Gynecology & Obstetrics
ISSN: 2161-0932

Thomas, et al., Gynecol Obstet (Sunnyvale) 2015, 5:2
DOI: 10.4172/2161-0932.1000270

Review Article Open Access

Medication used in Nausea and Vomiting of Pregnancy - A Review of Safety and Efficacy

Binny Thomas*, **Palli Valappila Abdul Rouf, Moza Al-Hail, Doua al Saad, Asma Tharannum, Wessam elKassem and Nora Al- hail**

Department of Pharmacy, Obstetrics and Gynecology-HMC, Qatar

***Corresponding author:** Binny Thomas, Department of Pharmacy, Obstetrics and Gynecology-HMC, Qatar, Tel: 97433750460; E-mail: binnyinhmc@gmail.com

Received date: 11 Jan, 2015; **Accepted date:** 09 Feb, 2015; **Published date:** 11 Feb, 2015

Abstract

Nausea and vomiting are common symptoms experienced by 50– 90% of women's in early pregnancy. 'Morning sickness' is a misnomer frequently used to describe nausea and vomiting in pregnancy (NVP), although the symptoms may persist the whole day and/or night. Pregnant women experience these symptoms mainly in the first trimester between 6 and 12 weeks of gestation, few of them continue till 20 weeks of gestation while in few others it continues throughout the pregnancy. The problem peaks at 9-week gestation, and approximately 60% of NVPs resolve by the end of first trimester. In a very small minority of these patients, the symptoms become severe leading to dehydration, weight loss, excessive vomiting, and mandate hospital admission; this condition is known as Hyperemesis Gravidarum.

Fairweather D.V proposed the most widely used definition of Hyperemesis Gravidarum (HG). He defined HG based on the symptoms, vomiting exceeding three times a day with significant ketonurea or weight loss more than or equal to 5% of pre pregnancy weight, electrolytic imbalance or fluid depletion, and onset occurs at 4 to 8 weeks of pregnancy till 14 to 16 weeks. Nausea and vomiting in pregnancy is of multifarious etiology (fluctuating levels of progesterone, estrogens, Thyroid Stimulating Hormone (TSH), slow peristaltic movement of Gastrointestinal (GI) tract); however, the exact mechanism remains still unclear.

Given the uncertainty in treatment of NVPs, both patients and healthcare practitioners often fear the use of antiemetic medications in pregnancy due to the potential risk to fetus and mother. The manifestation of nausea and vomiting in pregnancy is different among each woman, so its management should be tailored similarly. An early treatment of nausea and vomiting is important and beneficial since it prevents a more severe form of occurring, or a possible hospitalization, and prevents both emotional and psychological problems. It is very important for the women and the healthcare providers to understand that a safe and effective NVP treatment benefits both fetus and mother, thus all the treatment options should be open and considered.

Nonetheless, given the widespread prevalence of nausea and vomiting, its adverse effects and effects on psychological conditions of pregnant women, it is necessary to be treated effectively and safely during embryonic and fetal developmental stages. First trimester exposure is important to be assessed to monitor the teratogenic potential of the drug; however, randomized control trials are rarely conducted for pregnant women for ethical reasons. Whereas the epidemiological studies done are observational and lack population strength to establish safety and risk involved. This review will mainly focus on pharmacological drugs used in treatment of NVP, and explore their safety and efficacy and evidence based practice. There have been many studies examining the safety of drugs used in NVPs and few of them are covered in this review. The dietary, lifestyle modifications, and non-pharmacological approaches are not covered in this section.

Keywords: Nausea; Pregnancy; Etiology; Embryonic and fetal developmental stages

Pharmacological Agents

Various categories of pharmacological agents either singly or in combination are used in the treatment of NVPs. There are five neurotransmitter sites mainly used in the treatment of nausea and vomiting; M1-muscarinic acetylcholine, D2-dopamine, H1-histamine, 5-HT3-hydroxytryptamine (serotonin), and neurokinin-1 (NK-1) receptor-substance P.

These drugs are classified based on their mechanism of actions mainly; vitamins, antihistamines, anticholinergic, dopamine antagonistic, phenothiazine's (antagonizing the dopaminergic receptors of central nervous system), butyrophenones, serotonin antagonists, and corticosteroids [1-6]. It is also noted that all pregnancies have 1-3% baseline risk of having major birth defects and approximately 15% ends in miscarriages irrespective of any medication used by mother [7].

The usual dosage regimens for these pharmacological classes are shown in Table 1 [5,8-12]. The US Food and Drug Administration (FDA) provides categorization for medications according to their safety during pregnancy (Table 2). Lately, the FDA removed the letters labelling of medications because they do not effectively communicate the risk a drug may have during pregnancy [12].

Drug Name	Usual Dosage Range	Main Side Effects	FDA Pregnancy Category
Vitamins and Antihistamines			
Pyridoxine	25 mg q 8 h PO	-	A
Thiamine[1]	250 mg IV 3-5 days	-	A
Doxylamine	12.5 mg q 12 h PO or 12.5 mg am and 25 mg pm PO	-	A
Doxylamine-pyridoxine combination	10/10 mg up to 4 tablets (1 tablet am, 1 tablet afternoon, 2 tablets bedtime) PO	-	A
Diphenhydramine	50–100 mg q 4-6 h PO/IM/IV	Drowsiness	B
Dimenhydranate	50–100 mg q 4-6 h PO/PR 50 mg q 4-6 h IV	Drowsiness	B
Meclizine	25 mg every q 4-6 h PO	Drowsiness	B
Dopamine Receptor Antagonist			
Promethazine	25 mg q 4-6 h PO/IM/IV/PR	Sedation, dry mouth, EPS	C
Prochlorperazine	5-10 mg q 4-6 h (maximum 40 mg/day) PO/IM/IV, 25 mg q 12 h PR	Sedation, dry mouth, EPS	C
Metoclopramide	5-10 mg q 8 h PO/IM/IV	EPS	B
Chlorpromazine	10-25 mg q 4-6 h PO/IM 50-100 mg q 6-8 h PR 25-50 mg q 4-6 h IV	EPS, orthostatic hypotension (IM route), sedation	C
Droperidol	0.625-2.5 mg IV over 15 minutes, then 1.25 mg or 2.5 mg IM as needed; can be given IV continuously at 1-1.25 mg/h	EPS, black box warning (QT prolongation and torsades de pointes)	C
Serotonin Antagonist			
Ondansetron	4-8 mg q 6-8 h PO 4-8 mg q 12 h IV	Headache, constipation	B
Glucocorticoids[2]			
Prednisolone	40-60 mg/day PO (then taper)	Cleft palate	C
Methylprednisolone	16 mg q 8 h PO/IV (2-3 days, then taper over 2 weeks)	Cleft palate	C
PO: oral, am: morning, pm: night, IM: intramuscular, IV: intravenous, PR: rectal, EPS: extrapyramidal symptoms			
[1]dose for the prevention of wernicke's encephalopathy [2]avoid use before 10 weeks of gestation			

Table 1: Medications used in the management of nausea and vomiting

Vitamins (B6 and B1)

The commonly used vitamins are vitamin B6 or Pyridoxine used mainly in treatment of nausea and thiamine or vitamin B1 in the treatment of Wernicke's encephalopathy [1] (Figure 1).

Pyridoxine (vitamin B6)

Pyridoxine is a water-soluble vitamin and is a very essential co-enzyme for folate metabolism pathway; the drug was first licensed for the use of NVP in 1942 [13]. Pyridoxine was clinically proved to be efficacious in two different trials that showed significant reduction severity of nausea with a very little effect on the episodes of vomiting. The first trial [14] showed that it is efficacious only in severe form of nausea and vomiting, and concluded; pyridoxine is more effective in relieving the severity of nausea with less significance to episodes of vomiting. The second trial [15] with larger population and adequate settings revealed it to be efficacious in both mild and moderate forms of NVPs.

Pyridoxine can be used alone [15] or in combination with other antiemetic's (doxylamine succinate) in the treatment of NVPs.

Systematic reviews of randomized and/or control trials reveals pyridoxine improves mild to moderate nausea with little effect on vomiting [1,16]. Hence, used in combination with other antiemetics in the treatment of Hyperemesis Gravidarum. As a single agent the maximum dose in pregnancy is 200 mg/day; however, a cumulative dose up to 500 mg/day is found to be safe [17]. No teratogenicity has been found with the use of pyridoxine and safe to be used in pregnancy [11].

A	Adequate and well-controlled studies in pregnant women have failed to demonstrate fetal risk
B	Animal reproduction studies have failed to demonstrate fetal risk and there are no adequate and well-controlled studies in pregnant women OR an adverse effect have been demonstrated in animal reproduction studies, but adequate and well controlled studies in pregnant women have failed to demonstrate fetal risk
C	An adverse effect on the fetus has been shown by animal reproduction studies, but the benefits from the use may be acceptable despite its potential risks in pregnant women OR no animal reproduction studies and no adequate and well controlled studies in humans
D	Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks
X	Studies in animals or humans have demonstrated fetal abnormalities, or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit
FDA: US Food and Drug Administration. Adapted from 21 Code of Federal Regulations (CFR) 201.57 (f) (2007)	

Table 2: FDA pregnancy category definitions

Doxylamine Succinate and Pyridoxine

This combination was allegedly withdrawn from market in 1983 due to reports on teratogenicity (gastrointestinal and limb malformations) [18]. However, several studies support its safety and efficacy in pregnancy [19,20]. Recently, United States Food and Drug Administration (USFDA) approved doxylamine succinate (20 mg) an antihistamine and pyridoxine hydrochloride (20 mg) combination for the treatment of NVPs [21]. Although, doxylamine is known to interrupt the histamine pathway and reduce vomiting, the exact mechanism of action of this combination is still unclear [22]. It is well established that combination of pyridoxine and doxylamine has clinically shown significant effect over placebo in in a recently conducted clinical trials [23].

Various trials failed to confirm this report of any malformations, [24] even with higher dose [25] and thus doxylamine with pyridoxine is most extensively used drug to treat NVPs today.

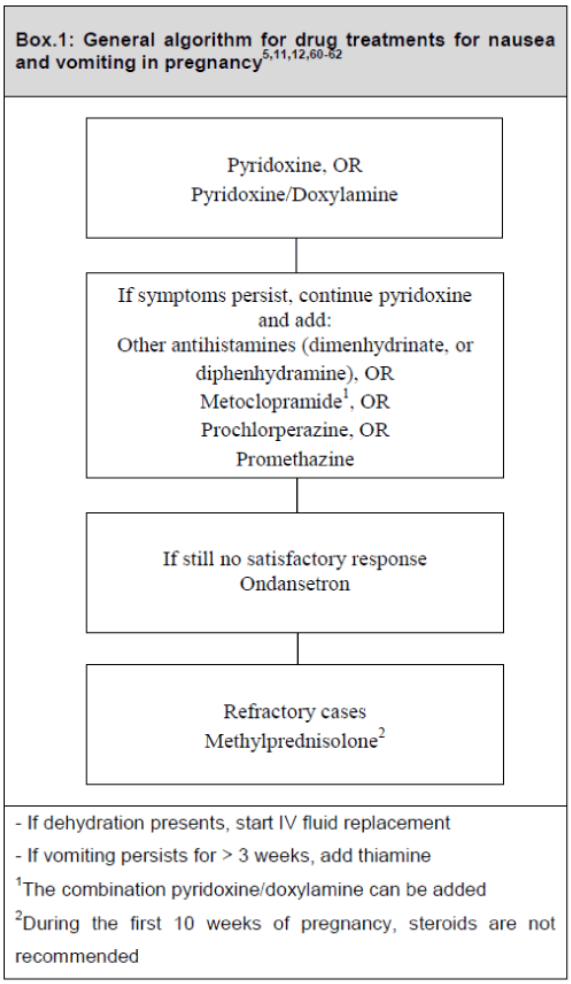

Figure 1: General algorithm for drug treatments for nausea and vomiting in pregnancy

Thiamine

Although thiamine is not used as an anti-emetic agent, it should be considered as an agent in the management of NVPs because in severe hyperemesis where vomiting persists for more than 3 weeks, thiamine deficiency has been observed (Wernicke's encephalopathy). Thiamine deficiency can lead to ataxia; memory loss, nystagmus, permanent neurological case or it could lead to maternal death. Early administration of thiamine is important to avoid such rare maternal complications like Wernicke's encephalopathy [26].

In such situation thiamine can be considered as an adjunct therapy to other antiemetic. Prophylactically 250 mg intravenously once daily for 3-5 days, and for the treatment 500 mg IV 3 times daily for 3 days, where if patient responded, lower doses are used for few more days as long as the patient continues to improve. It is advisable not to add dextrose to the thiamine since this combination could exacerbate Wernicke's encephalopathy [27].

Antihistamines

Antihistamines are most widely used first line medications for any women with NVPs. These agents block the histaminic receptors in both vestibular-system (H1) and chemoreceptor trigger zone (H2) receptors. A pooled data from seven randomized clinical trials have confirmed that antihistamines significantly reduce nausea and vomiting in pregnancy. Both first and second-generation antihistamines are safe in pregnancy. First generation antihistamines are known to have a sedative effect, and thus many women show discomfort in taking these medications throughout the day, and non-sedating antihistamines lack safety studies. The most commonly used antihistamine for NVPs are buclizine, cyclizine, dimenhydrinate, diphenhydramine, doxylamine, hydroxyzine and meclizine [6,28,29].

Buclizine, Cyclizine, Meclizine are all piperazine derivatives with both antihistaminic and anticholinergic property acting centrally with direct effect on labyrinthine apparatus and chemoreceptor zone. These classes of drugs are generally considered safe to use in pregnancy [30-32]. Dimenhydrinate is a chlorotheophylline salt that works by inhibiting the labyrinthine stimulation and vestibular system and is considered safe in pregnancy. Diphenhydramine is an ethanolamine antihistamine acts by competitively inhibiting the histamine (H1) receptors. Both diphenhydramine and Dimenhydrinate should be avoided during the third trimester due to the possible effect on uterine contraction [33,34].

First generation antihistamines are considered to be safe during pregnancy [35]. In a recent systematic review on safety of antihistamines in pregnancy majority of studies revealed lack of association of birth defects with antihistamine exposure. Only 2 out of 31 cohort studies found any significant positive link of malformations associated with antihistamines. Hence, antihistamines are considered unlikely to be a risk factor for any major birth defects [36]. A meta-analysis to assessing the relative risk of major malformation with antihistamines (H1) was carried out with 200000 women from 1960-1991. The analysis revealed H1 blockers are not associated with increase in teratogenicity to humans and hence, authors recommended the use of antihistamines.

Dopamine Antagonist

Considering the safety profile of these drugs various literatures and guidelines have marked them as second line agents used in NVPs. Dopamine receptor (D2) antagonists are considered to be a useful agent against NVP since they bind to the D2 receptors in the GI tract and inhibit the gastric motility. Dopamine is also known to act on chemoreceptor trigger zone and inhibit vomiting. There are three main classes of dopamine antagonists with different mechanism of action. Phenothiazine interfere dopamine to bind to its own receptors (promethazine, prochlorperazine and chlorpromazine); butyrophenones acts by blocking D2 receptors (droperidol), benzamides are both central and peripheral D2 receptor antagonist (metoclopramide) [11].

Phenothiazine like Chlorpromazine, perphenazine, prochlorperazine, promethazine (weak dopaminergic activity) and trifluoperazine inhibits vomiting by direct action by direct action on the GI tract and G2 receptors. Studies with larger population and long term experience did not show any adverse effects; however there were reports of cleft palate, skeletal, limb and cardiac abnormalities with their use. Chlorpromazine is used mainly for refractory cases. Promethazine's fetal safety and maternal efficacy is well demonstrated in larger trials [37,38]. Intrarterial, intrathecal or intravenous route of administration is contraindicated due to tissue necrosis and gangrene. Side effects include sedation and dystonic reaction. Few conflicting case reports have reported neonatal respiratory depression followed by administration of phenothiazine during labor.

Butyrophenones (droperidol) are more potent than phenothiazine mostly used to treat post-operative nausea, due to its maternal side effects it is rarely used to treat NVPs. There have been positive results in trial combining droperidol with diphenhydramine with significant shortening of length of stay of patients in hospitals and reduced readmission [37]. Although there are no concerns of fetal malformation, but when used at higher doses it causes QT prolongation and/or torsade's de pointes. A black box [38] warning is associated with the use of this drug and American College of Obstetrics and Gynecology warned it to be used with caution. Domperidone is another dopaminergic antagonist repeatedly used to treat NVPs, it is peripheral D2 and D3 receptor antagonist blocking the chemoreceptor trigger zone (CTZ) receptors and increasing the motility of GI tract [39].

Metoclopramide, one of the most frequently used anti-emetic in NVPs which acts both centrally (blocking the chemoreceptor zone) and peripherally (stimulating the motility of upper GI tract). Two different randomized trials assessing the effectiveness of metoclopramide over promethazine and ondanseterone found metoclopramide (10 mg) as effective as promethazine [40] (25 mg) and ondanseterone (4 mg) [41]. Metoclopramide is also considered as one of the safest options for infants, when exposed in the first trimester they did not have any increased risk of congenital malformation, miscarriage or stillbirth compared to non-exposed infants [42,43] and findings provided reassurance regarding the safety to the fetus when this drug is used in NVPs. However, maternal side effects were always a concern with this drug, since it causes drug induced movement disorders or extrapyramidal side effects. Early detection and discontinuing metoclopramide is important in to prevent permanent tardive dyskinesia or using metoclopramide with diphenhydramine or hydroxyzine to mask the dystonic effect produced by the drug. A dose of 50 mg diphenhydramine can be given before dose to prevent extrapyramidal side effects [44].

Serotonin Antagonist

Ondanseterone is a selective serotonin antagonist used mainly in treatment of chemotherapy-induced nausea and vomiting. They are known to act both centrally and peripherally (5-hydroxy-tryptamine-3 receptors) by blocking the signals generated by vomiting center in brain and prevent nausea and vomiting. It is now widely used in treatment of refractory cases of nausea and vomiting on pregnancy, however there is a paucity of data regarding it safety and efficacy since it crosses placenta. Various case reports have shown positive response to ondanseterone where other treatment failed to produce any effect [45-47].

Ondanseterone is reported to cause QT prolongation in patients underlying congenital cardiac abnormalities [43]. FDA has issued a warning for both QT prolongation and cardiac arrhythmias with the use of Ondanseterone. In a study examining birth defects after first trimester exposure to ondanseterone, no increased risk was found [48]. Various other studies have assessed the safety of ondanseterone during pregnancy and failed to report any major malformation or birth defects [49-51].

A recent cohort study investigating the risk of birth defects with ondanseterone use during pregnancy revealed ondanseterone was not associated with increased risk of spontaneous abortion, still birth, or delivery of a low birth weight or delivery of a small for gestational age infants [48]. A case study reported ondanseterone used in all the trimester for Hyperemesis Gravidarum and reported no adverse effects on both mother and fetus. Hence, there is an increase evidence for the use of ondanseterone during pregnancy [52].

Glucocorticoids

Glucocorticoids are known to treat severe intractable hyperemesis gravidarium. Several studies have evaluated the safety and effectiveness of corticosteroids during pregnancy. Hyperemesis Gravidarum associated with dehydration or severe form NVPs [35,53]. In a meta-analysis of 4 studies, use of glucocorticoid before 10 weeks gestation is associated with cleft palate defects, higher doses causing higher risks. Hence, it was recommended to use corticosteroids only after 10-week gestation [53].

Few studies conducted on efficacy of corticosteroids were found to be contradictory [54]. Nelson-Piercy compared 40 mg prednisolone with placebo over 25 patients and found no improvement in nausea and vomiting [55]. Steroid treatment for hyperemesis still remains controversial and is reserved for women with refractory cases and those who do not respond to any other antiemetic.

Management of Nausea and Vomiting in Pregnancy

A Limited number of guidelines that provide a clear algorithm for the selection of pharmacological agents are available. Some guidelines discuss the management of NVP very briefly, [56] while others have not been updated since 10 years or more [57,58]. Generally, there is a consistent agreement on the preference of the use of pyridoxine, or pyridoxine/doxylamine as first-line therapy in the management of NVP, due to its confirmatory efficacy and safety data [57-59]. On the other hand, the use of corticosteroids is reserved for severe nausea and vomiting in refractory cases, and should be avoided in the first 10 weeks of pregnancy due to possible increased risk of oral clefting [57-59]. The selection of other medication classes varies slightly between different algorithms [5,57-59]. An evidence-based treatment algorithm has been adapted from the Society of Obstetricians and Gynaecologists of Canada (SOCG) [58], American College of Obstetrics and Gynecology (ACOG) [57], Australian Prescriber, [59] and other references [5,11,12], which is shown in Box.1.

Clinical Implications

The current work reviewed the safety and efficacy of the commonly used agents for the management of nausea and vomiting of pregnancy. It helps clinicians to view different pharmacological agents' advantages and disadvantages compared to each other when selecting medications for pregnant women. Selection of these agents is also individualized according to mother symptoms and resonse.

This review is limited to the pharmacological agents, where some herbal products and non-pharmacological interventions are also shown to be effective in managing nausea and vomiting of pregnancy.

Conclusion

Given the high prevalence of nausea and vomiting in pregnancy, a wide variety of treatment options are used to reduce the symptoms. Although most of these are proven to be effective, there is a paucity of literatures to support the safety and efficacy of pharmacological agents used to treat NVPs. However, majority of findings revealed there is a lack of evidence associating prenatal antiemetic and birth defects. FDA approved the combination of pyridoxine-doxylamine was considered safe in pregnancy and recommended as first line therapy for NVPs. Teratogenicity of antihistamines and dopamine antagonists has still not been conclusively determined. The risk with diphenhydramine and dimenhydrinate appear to be low. Drugs like ondanseterone and corticosteroids should be preserved for refractory cases and glucocorticoids are advised only after 10-12 weeks gestation. It is advised, pharmacological treatment should not be withheld because of fear of harming the baby.

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