90.
14. Zhou Q, O'Brien B, Soeken K. Rhodes Index of Nausea and Vomiting—Form 2 in Pregnant Women: A Confirmatory Factor Analysis. Nurs Res. 2001;50(4):251-7.

15. Jordan V, MacDonald J, Crichton S et al. The incidence of hyperemesis gravidarum is increased among Pacific Islanders living in Wellington. N Z Med J. 1995;108(1006):342-4.
16. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. Br J Gen Pract. 1993;43(371):245-8.
17. Lacroix R, Eason E, Melzack R. Nausea and vomiting during pregnancy: a prospective study of its frequency, intensity, and patterns of change. AJOG. 2000;182(4):931-7.
18. Louik C, Hernandez-Diaz S, Werler MM, Mitchell AA. Nausea and vomiting in pregnancy: maternal characteristics and risk factors. Paed PerinEpidemiol. 2006;20(4):270-8.
19. Klebanoff MA, Koslowe PA, Kaslow R et al. Epidemiology of vomiting in early pregnancy. Obstet Gynecol. 1985;66(5):612-16.
20. Bustos M, Venkataramanan R, Caritis S. Nausea and vomiting of pregnancy - What's new? Auton Neurosci. 2017;202:62-72.
21. Verberg MFG, Gillott DJ, Al-Fardan N et al. Hyperemesis gravidarum, a literature review. Hum Reprod Update. 2005;11(5):527-39.
22. Grooten IJ, Den Hollander WJ, Roseboom TJ et al. Helicobacter pylori infection: a predictor of vomiting severity in pregnancy and adverse birth outcome. AJOG. 2017;216(5):512.e1-.e9.
23. Ng QX, Venkatanarayanan N, De Deyn M et al. . A meta-analysis of the association between Helicobacter pylori (H. pylori) infection and hyperemesis gravidarum. Helicobacter. 2018;23(1):e12455.
24. Sandven I, Abdelnoor M. Critical appraisal of case-control studies of risk factors or etiology of Hyperemesis gravidarum. Arch Gynecol Obstet. 2010;282(1):1-10.
25. Kramer J, Bowen A, Stewart N et al. Nausea and vomiting of pregnancy: prevalence, severity and relation to psychosocial health. Am J of Mat Child Nursing. 2013;38(1):21-7.
26. Colodro-Conde L, Cross SM, Lind PA et al. Cohort Profile: Nausea and vomiting during pregnancy genetics consortium (NVP Genetics Consortium). Int J Epidemiol. 2017;46(2):e17-e.
27. Colodro-Conde L, Jern P, Johansson A et al. Nausea and vomiting during pregnancy is highly heritable. Behav Genet. 2016;46(4):481-91.
28. Gadsby R, Barnie-Adshead AM, Jagger C. Pregnancy nausea related to women's obstetric and personal histories. Gynecol Obstet Investig. 1997;43:108-11.
29. Fejzo MS Ingles SA, Wilson M et al. High prevalence of severe nausea and vomiting of pregnancy and hyperemesis gravidarum among relatives of affected individuals. Eur J Obstet Gynecol Reprod. 2008;141:13-7.
30. Zhang Y, Cantor RM, MacGibbon K et al. Familial aggregation of hyperemesis gravidarum. AJOG. 2011;204(3): e1-230.e7.

31. Fejzo MS, Myhre R, Colodro-Conde L et al. Genetic analysis of hyperemesis gravidarum reveals association with intracellular calcium release channel (RYR2). Mol Cell Endocrinol. 2017;439:308-16.

32. Haghighat M, Rafie SM, Dehghani SM et al. Cyclic vomiting syndrome in children: experience with 181 cases from southern Iran. World J Gastroenterology. 2007;13(12):1833.

33. Fejzo MS, Sazanova O, Sathirapongsasuti JF et al. Placenta and appetite genes GDF15 and IGFBP7 are associated with hyperemesis gravidarum. NatCommun. 2018;9(1):1178.

33a. Fejzo MS, Fasching PA, Schneider MO et al. Geburtshilfe Frauenheilkd. 2019 Apr; 79(4): 382–388.

34. Vellacott ID, Cooke EJA, James CE. Nausea and vomiting in early pregnancy. Int J Gynecol Obstetr. 1988;27(1):57-62.

35. Fiaschi L, Nelson-Piercy C, Tata LJ. Hospital admission for hyperemesis gravidarum: a nationwide study of occurrence, reoccurrence and risk factors among 8.2 million pregnancies. Hum Reprod. 2016;31(8):1675-84.

36. Tan PC, Jacob R, Quek KF et al. Pregnancy outcome in hyperemesis gravidarum and the effect of laboratory clinical indicators of hyperemesis severity. J Obstet Gynaecol Res. 2007;33(4):457-64.

37. Chraïbi Z, Ouldamer L, Body G et al Hyperemesis gravidarum : étude de cohorte rétrospective française (109 patientes). La Presse Médicale. 2015;44(1):e13-e22.

38. Morali GA, Braverman DZ. Abnormal liver enzymes and ketonuria in hyperemesis gravidarum. A retrospective review of 80 patients. J Clin Gastroenterol. 1990;12(3):303-5.

39. Goel A, Jamwal KD, Ramachandran A, Balasubramanian KA, Eapen CE. Pregnancy-related liver disorders. J Clin Exper Hepatology. 2014;4(2):151-62.

40. Lee NM, Saha S. Nausea and vomiting of pregnancy. Gastroenterol Clin North Am. 2011;40(2):309-34.

41. Jueckstock JK, Kaestner R, Mylonas I. Managing hyperemesis gravidarum: a multimodal challenge. BMC Med. 2010;8:46.

42. Firoz T, Maltepe C, Einarson A. Nausea and vomiting in pregnancy is not always nausea and vomiting of pregnancy. JOGC. 2010;32(10):970-2.

43. Liu M-C Kuo SH, Lin CP et al. Effects of professional support on nausea, vomiting, and quality of life during early pregnancy. Biol Res Nursing. 2013;16(4):378-86.

44. Lombardi DG, Istwan NB, Rhea DJ et al. Measuring outpatient outcomes of emesis and nausea management in pregnant women. Managed Care. 2004;13(11):48-52.

45. Khan TN, Karpate S, Shehmar M. Hyperemesis day centre audit. BJOG. 2013;120(Supplement 1):527-8.

46. McCarthy FP, Murphy A, Khashan AS et al. Day care compared with inpatient management of nausea and vomiting of pregnancy: a randomized controlled trial. Obstet Gynecol. 2014;124(4):743-8.
47. Murphy A, McCarthy FP, McElroy B et al. Day care versus inpatient management of nausea and vomiting of pregnancy: cost utility analysis of a randomised controlled trial. Europ J Obstet Gynecol Reprod Biol. 2016;197:78-82.
48. Morris ZH, Azab AN, Harlev S et al. Developing and validating a prognostic index predicting re-hospitalization of patients with Hyperemesis Gravidarum. Europ J Obstet Gynecol Reprod Biol. 2018;225:113-7.
49. Frawley J, Hall H, Adams J et al. Health care utilisation of women who experience pregnancy-related reflux, nausea and/or vomiting. J Mat-Fetal Neonat Med. 2017;30(16):1938-43.
50. Heitmann K, Holst L, Lupattelli A et al. Treatment of nausea in pregnancy: a cross-sectional multinational web-based study of pregnant women and new mothers. BMC Preg Childbirth. 2015;15:321.
51. O'Donnell A, McParlin C, Robson SC et al. Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: a systematic review and economic assessment. Health Technol Assess. 2016;20(74):1-268.
52. Boelig RC, Barton SJ, Saccone G et al. Interventions for treating hyperemesis gravidarum: a Cochrane systematic review and meta-anaysis. Fetal Neonat Med. 2016;31(1):2492-2505.
53. Matthews A, Haas DM, O'Mathúna DP et al. Interventions for nausea and vomiting in early pregnancy. Cochrane Database of Systematic Reviews. 2015(9): Art. No.: CD007575. DOI: 10.1002/14651858.CD007575.pub.
54. McParlin C, O'Donnell A, Robson SC et al. Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: a systematic review. JAMA. 2016;316(13):1392-401.
55. Chou FH, Avant KC, Kuo SH. Relationships between nausea and vomiting, perceived stress, social support, pregnancy planning and psychosocial adaptation in a sample of mothers: a questionnaire survey. Int J Nurs Stud. 2007;45(8):1185-91.
56. Magee LA, Chandra K, Mazzotta P et al. Development of a health-related quality of life instrument for nausea and vomiting of pregnancy. AJOG. 2002;186(5 Suppl):S232-8.
57. O'Hara ME. Women's experience of hyperemesis gravidarum: results of self reported online surveys. 2013. InLondon, Biopyschosocial Understandings of Hyperemesis Gravidarum, 2nd National Conference, Pregnancy Sickness Support 2013
58. Bai G, Korfage IJ, Groen EH et al. Associations between nausea, vomiting, fatigue and health-related quality of life of women in early pregnancy: The Generation R Study. PLoS ONE. 2016;11(11):e0166133.

59. van Lier D, Manteuffel, B., Dilorio, C et al. Nausea and fatigue during early pregnancy. Birth. 1993;20(4):193-7.

60. O'Brien B, Naber S. Nausea and vomiting during pregnancy: effects on the quality of women's lives. Birth. 1992;1992(19):138-43.

61. Chandra K, Magee L, Einarson A et al. Nausea and vomiting in pregnancy: results of a survey that identified interventions used by women to alleviate their symptoms. J Psychosom Obstet Gynecol. 2003;24(2):71-5.

62. O'Brien B, Relyea J, Lidstone T. Diary reports of nausea and vomiting during pregnancy. Clin Nurs Res. 1997;6:239-52.

63. Crozier SR, Inskip, HM, Godfrey,KM et al. Nausea and vomiting in early pregnancy: Effects on food intake and diet quality. Mat Child Nutr. 2017;13(e):12389.

64. Pepper GV, Craig Roberts S. Rates of nausea and vomiting in pregnancy and dietary characteristics across populations. Proceedings of the Royal Society of London - Series B: Biological Sciences. 2006;273(1601):2675-9.

65. Chortatos A, Haugen M, Iversen P et al. Nausea and vomiting in pregnancy: associations with maternal gestational diet and lifestyle factors in the Norwegian Mother and Child Cohort Study. BJOG. 2013;120:1642-53

66. Signorello LB, Harlow BL, Wang S et al. Saturated fat intake and the risk of severe hyperemesis gravidarum. Epidemiol. 1998;9(6):636-40.

67. Kallen B, Lundberg G, Aberg A. Relationship between vitamin use, smoking, and nausea and vomiting of pregnancy. Acta Obstet Gynecol Scand. 2003;82(10):916-20.

68. Weigel MM, Weigel RM. The association of reproductive history, demographic factors, and alcohol and tobacco consumption with the risk of developing nausea and vomiting in early pregnancy. Am J Epidemiology. 1988;127(3):562-70.

69. Campbell K, Rowe H, Azzam H et al. The management of nausea and vomiting of pregnancy. JOGC. 2016;38(12):1127-37.

70. ACOG. ACOG Practice Bulletin No. 189: Nausea and vomiting of pregnancy. Obstet Gynecol. 2018;131(1):e15-e30.

71. Jednak MA, Shadigian EM, Kim MS et al. Protein meals reduce nausea and gastric slow wave dysrhythmic activity in first trimester pregnancy. Am J Physiol-Gastrol Liver Physiol. 1999;277(4):G855-G61.

72. Smith C, Crowther C. The placebo response and effect of time in a trial of acupuncture to treat nausea and vomiting in early pregnancy. Complementary Ther Med. 2002;10(4):210-6.

73. Knight B, Mudge C, Openshaw S et al. Effect of acupuncture on nausea of pregnancy: a randomized, controlled trial. Obstet Gynecol. 2001;97(2):184-8.
74. Adlan AS, Chooi KY, Mat Adenan NA. Acupressure as adjuvant treatment for the inpatient management of nausea and vomiting in early pregnancy: A double-blind randomized controlled trial. J Obstet Gynaecol Res. 2017;43(4):662-8.
75. McCormack D. Hypnosis for hyperemesis gravidarum. J Obstet Gynaecol. 2010;30(7):647-53.
76. Gill SK, Maltepe C, Koren G. The effectiveness of discontinuing iron-containing prenatal multivitamins on reducing the severity of nausea and vomiting of pregnancy. J Obstet Gynaecol. 2009;29(1):13-6.
77. Abeywardana S SE. Congenital anomalies in Australia 2002–2003. : AIHW National Perinatal Statistics Unit.2008:1-177.
78. McParlin C, Carrick-Sen D, Steen IN et al. Hyperemesis in Pregnancy Study: a pilot randomised controlled trial of midwife-led outpatient care. Europ J Obstet Gynecol Reprod Biol. 2016;200:6-10.
79. Mazzotta P, Magee LA. A Risk-Benefit Assessment of Pharmacological and Nonpharmacological Treatments for Nausea and Vomiting of Pregnancy. Drugs. 2000;59(4):781-800.
80. Gilboa SM, Ailes EC, Rai RP et al. Antihistamines and birth defects: a systematic review of the literature. Exp Opin Drug Safety. 2014;13(12):1667-98.
81. Dante G, Pedrielli G, Annessi E et al. Herb remedies during pregnancy: a systematic review of controlled clinical trials. The J Mat Fetal Neonat Med. 2013;26(3):306-12.
82. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk: Lippincott Williams & Wilkins; 2012.
83. Tan PC, Khine PP, Vallikkannu N et al. Promethazine compared with metoclopramide for hyperemesis gravidarum: a randomized controlled trial. Obstet Gynecol. 2010;115(5):975-81.
84. Mayhall EA, Gray R, Lopes V et al. Comparison of antiemetics for nausea and vomiting of pregnancy in an emergency department setting. Am J Emerg Med. 2015;33(7):882-6.
85. Furyk JS, Meek RA, Egerton-Warburton D. Drugs for the treatment of nausea and vomiting in adults in the emergency department setting. Cochrane Database of Systematic Reviews. 2015(9):CD010106.
86. Kashifard M, Basirat Z, Kashifard M et al. Ondansetrone or metoclopromide? Which is more effective in severe nausea and vomiting of pregnancy? A randomized trial double-blind study. Clin Exper Obstetr Gynecol. 2013;40(1):127-30.
87. Abas MN, Tan PC, Azmi N et al. Ondansetron compared with metoclopramide for hyperemesis gravidarum: a randomized controlled trial. Obstet Gynecol. 2014;123(6):1272-9.

88. Carstairs SD. Ondansetron use in pregnancy and birth defects: a systematic review. Obstet Gynecol. 2016;127(5):878-83.

89. Andersen JT, Jimmenez-SolemE, Andersen NL et al Ondansetron use in early pregnancy and the risk of congenital malformations. J Int Soc Pharmacoepidemiol. 2013;22:13-4.

90. Danielsson B Wikner B, Källén B Use of ondansetron during pregnancy and congenital malformations in the infant. Reprod Toxicol. 2014;50(Supplement C) 134-7.

91. Parker SE, Van Bennekom C, Anderka M et al. Gynecology. Ondansetron for treatment of nausea and vomiting of pregnancy and the risk of specific birth defects. Obstet Gynecol. 2018;132(2):385-94.

92. Anderka M, Mitchell AA, Louik C et al. Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. Birth Defects Res Part A: Clinical and Molecular Teratology. 2012;94(1):22-30.

93. Einarson A, Maltepe C, Navioz Y et al. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. BJOG. 2004;111(9):940-3.

94. Asker C, Wikner B, Källén B. Use of antiemetic drugs during pregnancy in Sweden. Europ J Clin Pharmacol. 2005;61(12):899.

95. Colvin L, Gill AW, S lack-Smith L et al. Off-label use of ondansetron in pregnancy in Western Australia. BioMed Research International. 2013;Article ID 909860.

96. Pasternak B SSvanström H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. N Eng J Med. 2013;368(9):814-23.

97. Zambelli-Weiner A, Via C, Yuen M et al. First trimester ondansetron exposure and risk of structural birth defects. Reprod Toxicol.2019;83:14-20.

98. Huybrechts KF, Hernández-Díaz S, Straub L et al. Association of Maternal First-Trimester Ondansetron Use With Cardiac Malformations and Oral Clefts in Offspring. JAMA. 2018;320(23): 2429-37.

98a. Richardson JL, Keskin-Arslan E, Erol-Coskun H. Maternal ondansetron use and the risk of congenital malformations; an updated meta-analysis. Reprof Toxicol. 2019;88:129.

99. Taylor LG, Bird ST, Sahin L, et al. Antiemetic use among pregnant women in the United States: the escalating use of ondansetron. Pharmacoepidemiology & Drug Safety. 2017;26(5):592-6.

100. Lehmann AS, Renbarger JL, McCormick CL et al. Pharmacogenetic predictors of nausea and vomiting of pregnancy severity and response to antiemetic therapy: a pilot study. BMC Preg Childbirth. 2013;13:132.

101. Kemp MW, Newnham JP, Challis JG et al. The clinical use of corticosteroids in pregnancy. Hum Reprod Update. 2016;22(2):240-59.

102. Safari HR, Fassett MJ, Souter IC et al. The efficacy of methylprednisolone in the treatment of hyperemesis gravidarum: a randomized, double-blind, controlled study. Am J Obstet Gynecol. 1998;179(4):921-4.
103. Nelson-Piercy C, Fayers P, DeSwiet M. Randomised, double-blind, placebo-controlled trial of corticosteroids for the treatment of hyperemesis gravidarum. BJOG. 2001;108(1):9-15.
104. Yost NP, McIntire DD, Wians FH et al. A randomized, placebo-controlled trial of corticosteroids for hyperemesis due to pregnancy. Obstet Gynecol. 2003;102(6):1250-4.
105. Ziaei S, Hosseiney FS, Faghihzadeh S. The efficacy low dose of prednisolone in the treatment of hyperemesis gravidarum. Acta Obstet Gynecol Scand. 2004;83(3):272-5.
106. Bondok RS, El Sharnouby NM, Eid HE et al. Pulsed steroid therapy is an effective treatment for intractable hyperemesis gravidarum. Crit Care Med. 2006;34(11):2781-3.
107. Adamczak J, Kasdaglis T, Rinehart B et al. Abstract 277: A prospective randomized trial of solumedrol dose pack vs. phenergan for the treatment of symptomatic nausea and vomiting in pregnancy. Am J Obstet Gynecol. 2007;197(6):S88.
108. Carmichael SL, Shaw GM, Ma C et al. Maternal corticosteroid use and orofacial clefts. Am J Obstet Gynecol. 2007;197(6):585.e1-.e7.
109. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. Am J Med Genetics. 1999;86(3):242-4.
110. Skuladottir H, Wilcox AJ, Ma C et al. Corticosteroid use and risk of orofacial clefts. Birth Defects Res A Clin Mol Teratol. 2014;100(6):499-506.
111. Källén B. Maternal drug use and infant cleft lip/palate with special reference to corticoids. Cleft Palate-Craniofac J. 2003;40(6):624-8.
112. Pradat P, Robert-Gnansia E, Di Tanna GL et al. First trimester exposure to corticosteroids and oral clefts. Birth Defects Res A Clin Mol Teratol. 2003;67(12):968-70.
113. Park-Wyllie L, Mazzotta P, Pastuszak A et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology. 2000;62(6):385-92.
114. Jugessur A, Farlie P, Kilpatrick N. The genetics of isolated orofacial clefts: from genotypes to subphenotypes. Oral Dis. 2009;15(7):437-53.
115. Bandoli G, Palmsten K, Forbess Smith CJ et al. A review of systemic corticosteroid use in pregnancy and the risk of select pregnancy and birth outcomes. Rheum Dis Clin. 2017;43(3):489-502.
116. Shepard TH, Brent RL, Friedman JM et al. Update on new developments in the study of human teratogens. Teratology. 2002;65(4):153-61.

117. Australian Medicines Handbook 2017: Australian Medicines Handbook Pty Ltd; 2018. Available from: https://amhonline.amh.net.au.acs.hcn.com.au/.

118. Klauser CK, Fox NS, Istwan N et al. Treatment of severe nausea and vomiting of pregnancy with subcutaneous medications. Am J Perinat. 2011;28(9):715-21.

119. Reichmann JP, Kirkbride MS. Reviewing the evidence for using continuous subcutaneous metoclopramide and ondansetron to treat nausea & vomiting during pregnancy. Managed Care. 2012;21(5):44-7.

120. Smith JA Refuerzo S, Ramin, SM. Treatment and outcome of nausea and vomiting of regnancy. Up to Date. (Accessed on October 10, 2018.).

121. Koren G, Clark S, Hankins GD et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. Am J Obstet Gynecol. 2010;203(6):571.e1-7.

122. Caritis S, Zhao Y, Chen HJ et al. Pharmacodynamics of transdermal granisetron in women with nausea and vomiting of pregnancy. Am J Obstet Gynecol. 2016;215(1):93.e1-4.

123. Maina A, Arrotta M, Cicogna L et al. Transdermal clonidine in the treatment of severe hyperemesis. A pilot randomised control trial. BJOG. 2014;121(12):1556-62.

124. Guclu S, Gol M, Dogan E et al. Mirtazapine use in resistant hyperemesis gravidarum: report of three cases and review of the literature. Arch Gynecol Obstet. 2005;272(4):298-300.

125. Rohde A, Dembinski J, Dorn C. Mirtazapine (Remergil) for treatment resistant hyperemesis gravidarum: rescue of a twin pregnancy. Arch Gynecol Obstet. 2003;268(3):219-21.

126. Saks BR. Mirtazapine: treatment of depression, anxiety, and hyperemesis gravidarum in the pregnant patient. A report of 7 cases. Archiv Women's Ment Health. 2001;3(4):165-70.

127. Smit M, Dolman KM, Honig A. Mirtazapine in pregnancy and lactation; a systematic review. Eur Neuropsychopharmacol. 2016;26(1):126-35.

128. Guttuso T, Jr., Shaman M, Thornburg LL. Potential maternal symptomatic benefit of gabapentin and review of its safety in pregnancy. Europ J Obstet Gynecol Reprod Biol. 2014;181:280-3.

129. Guttuso T, Jr., Robinson LK, Amankwah KS. Gabapentin use in hyperemesis gravidarum: a pilot study. Early Hum Devel. 2010;86(1):65-6.

130. Tasci Y, Demir B, Dilbaz S et al. Use of diazepam for hyperemesis gravidarum. J Mat Fetal Neonat Med. 2009;22(4):353-6.

131. Ditto A, Morgante G, la Marca A et al. Evaluation of treatment of hyperemesis gravidarum using parenteral fluid with or without diazepam. A randomized study. Gynecol Obstetric Invest. 1999;48(4):232-6.

132. Gill SK, Maltepe C, Koren G. The Effect of Heartburn and Acid Reflux on the Severity of Nausea and Vomiting of Pregnancy. Can J Gastroenterol. 2009;23(4).
133. Gill SK, Maltepe C, Mastali K et al. The effect of acid-reducing pharmacotherapy on the severity of nausea and vomiting of pregnancy. Obstet Gynecol Int. 2009;2009:4.
134. Koch KL. Gastrointestinal factors in nausea and vomiting of pregnancy. Am J Obstet Gynecol. 2002;186(5, Supplement 2):S198-S203.
135. Walsh JW HW, Nugent CE et al. Progesterone and estrogen are potential mediators of gastric slow wave dysrhthmias in nausea of pregnancy. Am J Physiol 1996;270:G506-14. .
136. Devine RE, McCleary N, Sheikh A et al. Acid-suppressive medications during pregnancy and risk of asthma and allergy in children: a systematic review and meta-analysis. J Allergy Clin Immun. 2017;139(6):1985-8. e12.
137. Nikfar S, Abdollahi M, Moretti ME et al. Use of proton pump inhibitors during pregnancy and rates of major malformations: a meta-analysis. Diges Dis Sci. 2002;47(7):1526-9.
138. Mahadevan U, Kane S. American Gastroenterological Association Institute medical position statement on the use of gastrointestinal medications in pregnancy. Gastroenterology. 2006;131(1):278-82.
139. Gill SK, O'Brien L, Koren G. The safety of histamine 2 (H2) blockers in pregnancy: a meta-analysis. Dig Dis Sci. 2009;54(9):1835-8.
140. Gill SK, O'Brien L, Einarson TR et al. The safety of proton pump inhibitors (PPIs) in pregnancy: a meta-analysis. The American Journal of Gastroenterology. 2009;104(6):1541-5.
141. Rungsiprakarn P, Laopaiboon M, Sangkomkamhang US et al. Interventions for treating constipation in pregnancy. Cochrane Database of Systematic Reviews. 2015(9):CD011448.
142. Selby W CC. Managing constipation in adults. Aust Prescr. 2010;33:116-9.
143. Godsey RK, Newman RB. Hyperemesis gravidarum. A comparison of single and multiple admissions. J Reprod Med. 1991;36(4):287-90.
144. Anaïs L, Evelyne R, Ema F et al. Determinants of Early Medical Management of Nausea and Vomiting of Pregnancy. Birth. 2009;36(1):70-7.
145. Goldenberg G, Bharathan T, Shifrin I. Transdermal clonidine in patients with swallowing dysfunction. J Pall Med. 2014;17(9):1042-4.
146. Ahmed M, Elsayed A, Soliman A. Role of Helicobacter pylori eradication in pregnant women with hyperemesis gravidarum. J Evid Based Womens Health. 2017;7:1-6.
147. Chiossi G, Neri I, Cavazzuti M et al. Hyperemesis gravidarum complicated by Wernicke encephalopathy: background, case report, and review of the literature. Obstet Gynecol Surv. 2006;61(4):255-68.

148. Spasovski G, Vanholder R, Allolio B et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Nephrol Dialy Transplant. 2014;29(suppl_2):i1-i39.
149. Tan PC, Norazilah MJ, Omar SZ. Dextrose saline compared with normal saline rehydration of hyperemesis gravidarum: a randomized controlled trial. Obstet Gynecol. 2013;121(2, Part 1):291-8.
150. McCarthy FP, Murphy A, Khashan AS et al. Day Care compared with inpatient management of nausea and vomiting of pregnancy: a randomized controlled trial. Obstet Gynecol. 2014;124(4):743-8.
151. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. Obstet Gynecol. 2009;114(6):1326-31.
152. Grooten IJ, Mol BW, van der Post JAM et al. Early nasogastric tube feeding in optimising treatment for hyperemesis gravidarum: the MOTHER randomised controlled trial (Maternal and Offspring outcomes after Treatment of HyperEmesis by Refeeding). BMC Preg Childbirth. 2016;16:22.
153. Stokke G, Gjelsvik BL, Flaatten KT et al. Hyperemesis gravidarum, nutritional treatment by nasogastric tube feeding: a 10-year retrospective cohort study. Acta Obstet Gynecol Scand. 2015;94(4):359-67.
154. Vaisman N, Kaidar R, Levin I et al. Nasojejunal feeding in hyperemesis gravidarum--a preliminary study. Clin Nutr. 2004;23(1):53-7.
155. Pearce CB, Collett J, Goggin PM et al. Enteral nutrition by nasojejunal tube in hyperemesis gravidarum. Clin Nutr. 2001;20(5):461-4.
156. Saha S, Loranger D, Pricolo V et al. Feeding jejunostomy for the treatment of severe hyperemesis gravidarum: a case series. J Parenter Enteral Nutr. 2009;33(5):529-34.
157. Irving PM, Howell RJ, Shidrawi RG. Percutaneous endoscopic gastrostomy with a jejunal port for severe hyperemesis gravidarum. Euro J Gastroenterol Hepatol. 2004;16(9):937-9.
158. Serrano P, Velloso A, Garcia-Luna PP et al. Enteral nutrition by percutaneous endoscopic gastrojejunostomy in severe hyperemesis gravidarum: a report of two cases. Clin Nutr. 1998;17(3):135-9.
159. Godil A, Chen YK. Percutaneous endoscopic gastrostomy for nutrition support in pregnancy associated with hyperemesis gravidarum and anorexia nervosa. J Parenter Enteral Nutr. 1998;22(4):238-41.
160. Anastasilakis CD, Ioannidis O, Gkiomisi AI et al. Artificial nutrition and intestinal mucosal barrier functionality. Digestion. 2013;88(3):193-208.
161. Peled Y, Melamed N, Hiersch L et al. The impact of total parenteral nutrition support on pregnancy outcome in women with hyperemesis gravidarum. J Mat Fetal Neonat Med. 2014;27(11):1146-50.

162. Christodoulou DK, Katsanos KH, Makrydimas G et al. Peripheral parenteral nutrition in protracted hyperemesis gravidarum--report of two cases and a literature review. Acta Gastro-enterol Belgica. 2008;71(2):259-62.
163. Nuthalapaty FS, Beck MM, Mabie WC. Complications of central venous catheters during pregnancy and postpartum: a case series. Am J Obstet Gynecol. 2009;201(3):311 e1-5.
164. Ogura JM, Francois KE, Perlow JH et al. Complications associated with peripherally inserted central catheter use during pregnancy. Am J Obstet Gynecol. 2003;188(5):1223-5.
165. Holmgren C, Aagaard-Tillery KM, Silver RM et al. Hyperemesis in pregnancy: an evaluation of treatment strategies with maternal and neonatal outcomes. Am J Obstet Gynecol. 2008;198(1):56 e1-4.
166. Cape AV, Mogensen KM, Robinson MK et al. Peripherally inserted central catheter (PICC) complications during pregnancy. J Parenter Enteral Nutr. 2014;38(5):595-601.
167. Majumdar S, Dada B. Refeeding syndrome: a serious and potentially life-threatening complication of severe hyperemesis gravidarum. J Obstet Gynaecol. 2010;30(4):416-7.
168. Poursharif B, Korst LM, Macgibbon KW et al. Elective pregnancy termination in a large cohort of women with hyperemesis gravidarum. Contraception. 2007;76(6):451-5.
169. Al-Ozairi E, Waugh JJ, Taylor R. Termination is not the treatment of choice for severe hyperemesis gravidarum: Successful management using prednisolone. Obstet Med. 2009;2(1):34-7.
169a. Nurmi M, Rautava P, Gissler M et al. Impact of hyperemesis gravidarum on the number of pregnancies and pregnancy terminations. Eur J O G Reprod Biol. 2019;234:e70.
170. Wood H, McKellar LV, Lightbody M. Nausea and vomiting in pregnancy: blooming or bloomin' awful? A review of the literature. Women Birth. 2013;26(2):100-4.
171. Fairweather DV. Nausea and vomiting in pregnancy. Am J Obstet Gynecol. 1968;102(1):135-75.
172. Mazzotta P, Stewart DE, Koren G et al. Factors associated with elective termination of pregnancy among Canadian and American women with nausea and vomiting of pregnancy. J Psychosom Obstet Gynecol. 2001;22(1):7-12.
173. Tan PC, Vani S, Lim BK et al. Anxiety and depression in hyperemesis gravidarum: prevalence, risk factors and correlation with clinical severity. Europ J Obstet Gynecol Reprod Biol. 2010;149(2):153-8.
174. Kjeldgaard HK, Eberhard-Gran M, Benth JS et al. Hyperemesis gravidarum and the risk of emotional distress during and after pregnancy. Arch Womens Ment Health. 2017;20:747-56.
175. Dean C, Bannigan, K, Marsden, J. Reviewing the effect of hyperemesis gravidarum on women's lives and mental health. Br J Midwifery. 2018;26(2):109-19.

176. Dean C. Does the historical stigma of hyperemesis gravidarum impact healthcare professionals' attitudes and treatment towards women with the condition today? A review of recent literature. MIDIRS Midwifery Digest. 2016;26:186.

177. Fejzo MS, Macgibbon K. Hyperemesis gravidarum: it is time to put an end to the misguided theory of a psychiatric etiology. Gen Hosp Psychiatry. 2012;34(6):699-700.

178. Mitchell-Jones N, Gallos, I, Farren, J et al. Psychological morbidity associated with hyperemesis gravidarum, a sytematic review and meta-analysis. BJOG. 2017;124(1):20-30.

179. Aksoy H, Aksoy, U, Karadag et al. Depression levels in patient with hyperemesis gravidarum: a prospective case-control study. Springer Plus. 2015;4(34):1-6.

180. Fiaschi L, Nelson-Piercy C, Tata LJ. Hospital admission for hyperemesis gravidarum: a nationwide study of occurrence, reoccurrence and risk factors among 8.2 million pregnancies. Hum Reprod. 2016;31(8):1675-84.

181. Trovik J, Vikanes A. Hyperemesis Gravidarum is associated with substantial economic burden in addition to severe physical and psychological suffering. Is J Health Policy Res. 2016;5:43.

182. Gadsby R, Barnie-Adshead T. Severe nause and vomiting of pregnancy: should it be treated with appropriate pharmacotherapy? The Obstetrician & Gynaecologist. 2011;13:107-11.

183. Alexander EK, Pearce EN, Brent GA et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid. 2017;27(3):315-89.

184. Glinoer D Soto MF, Bourdoux P et al. Pregnancy in patients with mild thyroid abnormalities: maternal and neonatal repercussions. J Clin Endocrinol Metab.1991;73(2): 421-7.

185. Cooper DS, Laurberg P. Hyperthyroidism in pregnancy. Lancet Diabetes Endocrinol. 2013;1(3):238-49.

186. Goldman AM, Mestman JH. Transient non-autoimmune hyperthyroidism of early pregnancy. J Thyroid Res. 2011; Article ID 142413.

187. Goodwin TM, Hershman JM, Cole L. Increased concentration of the free β-subunit of human chorionic gonadotropin in hyperemesis gravidarum. Acta Obstet Gynecol Scand. 1994;73(10): 770-72.

188. Yoshihara A Noh JK, Mukasa K et al. Serum human chorionic gonadotropin levels and thyroid hormone levels in gestational transient thyrotoxicosis: Is the serum hCG level useful for differentiating between active Graves' disease and GTT? Endocrine. 2015;62(6):557-60.

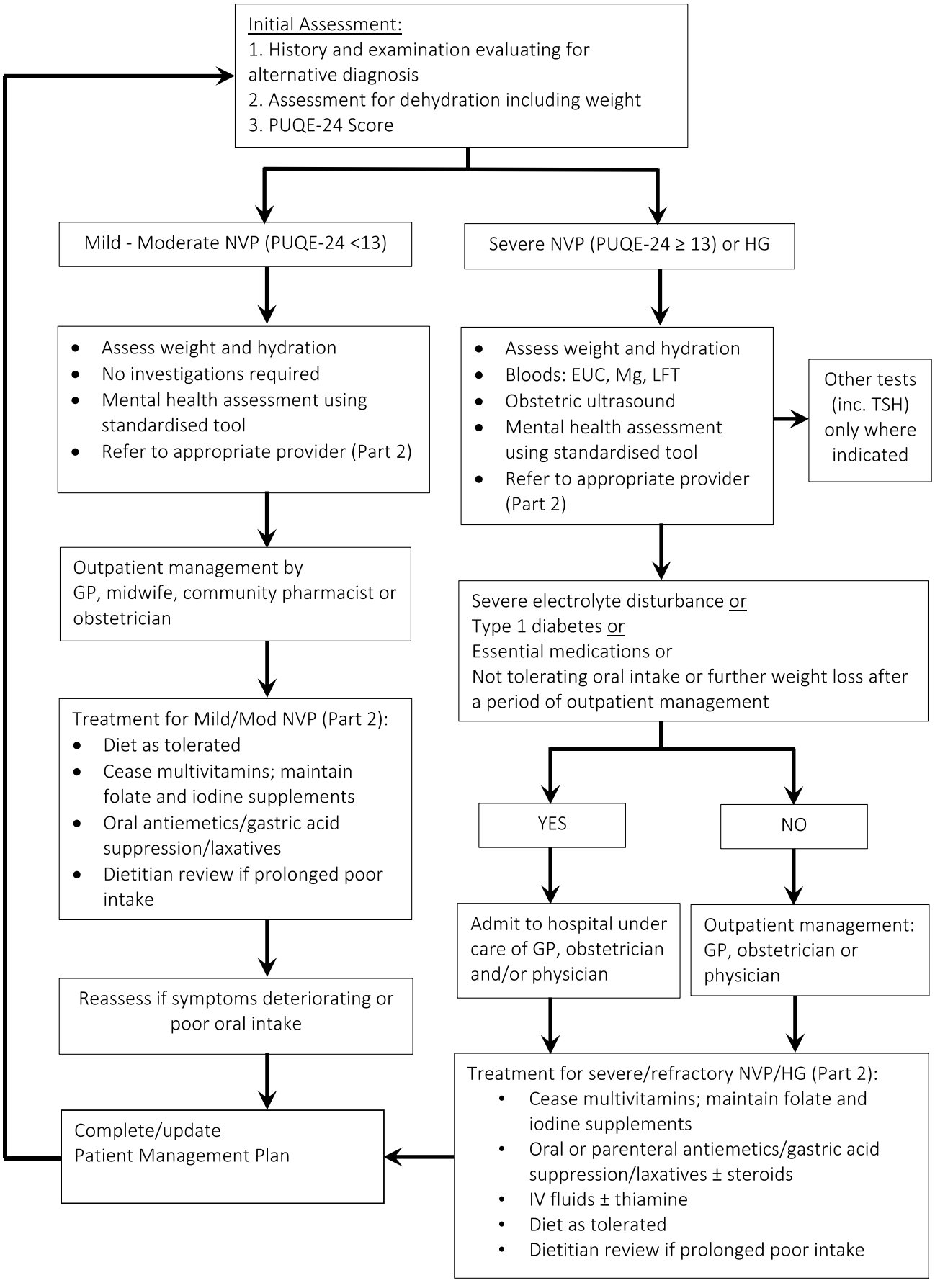
189. Bouillon R Naesens M, Van Assche FA et al Thyroid function in patients with hyperemesis gravidarum. Am J Obstet Gynecol. 1982;143(8):922-6.

190. Tsuruta E Tada H, Tamaki H et al Pathogenic role of asialo human chorionic gonadotropin in gestational thyrotoxicosis. J Clin Endocrinol Metab. 1995;80(2):350-5.

191. Kimura M Amino N, Tamaki H et al Gestational thyrotoxicosis and hyperemesis gravidarum: possible role of hCG with higher stimulating activity. Clin Endocrinol. 1993;38(4):345-50.
192. Grün JP,, Meuris S De Nayer P et al. The thyrotrophic role of human chorionic gonadotrophin (hCG) in the early stages of twin (versus single) pregnancies. Clin Endocrinol. 1997;46(6):719-25.
193. Hershman J. Human chorionic gonadotropin and the thyroid: hyperemesis gravidarum and trophoblastic tumors. Thyroid. 1999;9(7):653-7.
194. Glinoer D, de Nayer P, Bourdoux P et al. Regulation of maternal thyroid during pregnancy. J Clin Endocrinol Metab. 1990;71(2):276-87.
195. De Groot L, Abalovich M, Alexander EK et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(8):2543-65.
196. Abalovich M, Amino N, Barbour LA et al. Management of thyroid dysfunction during pregnancy and postpartum: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2007;92(8 supplement):s1-s7.
197. Tan JY, Loh KC, Yeo GS et al. Transient hyperthyroidism of hyperemesis gravidarum. BJOG. 2002;109(6):683-8.
198. Ross DS, Ardisson LJ, Meskell MJ. Measurement of thyrotropin in clinical and subclinical hyperthyroidism using a new chemiluminescent assay. J Clin Endocrinol Metab. 1989;69(3):684-8.
199. Fejzo MS Macgibbon K, Mullin PM. Why are women still dying from nausea and vomiting of pregnancy? Gynecol Obstet Case Rep. 2016;2(2).
200. Di Gangi S, Gizzo S, Patrelli TS et al. Wernicke's encephalopathy complicating hyperemesis gravidarum: from the background to the present. J Matern Fetal Neonatal Med. 2012;25(8):1499-504.
201. Eroglu A, Kurkcuoglu C, Karaoglanoglu N, et al. Spontaneous esophageal rupture following severe vomiting in pregnancy. Dis Esophagus. 2002;15(3):242-3.
202. Nguyen N, Deitel M, Lacy E. Splenic avulsion in a pregnant patient with vomiting. Can J Surg. 1995;38(5):464-5.
203. Christodoulou-Smith J, Gold JI, Romero R et al. Posttraumatic stress symptoms following pregnancy complicated by hyperemesis gravidarum. J Mat Fetal Neonat Med. 2011;24(11):1307-11.
204. Wright LB, Schoemaker MJ, Jones ME et al. Breast cancer risk in relation to history of preeclampsia and hyperemesis gravidarum: Prospective analysis in the Generations Study. Int J Cancer. 2018;143(4):782-92.
205. Enger SM, Ross RK, Henderson B et al. Breastfeeding history, pregnancy experience and risk of breast cancer. Br J Cancer. 1997;76(1):118-23.

206. Koren G, Madjunkova S, Maltepe C. The protective effects of nausea and vomiting of pregnancy against adverse fetal outcome—a systematic review. Reprod Toxicol. 2014;47:77-80.
207. Hinkle SN, Mumford SL, Grantz KL et al. Association of nausea and vomiting during pregnancy with pregnancy loss: a secondary analysis of a randomized clinical trial. JAMA. 2016;176(11):1621-7.
208. Chortatos A, Haugen M, Iversen PO et al. Pregnancy complications and birth outcomes among women experiencing nausea only or nausea and vomiting during pregnancy in the Norwegian Mother and Child Cohort Study. BMC Preg Childbirth. 2015;15:138.
209. Petry CJ, Ong KK, Beardsall K et al. Vomiting in pregnancy is associated with a higher risk of low birth weight: a cohort study. BMC Preg Childbirth2018;18(1):133.
210. Veenendaal MV, van Abeelen AF, Painter RC et al. Consequences of hyperemesis gravidarum for offspring: a systematic review and meta-analysis. BJOG. 2011;118(11):1302-13.
211. Bolin M, Akerud H, Cnattingius S et al. Hyperemesis gravidarum and risks of placental dysfunction disorders: a population-based cohort study. BJOG. 2013;120(5):541-7.
212. Vandraas KF, Vikanes AV, Vangen S et al. Hyperemesis gravidarum and birth outcomes-a population-based cohort study of 2.2 million births in the Norwegian Birth Registry. BJOG. 2013;120(13):1654-60.
213. Ayyavoo A, Derraik JG, Hofman PLet al. Severe hyperemesis gravidarum is associated with reduced insulin sensitivity in the offspring in childhood. J Clin Endocrinol Metab. 2013;98(8):3263-8.
214. Nulman I, Maltepe C, Farine D, Koren GJO, Gynecology. Neurodevelopment of children after maternal hospitalization for nausea and vomiting of pregnancy. Obstet Gynecol. 2015;125:81S.
215. Magtira A, Schoenberg FP, MacGibbon K et al. Psychiatric factors do not affect recurrence risk of hyperemesis gravidarum. JObstet Gynaecol Res. 2015;41(4):512-6.
216. Fejzo MS, Macgibbon KW, Romero R et al. Recurrence risk of hyperemesis gravidarum. J Midwif Women's Health. 2011;56(2):132-6.
217. Dean C, Bannigan K, O'Hara M et al. Recurrence rates of hyperemesis gravidarum in pregnancy: a systematic review protocol. Database of Systematic Reviews and Implementation Reports. 2017;15(11):2659-65.
218. Maltepe C, Koren G. Preemptive Treatment of Nausea and Vomiting of Pregnancy: Results of a Randomized Controlled Trial. Obstet Gynecol Inter. 2013;2013:809787.
219. Czeizel AE, Dudas I, Fritz G et al. The effect of periconceptional multivitamin-mineral supplementation on vertigo, nausea and vomiting in the first trimester of pregnancy. Archiv Gynecol Obstet. 1992;251(4):181-5.

SOMANZ Management of NVP/HG (Part 1)



SOMANZ Management of NVP/HG (Part 2)

	MILD PUQE-24: <7	MODERATE NVP (PUQE-24: 7-12)	SEVERE NVP (PUQE-24: ≥13) or HG Outpatient management	REFRACTORY SYMPTOMS or in HOSPITAL
General	Diet as tolerated Cease multivitamins (particularly those containing iron); maintain folate and iodine supplements If an antiemetic is ineffective, at maximal dose, discontinue before commencing an alternate agent. If an antiemetic is partially effective, optimise dosage and timing, and only add additional agents after maximal doses of the first agent have been trialled. Add laxatives as required (eg docusate 120 mg 1-2 BD with or without macrogol containing laxatives 1-2/daily)			
Investigations	Nil	Nil	Electrolytes, LFTs: repeat if persistent vomiting or requiring repeated IV fluids TSH if clinically indicated Obstetric US	Repeat electrolytes, LFTs if persistent vomiting or requiring IV fluids
Medications	Pyridoxine 10-50 mg QID PO or Ginger 200-600 mg TDS PO or Ginger plus Pyridoxine PO	One of the following PO up to TDS. Metoclopramide* 10 mg Prochlorperazine* 5 mg Doxylamine* 6.25-25 mg Promethazine* 25 mg or Ondansetron 4-8mg To avoid sedation and for prolonged use ie more than 5 days, preferentially use ondansetron during the day	Ondansetron 4-8 mg PO/IV BD-TDS and Consider night time dosing with either: Metoclopramide* 10 mg PO/IV or Prochlorperazine* 5-10 mg PO/IV or Doxylamine* 6.25-25 mg PO or Cyclizine 12.5-50 mg PO/IV and Consider prednisone: commence 40-50mg OD or hydrocortisone 100mg IV BD and wean prednisone over 7-10 days to minimal effective dose. May need to continue until symptoms resolve.	As for severe NVP/HG Convert to parenteral: IV/IM or subcutaneous treatment if not tolerating oral Convert back to oral equivalent when suitable.
Additional treatment		H2 antagonist PO BD eg Ranitidine 150-300 mg IV fluids 1-3 x per week as required	Cease H2 antagonist and substitute PPI PO BD eg esomeprazole or rabeprazole 20 mg IV fluids 1-3 x per week as required: add IV thiamine if poor oral intake or administering dextrose.	Continue PPI PO or IV if not tolerated. Continuous IV fluid and electrolyte replacement. Add IV thiamine if poor oral intake or administering dextrose Consider total parenteral nutrition
Treatment supervision and site	GP, midwife, obstetrician or community pharmacist Outpatient	GP or obstetrician Outpatient/Day Stay/Emergency Room	Obstetrician and/or physician Outpatient/Day Stay/Emergency Room	Obstetrician and physician Admit to hospital

OD: once a day, BD: twice a day, TDS: three times a day, QID: four times a day, PO: oral, IV: intravenous, H2: histamine 2, PPI: proton pump inhibitor, TSH: thyroid stimulating hormone.
Electrolytes: sodium, potassium, chloride, bicarbonate, magnesium, urea and creatinine, LFTs: Bilirubin, Alanine Transaminase, Aspartate Aminotransferase, Albumin.

SOMANZ
SOCIETY OF OBSTETRIC MEDICINE OF AUSTRALIA AND NEW ZEALAND

Sickness and Vomiting in Pregnancy
Patient information

Many pregnant women feel sick (nausea) or vomit during early pregnancy. This can vary from mild when it can be considered a normal part of pregnancy. If you can continue to eat and drink even with the sickness, this is considered reasonably normal. The exact cause of the sickness is not known but is probably due to the hormonal changes of early pregnancy.

It can occur more commonly in some families (genetic tendency), if you have twins or triplets, if your baby is a girl and if you had sickness and vomiting in your previous pregnancies. We don't really understand why some women suffer more, but the most important thing to know is that it's not your fault and it doesn't mean there is anything wrong with your pregnancy.

In this leaflet we answer some common questions about nausea and vomiting in pregnancy and provide some guidance for where you can get more information and help if you need it.

Although it is often called morning sickness, symptoms can occur at any time - not just in the morning. It usually starts from the early part of pregnancy and settles between 12 and 16 weeks. Rarely, women have some sickness throughout their entire pregnancy.

Even mild sickness and vomiting in pregnancy can be difficult to cope with. It can affect your mood, your work, your home situation and your ability to care for your family. If sickness and vomiting are really interfering with your life, particularly your ability to eat and drink, you should seek help from your doctor or midwife.

What is hyperemesis gravidarum?

If you have severe sickness and vomiting for more than a few days, you may find it hard to drink anything leading to dehydration (lack of fluid in your body) and difficulty eating enough food, causing weight loss and vitamin deficiencies. This severe sickness and vomiting in pregnancy is known as hyperemesis gravidarum.

If you have these symptoms, even for more than a few days, you need urgent, expert medical help. Treatment is effective and protects you and your baby from complications. You should see your family doctor (GP), obstetrician or attend the Emergency Room at your local hospital for advice and help.

Do sickness and vomiting affect the baby?

Not usually. The baby gets nourishment from your body's reserves even though you may not eat well when you are vomiting. The effort of retching and vomiting does not harm your baby. In fact, some studies have shown that having sickness and vomiting in early pregnancy is a good indication that your pregnancy is healthy and will have a successful outcome.

Your baby may be affected if you develop hyperemesis gravidarum and become very ill with lack of fluid in the body (dehydration) which is not treated. In this case, the most likely problem is that your baby will have a low birth weight when he or she is born. However, not all babies born to women with hyperemesis gravidarum have a low birth weight.

Do I need any special tests?

If you have mild feelings of sickness (nausea) and vomiting during pregnancy, you do not usually need any specific tests or investigations.

Sometimes your doctor or midwife will suggest some tests:

-
- If your symptoms become more severe.
- If you are not able to keep any food or fluids down.
  If you start losing weight.

Investigations may include blood or urine tests to look for a another cause for your nausea and vomiting or to check how your body is coping.

What can I do to help relieve sickness and vomiting?

In most cases, as the symptoms are often mild, no specific treatment is needed. However, there are certain things that you may like to try to help relieve your symptoms. They include the following:

- Eating small but frequent meals may help. Some people say that sickness is made worse by not eating anything at all. If you eat some food regularly, it may help to ease symptoms. Eat whatever you can, when you can. Don’t worry too much about a balanced diet at this time. There may be some foods you really want and others you can’t stand. Cold meals may be better if nausea is associated with food smells.

- Ginger. Some studies have shown that taking ginger tablets or syrup may be effective for relieving feelings of sickness (nausea) and vomiting in pregnancy. However, care should be taken, as the quality of ginger products varies. Before you take a ginger product, you should discuss this with a pharmacist, midwife or GP. Food containing ginger may also help.
- Avoiding triggers. Some women find that a trigger can set off the sickness. For example, a smell or emotional stress. If possible, avoid anything that may trigger your symptoms.
- Having lots to drink to avoid lack of fluid in the body (dehydration) may help. Drinking little and often rather than large amounts may help to prevent vomiting. Try to aim to drink at least one to two litres of some sort of fluid each a day.
- Rest. Make sure that you have plenty of rest and sleep in early pregnancy. Being tired is thought to make nausea and vomiting during pregnancy worse.

Note: generally, you should not use over-the-counter remedies for sickness and vomiting whilst you are pregnant unless recommended by your doctor, midwife or pharmacist.

When are anti-sickness medicines needed?

Anti-sickness medicine may be necessary and recommended if your symptoms are persistent and severe, or do not settle with the above measures. Although it is generally recommended to avoid medicines when you are pregnant, certain medicines have been used for a number of years to treat feelings of sickness and vomiting in pregnancy and are considered safe. Some of the more commonly used medicines are pyridoxine (vitamin B6), doxylamine, promethazine, cyclizine and prochlorperazine and there is no evidence that they harm a developing baby. If these are not helpful, metoclopramide, ondansetron, ranitidine and sometimes prednisolone may be used.

Always discuss with your doctor, community pharmacist or midwife before taking an anti-sickness medicine when you are pregnant.

They should inform you about any possible concerns regarding using medicines for sickness and vomiting during pregnancy. Feel free to ask them any questions you have before taking medicine in pregnancy.

It is best to use medication for the shortest time possible. For some women, medication may be needed for several weeks or even months until symptoms settle.

What if these treatments do not work very well?

A small number of women need to be seen at the hospital or Day Hospital facility to be given fluids by a drip. Admission to Hospital is sometimes needed if you do not respond to medication or can't keep it down. You may need to be admitted to hospital if you lose weight or can’t keep enough fluid down and become too dry (dehydrated).

Other causes of vomiting

Remember, not all vomiting may be due to the pregnancy. You can still get other illnesses such as a tummy bug (gastroenteritis) or food poisoning. Sometimes a bladder or kidney infection can cause vomiting in pregnancy. You should see a doctor urgently if you develop any symptoms that you are worried about, particularly any of the following symptoms:

-
- Very dark urine or not passing any urine for more than eight hours.
- Stomach pains.
- High temperature (fever).
- Pain on passing urine.
- Headache not responding to paracetamol.
- Runny stools (diarrhoea).
- Yellow skin (jaundice).
- Severe weakness or feeling faint.
- Blood in your vomit.
  Repeated, unstoppable vomiting.

Where can I get more information?

The following sites may be helpful if you want more information or support:

-
  SOMANZ Guideline for the management of nausea and vomiting in pregnancy.
- https://www.somanz.org/Index.asp
- Hyperemesis Gravidarum Australia: https://www.hyperemesisaustralia.org.au
  Pregnancy Sickness Support UK: https://www.pregnancysicknesssupport.org.uk/
- American College of Obstetrics and Gynecology: Morning Sickness: Nausea and Vomiting of Pregnancy: https://www.acog.org/Patients/FAQs/Morning-Sickness-
- Nausea-and-Vomiting-of-Pregnancy
  Various online forums and blogs are available for women to share their experiences. We cannot recommend individual sites as they do not contain supervised content.

Sickness in Pregnancy Plan

Date: _____
Doctor: _____
Contact: _____

Patient Label

My medications for sickness, vomiting and acid reflux				
	Morning	Middle of day	Evening	Bedtime
For sickness or dry heaves (nausea or vomiting or retching)				
For stomach acid (reflux)				
For constipation				
Other				

If you feel worse:

_____

_____

_____

If you feel better:

_____

_____

_____

Would you like to tell us how you're going?

Eating and drinking:

_____

_____

_____

_____

Work or study:

_____

_____

_____

_____

Family:

_____

_____

_____

_____

Mood:

_____

_____

_____

_____

_____

Did you have drip (IV) fluids this week? If so, when? Did it help?

_____

_____

_____

_____

_____