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EDITORIAL

Nausea and Vomiting of Early Pregnancy

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Abstract:

Nausea and vomiting in early pregnancy is very common. The severest form, hyperemesis gravidarum,is important as mismanagement can lead to Wernicke's encephalopathy, central pontine myelosis and death.

There is a lack of high-quality evidence in the management of nausea and vomiting in early pregnancy and in the safety of the commonly used drugs, especially the reported side effects and their management. Pregnancies following bariatric surgery are becoming more frequent and care should be taken managing nausea and vomiting in this group since thiamine is primarily absorbed in the small intestine, and Wernicke's encephalopathy has been described following some types of bariatric surgery. Severe cases of hyperemesis gravidarum warrant caution as Wernicke's has been described following total parenteral nutrition,and it must be remembered that thiamine needs to be supplemented in this group. The etiology remains unknown and there is scope for research in this area.

Key words: Nausea, Vomiting, Pregnancy, Hyperemesis Gravidarum, Antiemetic

Introduction:

Nausea and vomiting may be the first symptom of pregnancy,usually peaks between 7 and 9 weeks gestation, and the feeling of sickness and the inability to retain food and drink is common in early pregnancy and may be unique to humans(Gadsby et al, 1997).The symptoms even in its mildest form can still have a profound effect on the wellbeing of the woman, affecting her: physically, socially, psychologically and financially(Gadsby et al, 1997; Källén et al, 2003; Smith et al, 2000)and may have a negative impact on her health-related quality of life (Lacasse et al, 2008). These effects could extend to other members of the family.The management of the disease has an impact on health economics in term of bed occupancy, high readmission rate (Gadsby et al, 1997) and treatment costs.

The symptoms may follow certain patterns, allowing some women to predict the timing of its occurrence(Gadsby et al, 1997) and to develop certain coping strategies, some of which are built on the women's local community heritage acquired through the years (Thomson et al, 2014). Not all affected women are capable of coping with the symptoms and some become severely affected to the degree that they become severely dehydrated or malnourished.

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The treatment of nausea and vomiting of pregnancy is mainly symptomatic and supportive, and early treatment is more effective. In some cases, the disease can be protracted and may not respond to any medications or interventions(Gadsby et al, 1997).A wide range of interventions have been tried in the management of the condition with different claims of effectiveness and success, however, there is a lack of high-quality evidence to support any particular intervention (Matthews et al, 2010; Sanu and Lamont, 2011).

The severe form of nausea and vomiting of pregnancy is termed **H**yperemesis **G**ravidarum (HG). There is no consensus on or universal definition of HG. The International Statistical Classification of Disease and Related Health Problems defines HG as persistent and excessive vomiting starting before the end of the 22nd week of gestation, and in its severe form is associated with metabolic disturbances such as carbohydrate depletion, dehydration, or electrolyte imbalance (RCOG, 2016; WHO, 2007).HG is best defined as any combination of nausea, vomiting, dehydration, weight loss, or hospitalization for nausea and/or vomiting in pregnancy, in the absence of any other obvious cause for these complaints (Niemeijer et al, 2014).

An understanding of the condition is vital as mismanagement of these cases can lead to iatrogenic maternal deaths from Wernicke's encephalopathy, which is characterized by diplopia, abnormal ocular movements, ataxia and confusion and/or central pontine myelosis, which is characterizedby spastic quadraparesis, pseudobulbar palsy and impaired consciousness (McClure et al, 2011).

Despite being described many years ago, Wernicke's encephalopathy secondary to HG is still being reported in the literature (Berdai et al, 2016), though, thankfully, mortalities are now rare. It has also been described following some types of bariatric surgery(Bohan et al, 2016), and should be kept in mind as pregnancy following bariatric surgery is becoming more common.

Neglected cases and/or poor management can also lead to other significant morbidities, e.g. oesophageal tears, **V**enous **T**hrombo-**E**mbolic disease (VTE), depression and placental abruption, especially for women with HG in the second trimester (Bolin et al, 2013).

Incidence and associated risk factors:

The reported incidence of nausea and vomiting in pregnancy varies from 35 to 91% (Einarson et al, 2013).Nausea is more frequent and causes most of the distress, and occurs in 99% of the women who have nausea and vomiting of pregnancy compared with vomiting, which occurs in 47% of the affected women (Gadsby et al, 2011), the same authors noticed that vomiting often signals the relief of symptoms. Nausea and vomiting may recur in subsequent pregnancies in as many as half to two thirds of the women, and the recurrence rate is even higher for HG (Gadsby et al, 2011; Trogstad et al, 2005).In contrast, the incidence of HG is about 11 to 15% (Einarson et al, 2013; Fiaschi et al, 2016; Vikanes et al, 2010)and is second only to preterm labour for admission to hospital (ACOG, 2004).Asian and black ethnicity appear to increase the risk of HG recurrence (Fiaschi et al, 2016).

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Factors associated with nausea and vomiting of pregnancy include: lower maternal age, lower gravidity/parity, lower level of education, lower income, poorly-controlled diabetes, alcohol consumption,smoking, lower body mass index, and helicobacter pylori (Chan et al, 2011; Chou et al, 2008; Källén et al, 2003; Louik et al, 2006; Sandven et al, 2009).

Etiology and pathophysiology:

The etiology and pathogenesis of nausea and vomiting of pregnancy is unknown; however, there is likely to be an interaction of multiple factors including:hormonal, genetic, cultural and placental.Alterations in steroid hormone homeostasis, higher concentration of androstanediol glucuronide and decreased androstenedione concentrations have been observed in women with HG (Helseth et al, 2014).

The symptoms of nausea and vomiting are usually worse with hydatidiform mole and multiple pregnancy, both of which are associated with higher concentrations of human chorionic gonadotrophin (hCG). The acidic isoforms of hCG may play a role in the etiology of HG (Jordan et al, 1999). Several studies have suggested a genetic link with HG (Fejzo et al, 2012; Fejzo et al, 2008; Zhang et al; 2011).

Vomiting involves an interaction of neurophysiological connections to the chemoreceptor trigger zone, emetic centre and vestibular centre in the brainstem and medulla oblongata (Sanu andLamont, 2011). Further studies including functional **M**agnetic **R**esonance **I**maging (MRI) may help clarify the pathophysiology.

The effect of HG on the fetus:

There is evidence that HG is associated with a higher female/male ratio of offspring, higher incidence of **L**ow **B**irth**W**eight (LBW), **S**mall for **G**estational **A**ge (SGA) and **P**re-**T**erm **B**irth(PTB) (Veenendaal et al, 2011). Little is known about the long-term health effects of babies born to mothers whose pregnancies were complicated by HG (Koren et al, 2014).There is no association between nausea and vomiting or HG and Apgar scores, the birth weight of the baby,birth defects, congenital anomalies, stillbirth or perinatal death (Gadsby et al, 2011; Veenendaal et al, 2011).On the other hand, more recent studies suggest that nausea and vomiting of pregnancy may actually be associated with favorable fetal outcome (Koren et al, 2014; Vikanes et al, 2013)

Diagnosis:

The condition is usually self-limiting; however, in some women the symptoms may become protracted and difficult to manage. The start of the symptoms could be as early as 5 weeks gestation and it usually peaks between 7 and 9 weeks, and resolves by 22 weeks (Gadsby et al, 2011). The symptoms can continue into the third trimester in about 23% of women(Einarson et al, 2013).

It is important to remember that nausea and vomiting of pregnancy and HG are diagnoses of exclusion (RCOG, 2016).Therefore, affected women should be systematically reviewed to exclude other causes of nausea and vomiting, and the differential diagnosis for nausea and

vomiting in pregnancy could be exhausting and may include both medical and surgical causes, see table (1).

Table (1) Showing the list of differential diagnoses for nausea and vomiting in early pregnancy.

System	Disease
Pregnancy-related	Molar pregnancy Gestational trophoblastic disease Multiple pregnancy Threatened miscarriage
Gastric	Gastro-oesophageal reflux Peptic ulcer Gastritis Diaphragmatic hernia Gastric neoplasia
Bowel	Small bowel obstruction Gastroenteritis Appendicitis Bowel diseases e.g. Crohn's disease
Liver and gallbladder	Acute Cholecystitis Gall stones Cholestasis of pregnancy Cholangitis Acute fatty liver Hepatitis
Pancreatic	Pancreatitis
Uro-Renal	Urinary infection Pyelonephritis Uremia Nephrolithiasis
Endocrinological	Poorly controlled Diabetes Mellitus Addison disease Hyperthyroidism Hyperparathyroidism
Other rare causes:	Torsion of an ovarian cyst Oesophageal pouch and stricture Reaction to medications Drug intoxication Drug abuse during pregnancy Food allergy Food poisoning

	Eating disorders Vestibular disease Migraine Porphyria Increased intra-cranial pressure and brain tumors Pcychatric causes

There is no widely accepted point at which nausea and vomiting in pregnancy becomes HG (O'Donnell et al, 2016) and there are no agreed diagnostic criteriafor HG and the symptoms are non-specific, but the following combinations of criteria are frequently described; however, evidence for the association between ketonuria and presence or severity of HG is lacking (Sandven et al, 2009):

- Persistent vomiting in early pregnancy
- Intractable vomiting occurring before 20 weeks of gestation
- Recurrent vomiting that occurs more than three times per day
- Recurrent vomiting that warrants hospital admission
- Nauseaand vomiting with fluid and electrolyte disturbance
- Nausea and vomiting with significant weight loss described as:
    - Loss greater than 3 kg or
    - Loss exceeding 5% of body weight
- Nausea and vomiting with ketonuria unrelated to other causes
- Hypersalivation

Investigations:

The investigations are decided by the circumstances of each individual case, but the following investigations are invariably requested, see table (2)

Table (2) Shows the frequently-requested investigations in cases of nausea and vomiting of early pregnancy.

Type of investigations	
Preliminary investigations	Ultrasound pelvis Urine dipstick Mid-stream urine for culture and sensitivity (MSU) Full Blood Count Liver Function Tests Urea and Electrolytes (U&E) blood sugar
Additional investigations as indicated by cases	Thyroid Function Tests Calcium and magnesium Serum amylase

	Hepatitis screening Renal and hepatic ultrasound Serum human chorionic gonadotrophin (HCG)

The Management:

The main objective of the treatment is to correct dehydration, prevent complications and make the woman feel better. Early and effective management is important. The average length of stay in hospital for HG is 3 to 4 days, and 25% of women with HG require readmission to hospital (Gadsby et al, 2011).The disease has a significant effect on the physical wellbeing of the woman and on her quality of life, as well as a financial impact on the health care system. The ambulatory treatment of nausea and vomiting of pregnancy is gaining popularity, reducing hospital inpatient stay and is acceptable to patients (McCarthy et al, 2014).

The non-medical approach to the treatment of nausea and vomiting of pregnancy is complementary to supportive and symptomatic treatment and should not be underestimated. There are several natural approaches adopted by women to alleviate the symptoms with variable success including the avoidance of precipitating factors such as certain smells or tastes, eating plain food such as toast and the use of ginger (Swallow et al, 2005; Matthews et al, 2014; Thomson et al, 2014). There is evidence that ginger extracts can accelerate gastric emptying and stimulate gastric antral contraction (Giacosa et al, 2015). However, there is a paucity of data on the safe use of ginger in pregnancy and larger randomized controlled trials are required (Boltman-Binkowski, 2016).

Reassurance and emotional support along with counselling are also recommended (RCOG, 2016). There is presently a dearth of evidence for the use of acupuncture or hypnosis. Women should be informed that acupuncture is safe during pregnancy; however hypnosis is not recommended (RCOG, 2016).

Pharmacological treatment and fluid therapy

The majority of prescriptions for the treatment of nausea and vomiting in pregnancy, in the USA, are with medications not licensed for use in pregnancy, and are not specifically antiemetics and are not classified as safe in pregnancy (Cohen et al, 2014).

The pharmacological treatment is generally symptomatic and supportive with antiemetics, fluid and electrolyte replacement, supplementation with thiamine (vitamin B1), pyridoxine (vitamin B6), dietary advice and prevention of venous thromboembolic disease, see Table (3). Women who are dehydrated and severely ketotic require hospital admission.

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Table (3) Showing the list of medications used in the treatment of nausea and vomiting of early pregnancy

Medication	Dose	Route of administration
Pyridoxine (vitamin B6)	10-25 mg 8 hourly	Oral
Thiamine (vitamin B1)	75-150 mg per day	Oral or Intravenous
Cyclizine	50 mg 8 hourly	Oral, Intramuscular and Intravenous
Meclizine	25 mg every four to six hours	Oral
Promethazine (Phenergan)	12.5 mg to 25 mg every hours	Oral, Intramuscular, Intravenous and Rectal
Doxylamine	25 mg once a day	Oral
Doxylamine and pyridoxine	Doxylamine 10 mg and Pyridoxine 10 mg	Oral
Diphenhydramine	Oral: 25 to 50 mg every four to six hours Intravenous: 10 to 50 mg every four to six hours	Oral and Intravenous
Metoclopramide	10 mg 8 hourly	Oral, Intramuscular and Intravenous
Prochlorperazine	5 mg three times a day	Oral
Droperidol	10 mg four times a day	Oral
Ondansetron	4 mg every eight hours	Oral and Intravenous
Corticosteroid: Hydrocortisone and prednisolone Or Methylprednisolone and prednisolone	Initial dose 100 mg of Hydrocortisone 12 hourly followed by 40 mg of prednisolone once a day Or 16 mg of Methylprednisolone every 8 hours for 48 to 72 hours, followed by 40 mg oral prednisone per day for one day, followed by 20 mg per day for three days, followed by 10 mg per day for three days, and then 5 mg per day for seven days.	Intravenous and Oral
Mirtazapine	15 to 30 mg once a day	Oral and Intravenous
Ranitidine	150 mg 12 hourly	Oral
Cimetidine	200 mg once a day	Oral
Lansoprazole	30 to 40 mg once a day	Oral and Intravenous
Esomeprazole	30 to 40 mg once a day	Oral and Intravenous
Alginates combined with antacid (Gaviscon)	10-20 mls 8 hourly	Oral

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Thiamine (Vitamin B1) is a water-soluble vitamin primarily absorbed in the small intestine, and constant supplementation is critical. Thiamine acts as a cofactor for glucose metabolism and in dependent areas of the brain, in particular thalami and mammillary bodies, excess carbohydrate causes damage leading to Wernicke's encephalopathy, which manifests as confusion, ataxia and eye movement abnormalities. Treatment must be prompt with the immediate administration of thiamine (Giugale et al, 2015).Dextrose infusion should be avoided.

All hospital units should have guidelines and protocols for the treatment of HG with thiamine supplementation and intravenous fluid administration, see suggested pathways (1) and (2) for management.

Normal Saline is recommended with Potassium Chloride (KCl) added as indicated by **U**rea and **E**lectrolytes (U&E) in preference to Hartmann's or Ringer's, as it contains a higher concentration of Sodium Chloride (NaCl), and care must be taken to avoid hyponatraemia, which can lead to central pontine myelosis.

Double strength Saline should not be used as rapid correction of sodium depletion itself can cause central pontine myelosis. Thiamine can be given orally 25-50mg three times a day or intravenously 100mg diluted in 100 ml of Normal Saline over 60 minutes, especially, if the patient is on Dextrose infusion or parenteral feeding (RCOG, 2016). Treatment doses in established Wernicke's are higher e.g. 500 mg twice a day (Berdai et al, 2016).

First-line antiemetics Medications:

Antiemetics should be offered to women whose condition does not improve after rehydration and correction of electrolyte imbalance. Different antiemetics have been used safely in early pregnancy,either singularly or in combination with no difference in efficacy (Mayhall et al, 2015).

Vitamin B6 or pyridoxine has an effect on nausea rather than on vomiting; however, how it causes its therapeutic effect remains unknown or speculative, and it may correct a deficiency or it may have an intrinsic anti-nausea effect, and there is no evidence that it has any adverse effect on the fetus (Koren et al, 2010; Nuangchamnong N, and Niebyl J, 2014).

The antihistamines:include Cyclizine, Promethazine and Doxylamine, which are H1 receptor agonists have been used as first line treatment for nausea and vomiting of pregnancy with efficacy and good safety profile (Seto et al, 1997). There are three possible mechanisms of action that explain their antiemetic effect: direct inhibition of H1 receptor, indirect effect on the vestibular system and inhibition of the muscarinic receptor.Antihistamines however can cause drowsiness.

Dopamine-receptor agonists: The antiemetic effect of these medications is via their action on the dopamine receptors in the stomach. The commonly used two medications are:Metoclopramide and Prochlorperazine. These drugs are known to potentially cause extrapyramidal side effects such as dystonia, dyskinesia or oculogyric crises which will require prompt treatment with Procyclidine 5mg intramuscular or intravenous; hence, some authorities recommend its use as a second-line therapy (RCOG, 2016).

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Second-line antiemetics Medications:

Antidopaminergic: Droperidol. There are no reported fetal congenital anomalies with its use in early pregnancy; however, the drug has maternal side effects including extrapyramidal (torsades de pointes) and cardiac (QT prolongation).

Serotonin 5-HT receptor antagonist: Ondansetron is effective as an antiemetic; however, some studies have raised concerns over possible increased risk of congenital heart disease (Anonymous, 2015; Carstairs, 2016). Other authors however have shown a similar number of defects in the untreated versus Ondansetron treated groups leading them to conclude that there was no increased risk of teratogenicity (Fejzo et al, 2016). The numbers in all the studies were relatively low. A possible rare association of Ondansetron and intestinal obstruction has been reported(Cohen et al, 2014), and the assertion of this link has been repeated by other authors (Fejzo et al, 2015). Advice includes maintaining a regular bowel habit and consideration of stopping the drug if constipation becomes severe. Further safety studies involving greater numbers of patients are required.

Severe HG management:

Severe HG, unresponsive to conventional management is a disabling condition associated with prolonged and multiple admissions to hospital. It can be difficult to treat and in extreme cases a woman may request termination of pregnancy. In severe HG, some reports suggest that corticosteroid therapy may produce an improvement (Neill and Nelson-Piercy, 2003; Taylor, 1996), but the mechanism of action of corticosteroids for the treatment of HG is unknown. This type of treatment should be reserved to the few cases when conventional therapies fail, and should be used with caution in the first trimester.An initial regimen of hydrocortisone 100mg twice a day followed by 40 mg prednisolone daily is recommended (Neill and Nelson-Piercy, 2003), and should be gradually tapered down. The aim is to stop steroid treatment by 20 weeks; however, some patients may require them beyond this, and this can have side effect implications, including: osteoporosis, hip necrosis, gestational diabetes and immunosuppression.Long-term prednisolone use at these doses is not known to be associated with poor fetal outcome. If corticosteroids fail, a trial of total parenteral nutrition may be necessary (Subramaniam et al, 1998). At all stages, patients need psychological support, and physicians prescribing **T**otal **P**arenteral **N**utrition (TPN) for severe cases of HG must remember that compositions of TPN are not standardized and that Wernicke's may develop if thiamine is not included (Giugale et al, 2015).

Adjunctive therapy:

Antacids with or without alginates, H2 blockers and**P**roton **P**ump **I**nhibitors (PPI) have been used alone, or in combination with antiemetic therapy, for reflux oesophagitis and nausea and vomiting in early pregnancy with some success. They have not been associated with any increased risk for congenital malformations in humans despite animal evidence of arthropathy (Matok et al, 2012; Strugala et al 2012). H2 receptor antagonistshave also been used for reflux oesophagitis alone in pregnancy, with no apparent increased risk of teratogenicity, however patient numbers in the studies were low (Garbis et al, 2005; Magee et al, 1996), and of concern

is that cimetidine is known to have side effects including a risk of gynecomastia in males (García Rodríguez and Jick, 1994).

Thromboprophylaxis:

The combination of dehydration, hospitalization and pregnancy increase the risk of venous thromboembolic disease; hence, thromboprophylaxis by hydration, low molecular weight heparine.g. Enoxaparin 40mg subcutaneousdailyand mechanical means such as TED stockings and pneumatic cuffs is recommended, where there are no contraindications(RCOG, 2016; Neill and Nelson-Piercy, 2003).

Complications:

Complications are rare, but may develop in severe cases not responding to treatment or in badly-managed cases and include:

- Haemetemesis and Mallory-Weiss Syndrome
- Wernicke's encephalopathy
- Central Pontine Myelosis
- Electrolyte imbalance
- Acute renal failure
- Malnutrition and vitamin deficiency
- VTE and Coagulopathy
- Pneumothorax and spontaneous pneumomediastinum
- Depression
- Splenic avulsion

Summary and conclusions:

- There is a lack of high quality evidence for the management of HG in pregnancy
- Nausea and vomiting of pregnancy is common
- The approach to management should be systematic and holistic
- It is important to exclude other causes of HG
- Early supportive treatment is usually effective and reduces the risk of complications
- Some of the non-medical remedies are effective and are favored by some women
- Thiamine and intravenous fluids (Normal Saline) are the mainstay of therapy
- Antihistamines and Dopamine-receptor agonists should be the first line antiemetic treatment
- Corticosteroid therapy should be reserved for severe cases unresponsive to conventional therapy
- Wernicke's encephalopathy has been associated with some types of Bariatric Surgery and with TPN treatment, and Thiamine supplementation should not be forgotten in this group, particularly as there is an increasing number of pregnancies following Bariatric Surgery.

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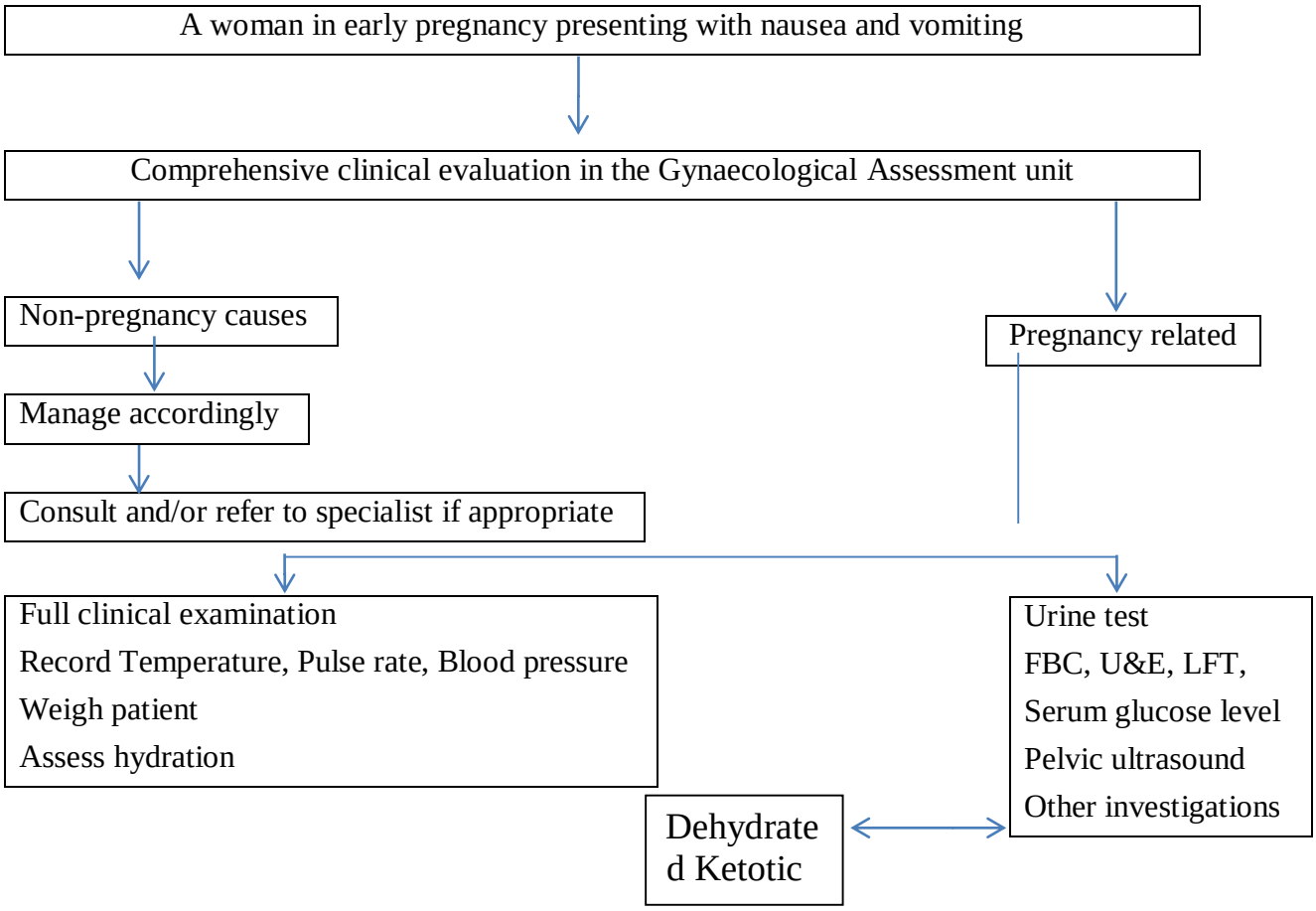
Pathway (1) for the management of nausea and vomiting of pregnancy#



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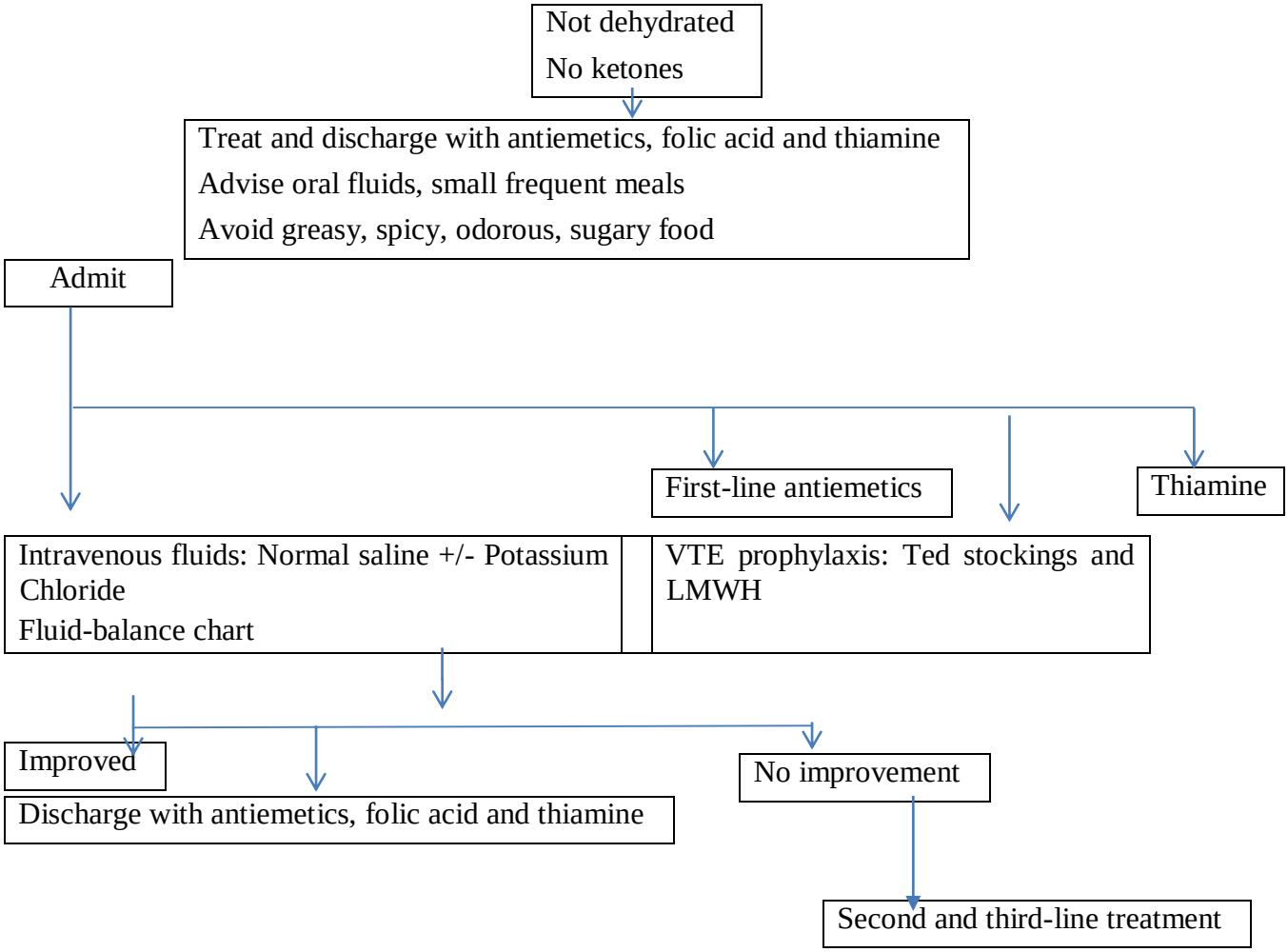
Not dehydrated
No ketones
Treat and discharge with antiemetics, folic acid and thiamine
Advise oral fluids, small frequent meals
Avoid greasy, spicy, odorous, sugary food
Admit
First-line antiemetics
Thiamine
Intravenous fluids: Normal saline +/- Potassium Chloride
Fluid-balance chart
VTE prophylaxis: Ted stockings and LMWH
Improved
Discharge with antiemetics, folic acid and thiamine
No improvement
Second and third-line treatment

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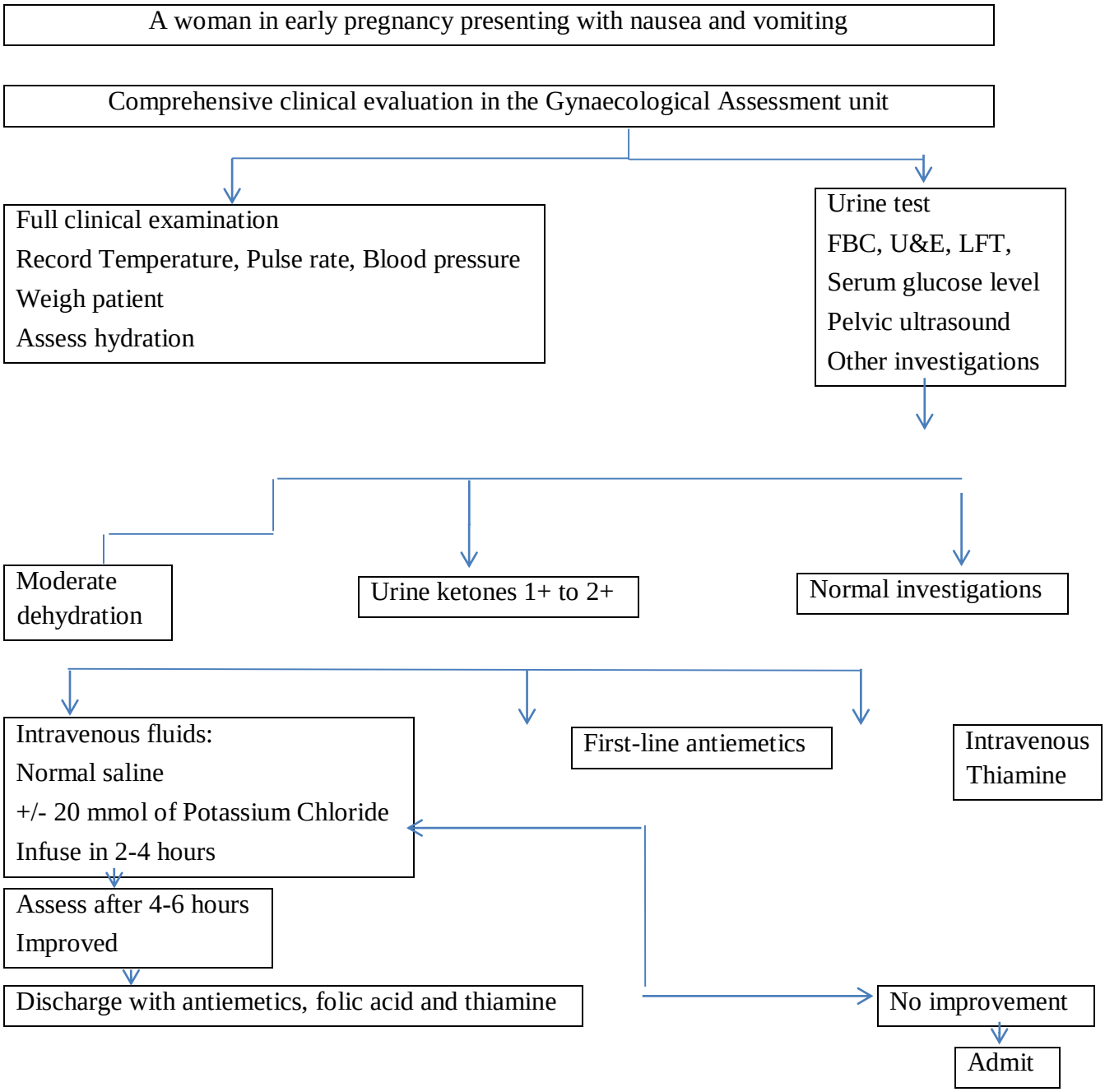
Pathway (2) for the management of nausea and vomiting of pregnancy as an outpatient[#]



Based on RCOG Guidelines, 2016

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Current Research Questions:

1- What is the pathophysiology of HG? Vomiting involves an interaction of neurophysiological connections to the chemoreceptor trigger zone, emetic centre and vestibular centre in the brainstem and medulla oblongata. Further studies including functional MRI may help to clarify the pathophysiology.
2- Large randomized controlled trials are required to clarify the safety and efficacy of the drugs used for the treatment of nausea and vomiting in pregnancy and HG.
3- Large randomized controlled studies are required to clarify the role of acupuncture and hypnosis in the treatment of nausea and vomiting in pregnancy and HG.

Self-assessment questions:

Please answer True or False to the following statements:

1- HG is a clearly defined medical condition
2- HG has an adverse effect on the fetus
3- Treatment of HG requires intravenous administration of Dextrose
4- Corticosteroids are useful in the management of HG
5- Wernicke's encephalopathy is now a diagnosis of the past

Answers:

1- False. There is no widely accepted point at which nausea and vomiting in pregnancy becomes HG, nor is there any universal definition.
2- False. There is no association with Apgar scores, congenital anomalies or perinatal death. Little is known about the long term health effects of babies born to mothers whose pregnancies were complicated by HG, however studies suggest that nausea and vomiting of pregnancy may be associated with a favorable fetal outcome.
3- False. Thiamine acts as a cofactor for glucose metabolism and in dependent areas of the brain, (in particular thalami and mammillary bodies), excess carbohydrate causes damage leading to Wernicke's encephalopathy, which manifests as confusion, ataxia and eye movement abnormalities. Treatment must be prompt with the immediate administration of thiamine. Dextrose should therefore be avoided, and nausea and vomiting must be treated with thiamine supplementation. Normal Saline is recommended with KCl added as indicated by U&E that in preference to Hartmann's or Ringer's, as it contains a higher concentration of Sodium, and care must be taken to avoid hyponatraemia, which can lead to central pontine myelosis.
4- True. In women with severe HG there are data suggesting that corticosteroid therapy may produce an improvement. The mechanism of action of corticosteroids for the treatment of HG is unknown, and they are reserved when conventional treatment fails.
5- False. Wernicke's encephalopathy secondary to HG is still being reported in the literature, though mortalities are now rare. It has been described following

some types of bariatric surgery, and should be kept in mind as pregnancy following bariatric surgery is becoming more common.

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