REVIEW ARTICLE

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A Risk-Benefit Assessment of Pharmacological and Nonpharmacological Treatments for Nausea and Vomiting of Pregnancy

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Abstract

Despite evidence of fetal safety, most antiemetics are contraindicated in pregnancy. We summarise a risk-benefit analysis of the literature on safety and effectiveness of pharmacotherapy and nontraditional therapy for nausea and vomiting of pregnancy (NVP) to provide evidence-based guidelines on the management of NVP.

The medical literature was scanned for controlled studies on the human teratogenicity and effect of various antiemetics in pregnant women. Data were pooled based on drug/therapy class and summarised to determine relative risk with 95% confidence interval (for malformations and failure rates for NVP) and homogeneity (chi-square test).

Evidence from controlled trials has demonstrated the safety and efficacy of the following drugs for the treatment of varying degrees of NVP: doxylamine/pyridoxine±dicycloverine (dicyclomine), antihistamine H_1 receptor antagonists, and phenothiazines (as a group). However, pooled data for doxylamine/pyridoxine±dicycloverine, H_1 antagonists and phenothiazines were not homogeneous. Other therapies, such as pyridoxine alone, metoclopramide, ondansetron and the corticosteroids may be beneficial in managing NVP. However, limited efficacy studies and the paucity of well-controlled safety studies may limit the use of some of these agents among patients not responsive to first-line agents. Well-controlled safety and effectiveness trials in patients with NVP are lacking for nonpharmacological treatments (e.g. acupressure).

NVP can be managed safely and effectively. Further trials must be conducted in order to determine the true effectiveness of certain agents in patients with NVP.

1. Epidemiology of Nausea and Vomiting of Pregnancy (NVP)

Descriptions of nausea and vomiting of pregnancy (NVP) date back to writings from the second century AD. This is not surprising given that NVP affects up to 80% of pregnant women to some degree.[1] Symptoms are usually limited to 7 to 12 weeks' gestation, although fewer than 1% of women develop 'hyperemesis gravidarum', which is characterised by severe physical symptoms and/or medical complications later on during the pregnancy.[2]

2. Aetiology of NVP

The pathogenesis of NVP is poorly understood, and proposed aetiologies abound.[3] Aetiological roles have been proposed for gestational hormones[4] (e.g. human chorionic gonadotropin), thyroid hormones,[5-8] blunted autonomic nervous system function and dysregulation of gastric rhythms,[9] and psychological factors.[10,11] However, no causal associations have been proven. The aetiology of NVP is likely to be multifactorial, and NVP remains a diagnosis of exclusion after other potential causes of nausea and vomiting have been ruled out.[12] The

diagnosis of NVP is confirmed by symptoms which are self-limited, usually to early pregnancy, but definitely to pregnancy itself.

3. Evidence-Based Guidelines

No evidence-based formal guidelines exist for the management of NVP. In the aftermath of the thalidomide disaster, most antiemetics have been considered to be contraindicated in pregnancy, despite evidence of safety in human pregnancy.[13] Most reviews and editorials[14-17] advise that antiemetic therapy be instituted only when women are unable to maintain hydration and/or nutrition.[16]

4. Methods of Evaluation of Clinical Trials of Safety and Efficacy

The following sources were searched for relevant articles: i) Medline (1966 to June 1998 - key words used were nausea, vomiting, emesis, hyperemesis gravidarum, morning sickness, pregnancy, pregnancy complications, treatment, efficacy, effectiveness, teratogens, abnormalities drug-induced, placenta, embryo, fetus, maternal fetal exchange, toxicology); ii) Pregnancy and Childbirth Module of Cochrane Database of Systematic Reviews (specifically for clinical trials on therapies to treat NVP); iii) bibliographies of retrieved papers; iv) a standard toxicology text;[18] and v) records of personal communication with various pharmaceutical companies, as well as with researchers and clinicians in the fields of pharmacology, toxicology, obstetrics and paediatrics. Of interest were both nonpharmacological (e.g. dietary) and pharmacological therapies for NVP.

Table I lists the available antiemetics based on knowledge of physiological pathways mediating nausea and vomiting, and drug effectiveness data from nonpregnant patients. These drugs include antagonists to histamine, acetylcholine, dopamine and/or serotonin (5-hydroxytryptamine; 5-HT_3) receptors, located in the chemoreceptive trigger zone, vestibular apparatus and visceral afferents. Both safety and efficacy were evaluated for each drug/drug class.

For evaluation of safety, we sought observational, controlled studies of either inadvertent drug exposure or treatment of life-threatening complications in early pregnancy, given that NVP is usually limited to the first trimester. Case reports/series and animal data were included only in the absence of controlled data. Inclusion criteria (for evaluation of safety) were English/French language, pregnancy, pharmacological or nonpharmacological treatment for NVP, and assessment of major/minor malformations after first trimester exposure.

For evaluation of efficacy, we sought randomised, controlled trials of treatment versus placebo or standard care for the treatment of NVP. Inclusion

Table I. Summary of antiemetic therapies[a] and related medications for nausea and vomiting of pregnancy.

Antiemetics and antinauseants	
Antihistamines (H_1 receptor antagonists)	Buclizine, cyclizine, dimenhydrinate, diphenhydramine, doxylamine (± pyridoxine), hydroxyzine, meclozine, promethazine, trimethobenzamide
Vitamins	Pyridoxine (vitamin B_6), cyanocobalamin (vitamin B_{12})
Anticholinergics	Dicyclomine, scopolamine
Dopamine antagonists	Chlorpromazine, perphenazine, prochlorperazine, promethazine, trifluoperazine, trimethobenzamide, domperidone, droperidol, metoclopramide
Serotonin (5-hydroxytryptamine; 5-HT_3) receptor antagonists	Ondansetron, granisetron, tropisetron
Prokinetics	Domperidone, metoclopramide, cisapride
Corticosteriods	Cortisone, dexamethasone, prednisone
Ginger	
Cannabinoids	Dronabinol, nabilone
Ancillary therapy	
Antacids	Aluminum hydroxide, magnesium hydroxide, calcium carbonate
H_2 receptor antagonists	Cimetidine, famotidine, nizatidine, ranitidine
Proton-pump inhibitors	Lansoprazole, omeprazole
Non-pharmacological therapies	
Acupuncture/Acupressure	
Psychotherapy	

a Some drugs fall into more than one class.

GI = gastrointestinal.

criteria (for evaluation of efficacy) were English/French language, human pregnancy, pharmacological or nonpharmacological treatment for NVP compared with no therapy/other therapy for NVP, and assessment of the effect of treatment on maternal physical (i.e. nausea, vomiting, hospitalisation), emotional or social functioning.

Abstracted data were entered into 2 × 2 tables using the Cochrane Review Manager version 3.0.1. software for IBM-compatible computers. Data entry was double-checked. For each grouping of trials, the following explanatory variables were considered as potential sources of between-study variability in outcomes: study design (for observational studies), and characteristics of participants, intervention and outcome definitions.

The summary statistic for pooled safety and efficacy data was the relative risk (RR), defined as the event rate among drug-exposed (n_1/N_1, where n_1 = number of individuals exposed to drug with an event and N_1 = total number of individuals exposed to the drug) compared with non-exposed (n_2/N_2, where n_2 = number of individuals not exposed to the drug with an event and N_2 = total number of individuals not exposed to the drug). Pooling of study results in the form of a summary RR and 95% confidence interval (CI) was based on the fixed effects model. Studies in which no outcomes were observed in either arm were not informative for analysis. The null hypothesis (of no variation in outcome between 'n' studies) was not rejected (and the pooling of outcomes was considered valid) if the chi-square test of homogeneity was less than the upper 95th percentile of the chi-square distribution with (n-1) degrees of freedom (df). An RR of 1 reflected no treatment effect. An RR of <1 reflected fewer events among antiemetic-treated groups.

5. Summary of Eligible Trials

For evaluation of safety, 26 cohort studies, 11 case-control studies and 1 record linkage study were identified from the period 1962 to 1998. All were controlled trials comparing malformation rates after first-trimester exposure to antiemetic(s) with rates of malformations after no exposure to a specific antiemetic(s). The exception was the Michigan Medicaid record linkage study[18] which only documented the proportion of malformations reported in patients exposed to the drug in question.

For evaluation of efficacy, 19 randomised, controlled trials (RCT) with placebo, 4 alternate allocation trials with placebo ± standard treatment and 2 RCT with standard treatment were identified from the period 1951 to 1998. Outcomes assessed have included only physical outcomes (e.g. nausea, vomiting); no trial examined any impact that treatment may have on emotional and social health.[19] Most trials reported 'treatment failure' (variably defined subjectively as resolution or a clinically important reduction in vomiting). Also reported variably were the effect of treatment on the duration of symptoms during the pregnancy, or the rate of hospitalisation.

The review will first focus on diet and lifestyle changes given that appropriate nutritional intake and modification of daily activities are usually recommended as first-line management by physicians and other caregivers. Then pharmacological therapy will be discussed followed by nonpharmacological and ancillary therapies.

6. Dietary and Lifestyle Changes

Traditionally, diet has been the mainstay of treatment for women with NVP. Recommendations have included eating small frequent meals, avoiding fatty foods, eating potato chips, and drinking cold, tart or sweet beverages.[14,20] Recent guidelines have listed a number of foods that may appeal to women with NVP.[21]

There is little reason to question the assumption that dietary recommendations are safe, especially when vitamin supplements (including B-complex) are routinely ingested during pregnancy. However, caution is warranted with diets containing supra-pharmacological doses of individual vitamins given the paucity of data.

A search of the medical literature has failed to reveal evidence-based research on the effectiveness of dietary treatment for NVP.

7. Pharmacological Therapies

7.1 Antihistamines

Although a large number of histamine antagonists are available, only the following have been evaluated for nausea and/or vomiting: buclizine, cyclizine, dimenhydrinate, diphenhydramine, doxylamine, hydroxyzine, and meclozine (meclizine).

7.1.1 Doxylamine

Safety

Doxylamine, originally marketed as 10mg with 10mg of pyridoxine (vitamin B_6) and dicycloverine (dicyclomine), is currently marketed in Canada as a fixed combination with 10 mg of pyridoxine. The drug combination was first introduced in 1957 just after the thalidomide tragedy. Soon after the introduction of doxylamine/pyridoxine±dicycloverine, thousands of claims were made alleging teratogenic effects of the medication. As a result, the combination was voluntarily withdrawn from the world market, even though epidemiological studies were not able to demonstrate an association between the drug and malformations. Figure 1 summarises a meta-analysis which pooled data from 12 cohort and 3 case-control studies (n = 15), involving 17 427 first trimester exposures, which were published between 1963 and 1991.[37] First-trimester exposure to doxylamine/pyridoxine±dicycloverine was not associated with an increased risk for major/minor malformations, whether the malformations were pooled or individually isolated, and the pooled data exhibited homogeneity [pooled RR for major/minor malformations was 0.98, (95% CI 0.93,1.03); $\chi^2 = 16.79$ with 14 df].

Effectiveness

To date, 4 clinical trials of doxylamine/pyridoxine±dicycloverine compared with placebo have been published.[38-41] Figure 2 indicates that there was significant between-trial heterogeneity in estimates of treatment failure ($\chi^2 = 14.39$ with 3 df). The heterogeneity could not be explained by the characteristics of the participants enrolled (who had moderate NVP) or outcome definitions (which, when reported, detailed treatment failure as being subjectively assessed). However, the trial that administered up to 4 tablets per day of doxylamine/pyridoxine±dicycloverine[38] (as currently recommended by the drug manufacturer) showed the greatest treatment effect.

7.1.2 Other Antihistamines

Safety

A wide body of evidence suggests that H_1 receptor antagonists (e.g. dimenhydrinate, diphenhydramine, hydroxyzine) have no human teratogenic potential.[57] The safety of antihistamines in pregnancy was confirmed by a recent meta-analysis which reviewed 24 controlled studies involving over 200 000 first-trimester exposures published between 1960 and 1991. First trimester exposure to various antihistamines actually revealed a slightly lower risk for major/minor malformations [pooled odds ratio (OR) = 0.76 (95% CI 0.60,0.94)].[58] Figure 3 summarises 11 trials involving 4688 first trimester exposures (not necessarily mutually exclusive) to buclizine (n = 59),[25,60] cyclizine (n = 23),[25,60] dimenhydrinate (n = 394),[25,59,63] diphenhydramine (n = 1251),[25,29,34,61] doxylamine (n = 1333),[24,25] hydroxyzine (n = 167)[25,47,64] and/or meclozine (n = 1131).[24,25,60,62] Although exposure to any of these agents does not pose an increased risk for congenital anomalies [RR = 1.02 (95% CI 0.94,1.12)], the pooled data were not homogeneous (i.e. $\chi^2 = 21.97$ with 10 df). A source of heterogeneity may be the combining of different antihistamines which have distinct chemistry and therefore may not act similarly at the cellular level. It should also be noted that another prospective cohort study failed to find an association between major malformations and first trimester exposure to 1 or more antihistamines (including meclozine, cyclizine, trimethobenzamide and/or doxylamine) or phenothiazines [RR = 1.14 (95% CI 0.81,1.60)][65]

Effectiveness

A summary of 7 controlled trials examining the effectiveness of various antihistamines for NVP is outlined in figure 2.[41-47] Although pooled data indicate that antihistamines are effective in reducing treatment failure [RR = 0.34 (95% CI 0.27,0.43)],

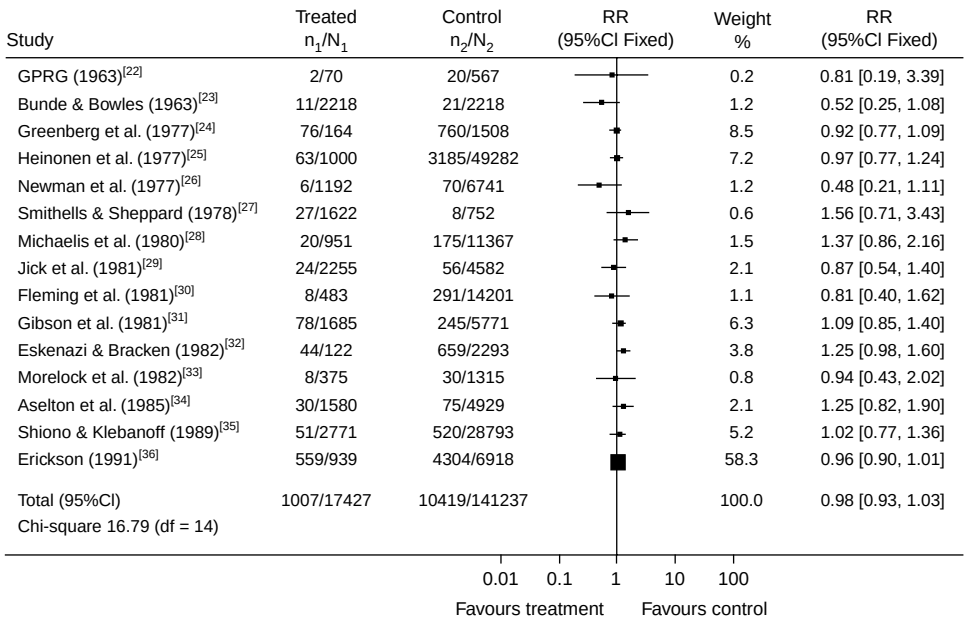

Fig. 1. Summary analysis for controlled observational teratogenicity studies (n = 15) of doxylamine/pyridoxine±dicycloverine. **CI** = confidence interval; **control** = untreated control; **df** = degrees of freedom; **GPRG** = General Practitioner Research Group; **n/N** = see methods section 4 for definition; **RR** = relative risk.[37]

the studies are not homogeneous (χ^2 = 28.88 with 6 df). The reason for the heterogeneity may be due to the variety of histamine antagonists used in each trial. It may be inappropriate to combine different antihistamines given that they are structurally distinct and may have effects at various receptor sites. When trials of meclozine versus placebo were combined, the pooled relative risk was significant but the studies did not exhibit homogeneity [i.e. RR = 0.24, (95% CI 0.14,0.40), χ^2 = 15.49 with 3 df].[24,25,60,62]

7.2 Vitamins

7.2.1 Pyridoxine (Vitamin B_6)

Pyridoxine is a water-soluble B complex vitamin that is a necessary coenzyme in the metabolism of amino acids, carbohydrates and lipids.[66] Although pyridoxine, as part of a fixed combination with doxylamine, is found in doses of 10mg per tablet, prenatal supplements contain 10mg or less in each tablet.

Safety

Pyridoxine has proven not to be teratogenic in combination with doxylamine, with or without dicycloverine (see section 7.1.1). In addition, a retrospective cohort study failed to link pyridoxine monotherapy with an increase in major malformations [18/458 (cases) *vs* 34/911 (controls); RR = 1.05 (95% CI 0.60,1.84)].[60]

Effectiveness

Original placebo-controlled trials conducted by the manufacturers of doxylamine/pyridoxine±dicycloverine determined that pyridoxine was effective for the reduction of NVP,[41] although the pharmacological action of pyridoxine was not fully understood. Subsequently, two RCT using pyridoxine alone (25mg orally every 8 hours,[52] and 10mg orally three times daily[53]) versus placebo were conducted. When pooled with the original doxylamine/pyridoxine±dicycloverine data,[41] the trials were homogeneous (χ^2 = 4.44 with 2 df). Although treatment failure did not differ significantly

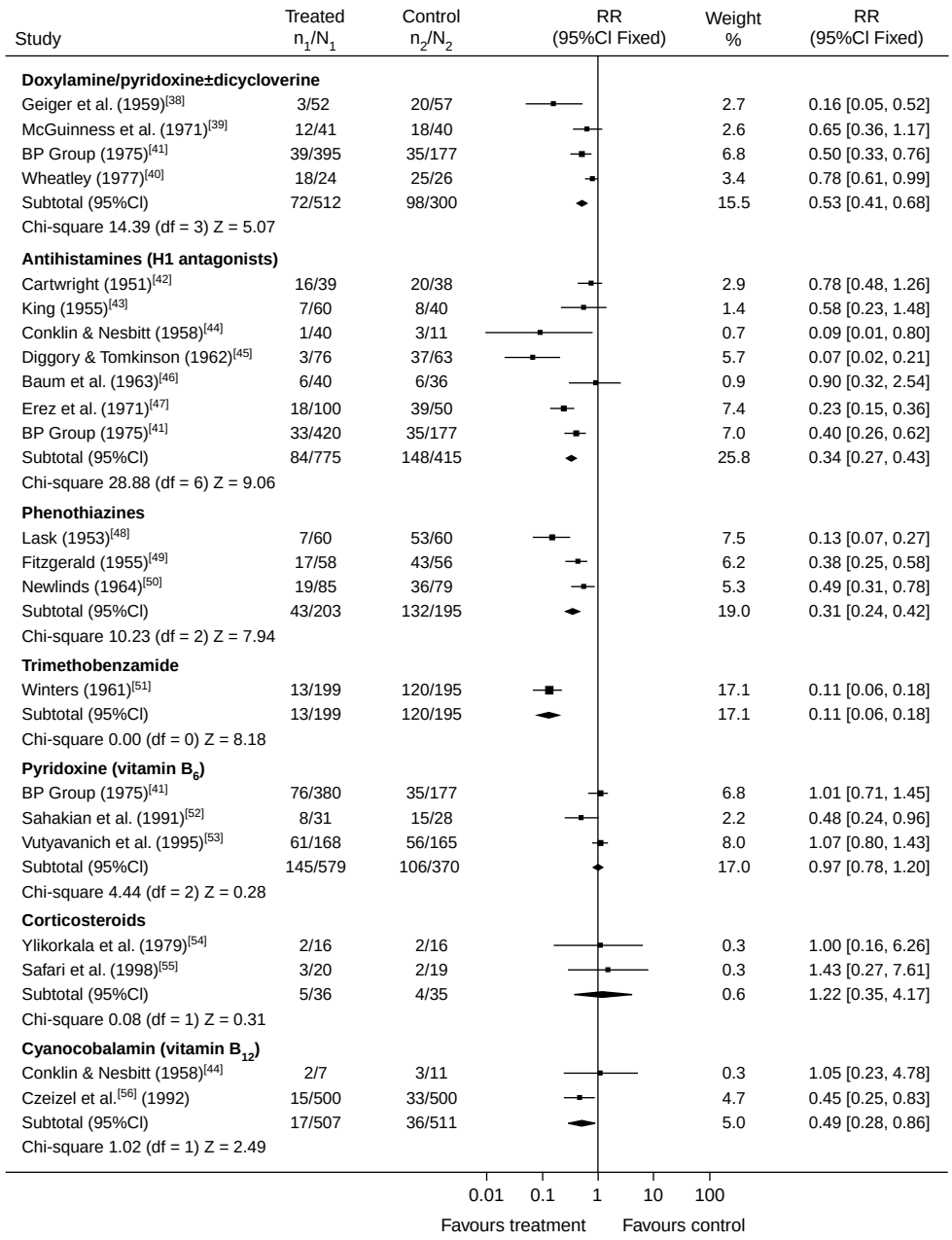

Fig. 2. Treatment failure rates for doxylamine/pyridoxine±dicycloverine, antihistamine (H_1 receptor antagonists), phenothiazine, trimethobenzamide, pyridoxine, corticosteroid and cyancobalamin (vitamin B_{12}) in controlled effectiveness trials for nausea and vomiting of pregnancy. **CI** = confidence interval; **control** = untreated controls; **df** = degrees of freedom; **n/N** = see methods section 4 for definition; **RR** = relative risk .

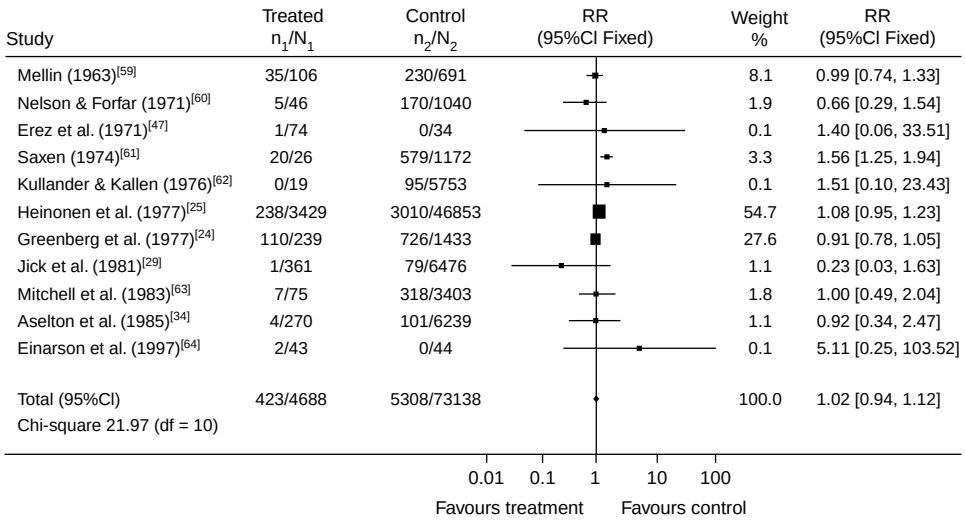

Fig. 3. Summary analysis for controlled observational teratogenicity studies (n = 11) of antihistamines (H1 receptor antagonists). **CI** = confidence interval; **control** = untreated control; **df** = degrees of freedom; **n/N** = see methods section 4 for definition; **RR** = relative risk.

between groups [pooled RR = 0.97 (95% CI 0.78,1.20); fig. 2], pyridoxine was shown to significantly decrease nausea score [pooled weighted mean difference for change in nausea score = 0.918 (95% CI 0.441,1.395) fig. 4].

7.2.2 Cyanocobalamin (Vitamin B_{12})

Cyanocobalamin (vitamin B_{12}) is a water-soluble vitamin that is responsible for normal blood formation, renal function and growth. It has been suggested that cyanocobalamin, along with pyridoxine, is therapeutic in the management of NVP.[67]

Safety

Although cyanocobalamin has been shown to cross the human placenta,[68] recent evidence suggests that cyanocobalamin in combination with folic acid may prevent neural tube defects.[69] There have been no other controlled trials to determine the potential teratogenicity of cyanocobalamin in human pregnancy, although given its role in inhibiting malformations, teratogenicity is unlikely.

Effectiveness

Two RCT exist on the effectiveness of cyanocobalamin to treat NVP. Pooled data comparing cyanocobalamin[44] and multivitamins (including cyanocobalamin)[56] with placebo show homogeneity and a significant effect in the reduction of nausea and vomiting [χ^2 = 1.02 with 1 df, pooled RR = 0.49 (95% CI 0.28,0.86); fig. 2].

7.3 Anticholinergics

Only dicycloverine and scopolamine are in use for the treatment of nausea and vomiting in the nonpregnant population.

7.3.1 Dicycloverine

Safety

The meta-analysis of doxylamine/pyridoxine± dicycloverine failed to demonstrate an increased risk associated with the combination.[37] In addition, a prospective cohort study could not detect an increase in malformations, compared with controls, in women exposed to dicycloverine during the first trimester [48/1024 (cases) *vs* 3200/49 258 (controls); RR = 1.04 (95% CI 0.82,1.30)].[25]

Effectiveness

Dicycloverine failed to demonstrate independent or synergistic effectiveness in combination with doxylamine and pyridoxine for the treatment of NVP.[41]

7.3.2 Scopolamine

Safety

Teratogenicity studies are limited to two controlled observational studies: a prospective cohort of 309 first trimester exposures[25] and a record linkage study of 27 first trimester exposures.[18] Neither revealed an increased risk for malformations [14/309 (cases) *vs* 3234/49 973 (controls); RR = 1.05 (95% CI 0.70,1.59) and 1/27 exposed (malformation rate = 3.7%), respectively].

Effectiveness

No RCT for treatment of NVP with scopolamine are available.

7.4 Dopamine Antagonists

A number of dopamine antagonists may be used to treat NVP: phenothiazines (i.e. chlorpromazine, perphenazine, prochlorperazine, promethazine and trifluoperazine), domperidone, droperidol, metoclopramide and trimethobenzamide.

7.4.1 Phenothiazines

Safety

Anecdotal case reports have tried to associate first trimester phenothiazine use with major malformations.[70-75] However, prospective cohort,[25,62,65,76,77] retrospective cohort,[60] case-control[24,63] and record-linkage[34] studies of patients with exposure to various and multiple phenothiazines [chlorpromazine (n = 199), perphenazine (n = 203), prochlorperazine (n = 1018), promethazine (n = 1006), and trifluoperazine (n = 522)] have failed to demonstrate an increased risk for major malformations [pooled RR = 1.03 (95% CI 0.88,1.22)]. However, the pooled studies exhibit heterogeneity (χ^2 = 19.23 with 7 df). Rumeau-Rouquette and colleagues[76] conducted the one study that found a relationship between phenothiazine use in pregnancy and congenital anomalies. However, the study did not take into account time of exposure and other confounders such as concomitant medical conditions and concurrent medication, alcohol or smoking use during pregnancy. When the study by Rumeau-Rouquette et al.[76] is removed from the pooled data analysis, the remaining trials are homogeneous and present a negative association between phenothiazine use and the risk for malformations [χ^2 = 7.05 with 6 df, pooled RR = 1.00 (95% CI 0.84,1.18); fig. 5]. Therefore, the bulk of evidence suggests that phenothiazines show no evidence of teratogenicity.

Effectiveness

There have been 3 RCT of various phenothiazines versus placebo for treatment of (usually severe) NVP.[48-50] In total, 43/203 patients randomised to a phenothiazine failed to experience improvement of their NVP, compared with 132/195 randomised to placebo or no therapy. The pooled RR of 0.31

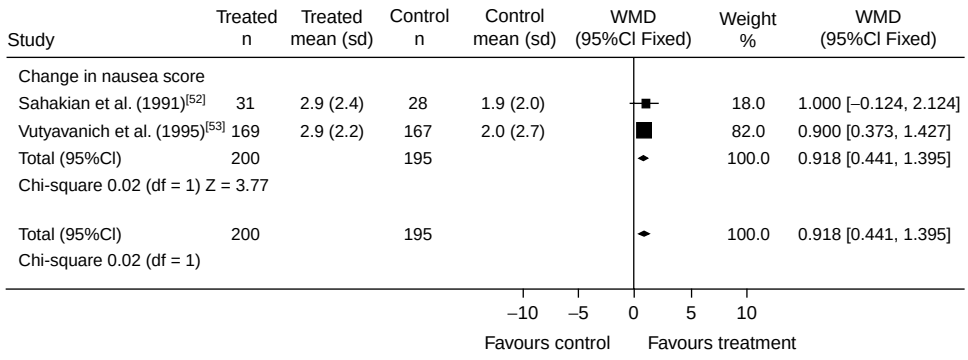

Fig. 4. Change in nausea score from a controlled effectiveness trials of pyridoxine (vitmain B_6). **CI** = confidence interval; **df** = degrees of freedom; **n** = number of patients; **sd** = standard deviation; **WMD** = weighted mean difference.

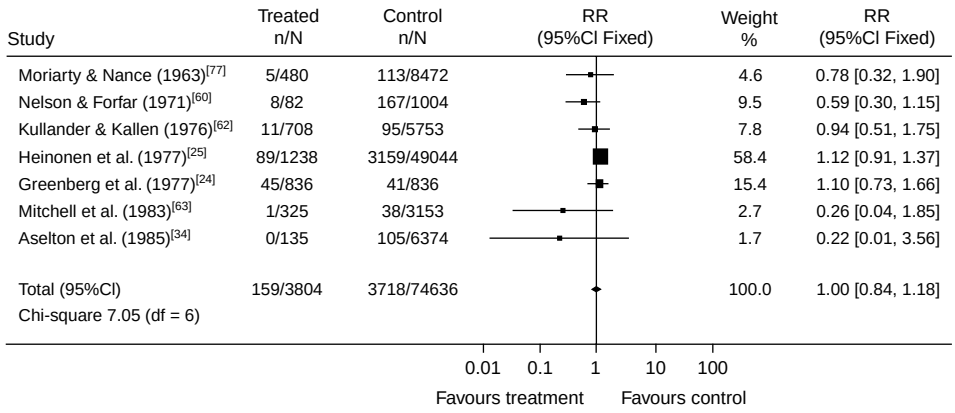

Fig. 5. Summary analysis for controlled observational teratogenicity studies (n = 7) of phenothiazines. **CI** = confidence interval; **control** = untreated control; **df** = degrees of freedom; **n/N** = see methods section 4 for definition; **RR** = relative risk.

(95% CI 0.24,0.42) reflected a significant therapeutic effect (fig. 2). Although the trials were inconsistent with respect to their results ($\chi^2 = 10.23$ with 2 df), all reported a significant reduction in symptoms with phenothiazine treatment. Therefore, what is at issue is the magnitude of the effectiveness of phenothiazines for NVP, and not the effectiveness of phenothiazines *per se*. Individual phenothiazines may act at distinct receptors or receptor subtypes.

7.4.2 Domperidone

Safety

Domperidone was not teratogenic in animals in doses greater than 100 times the recommended human dose.[78] No published human data are available.

Effectiveness

No RCT of domperidone in pregnancy have been published.

7.4.3 Droperidol

Safety

Only 1 study exists in the medical literature on first trimester exposure to droperidol. The study was a report of a prospective series of 80 women with hyperemesis gravidarum, treated with a combination of droperidol and diphenhydramine. They were compared with a retrospective series of 73 women with a similar severity of hyperemesis gravidum, who had been treated with a variety of other antiemetics.[79] The authors reported 3 malformations in the exposed group and 2 malformations in the control group. However, some malformations were suspect to other potential confounders (e.g. genetic predisposition). Hence, the safety of droperidol has not been established and awaits further controlled trials.

Effectiveness

The aforementioned study of droperidol and diphenhydramine is the only one available.[79] The authors reported women treated with the droperidol/diphenhydramine combination had significantly shorter hospitalisations (3.1 ± 1.9 *vs* 3.8 ± 2.4 days, $p = 0.03$) and fewer readmissions (15.0% *vs* 31.5%, $p = 0.02$). However, given the variety of agents used by controls in this study (e.g. prochlorperazine, promethazine, metoclopramide), and the reported lack of standardisation of post-discharge therapy among historical controls, confirmation of the effectiveness of droperidol awaits RCT.

7.4.4 Metoclopramide

Metoclopramide has not been extensively studied for treatment of NVP, even though in many countries, it is commonly used in clinical practice.[80,81]

Safety

Studies of the teratogenic potential of metoclopramide are limited. No malformations were reported among 4 first trimester exposures.[82,83] In a retrospective record linkage study,[18] no increase in major malformations above baseline [10/192 exposed (malformation rate = 5.2%)] and no pattern of defects were detected. Therefore, the data do not support an association between the drug and congenital defects.

Effectiveness

No RCT have been published to support the effectiveness of metoclopramide in the treatment of NVP.

7.4.5 Trimethobenzamide

Safety

Two cohort studies[25,34] and 1 case-control trial[63] have been published on the safety of first-trimester exposure to trimethobenzamide in human pregnancy. When combined, the pooled risk included unity [RR = 0.81 (95% CI 0.53,1.23)] and the trials were homogeneous (χ^2 = 0.66 with 2 df). Hence, trimethobenzamide does not seem to pose a teratogenic risk to the fetus.

Effectiveness

A single double-blind trial exists focusing on effectiveness of trimethobenzamide in treating NVP.[51] Trimethobenzamide alone or in combination with pyridoxine significantly improved symptoms of nausea and vomiting compared with placebo [RR = 0.11 (95% CI 0.06,0.18)].

7.5 Serotonin 5-HT_3 Antagonists

This class of drugs has recently been introduced for the management of chemotherapy-induced nausea and vomiting.

7.5.1 Ondansetron

Safety

Ondansetron failed to produce developmental toxicity in rats and rabbits at doses 70 times those administered to humans.[84] Use of ondansetron in the first trimester of human pregnancy has been limited. No malformations were reported in 3 case reports[85-87] nor in the setting of a RCT of 15 patients exposed during the first trimester.[88]

Effectiveness

There is one trial of intravenous ondansetron versus promethazine for the treatment of severe NVP.[88] Ondansetron did not demonstrate a benefit over promethazine using the following outcome measures: severity of nausea, daily weight gain, days requiring hospitalisation, treatment failures and voluntary use of the drug. It did not appear that the lack of statistical differences between groups resulted from low statistical power.

7.5.2 Granisetron and Tropisetron

Safety

There are no controlled human studies on the safety of either granisetron or tropisetron in pregnancy.

Effectiveness

There are no RCT on the effectiveness of either granisetron or tropisetron for treating NVP.

7.6 Prokinetics

7.6.1 Cisapride

Cisapride in a prokinetic agent which lacks central and peripheral antidopaminergic effects.

Safety

A recent multicentre prospective controlled study of 88 first trimester exposures to cisapride failed to detect an increase in major malformations when compared with disease-paired (DPC) and nonteratogenic controls (NTC) [i.e. 6.8% (cisapride) *vs* 5.7% (DPC) p = 0.77, *vs* 3.4% (NTC) p = 0.33].[89]

Effectiveness

No RCT have been published on the effectiveness of cisapride in treating NVP.

7.7 Corticosteroids

It has been hypothesised that severe NVP results from corticotropin (adrenocorticotropic hormone; ACTH) deficiency.[90] This, coupled with the successful use of corticosteroid treatment for chemotherapy-induced emesis,[91] has increased aware-

ness of the potential benefit of corticosteroids in treating NVP. Steroids that have been proposed include cortisone, dexamethasone and prednisolone.

Safety

Preliminary animal data suggested corticosteroid use was associated with an increased risk for cleft palate.[92] In a recent meta-analysis, the pooled RR for cohort[25,93-97] and case-control studies[98,99] combined revealed no increase in the risk of major malformations associated with first trimester exposure to corticosteroids [RR = 1.24, 95% CI (0.97, 1.60), and the results were homogeneous between studies (χ^2 = 5.21 with 6 df)[100] [fig. 6]. However, a subanalysis involving only the case-control studies (which have greater statistical power for unusual events such as major malformations) revealed a significant, small increase in the risk of oral clefting associated with first trimester exposure to corticosteroids[56,101,102] [RR = 7.08, 95%CI (3.00,16.68)], and the results were homogeneous between studies (χ^2 = 2.57 with 2 df).

Effectiveness

Case reports and case series, involving a total of 49 patients, have reported the use of corticosteroids in patients with hyperemesis gravidarum.[90,103-106] Figure 2 summarises 2 trials using either corticotropin or corticosteroids. Ylikorlaka et al.[54] compared intramuscular corticotropin to placebo in women with hyperemesis gravidarum while Safari et al.[55] compared methylprednisolone to promethazine in women with hyperemesis gravidarum. The pooled results failed to show a reduction in the number of subsequent re-admissions to hospital compared with controls. In addition, corticotropin was not found to be superior to placebo based on 'severity' or 'relief' scores (fig. 7).[54]

7.8 Ginger

Ginger (*Zingiber officinale*) is a common spice used for the treatment of nausea and vomiting. It can be obtained through tablet extracts, teas or direct ingestion of the ginger root.

Safety

Data on the safety of ginger in pregnancy are lacking. However, it is found in the diet of many cultures in doses recommended for the treatment of NVP (1000 mg/day).[107]

Effectiveness

A small crossover trial with placebo failed to demonstrate the effectiveness of ginger in women with hyperemesis gravidarum, based both on 'severity' and 'relief' scores (fig. 8).[107]

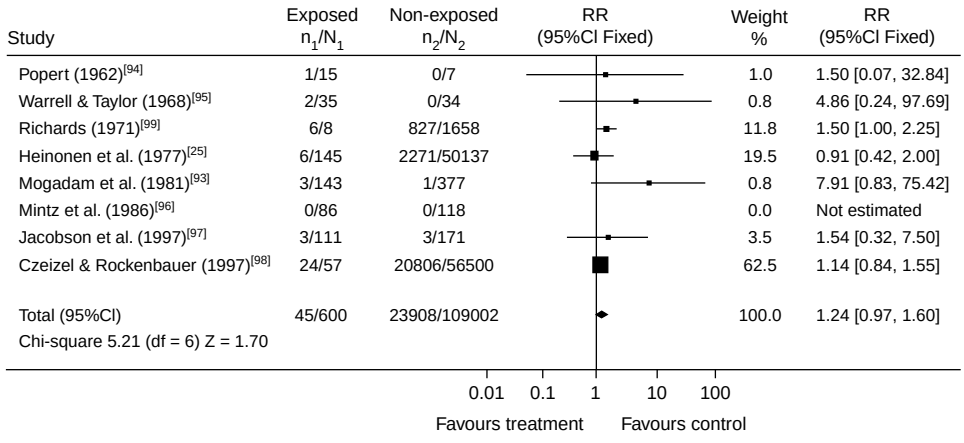

Fig. 6. Summary analysis for controlled observational teratogenicity studies (n = 7) of corticosteroids. **CI** = confidence interval; **control** = untreated control; **df** = degrees of freedom; **n/N** = see methods section 4 for definition; **RR** = relative risk.

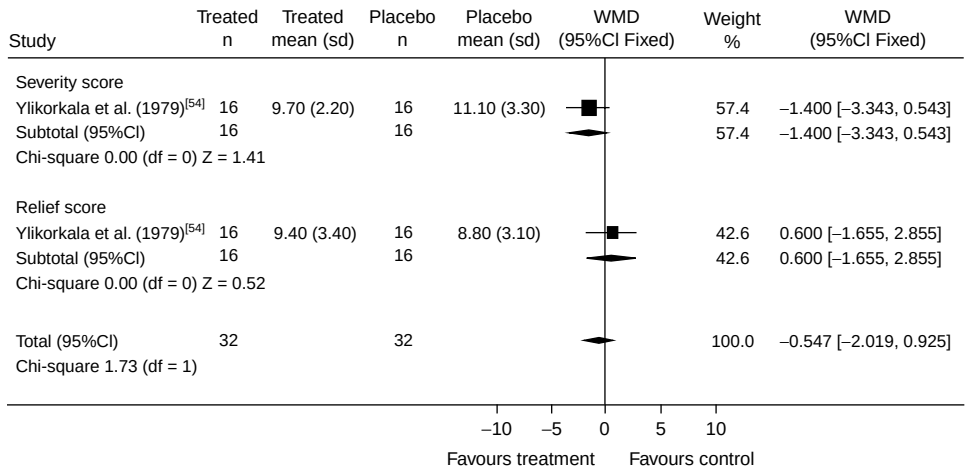

Fig. 7. Severity and relief NVP scores from a placebo controlled trial of corticotropin. **CI** = confidence interval; **df** = degrees of freedom; **n** = number of patients; **NVP** = nausea and vomiting of pregnancy; **sd** = standard deviation; **WMD** = weighted mean difference.

7.9 Cannabinoids

Delta-9-tetrahydrocannabinol (δ-9-THC), the major pharmacologically active constituent of cannabis, has been shown to relieve chemotherapy-induced nausea and vomiting in a number of randomised, placebo-controlled trials.[108-110] Nabilone, a synthetic cannabinoid with antiemetic properties, is indicated for the control of chemotherapy-induced nausea and vomiting. However, human studies on the use of cannabinoids in pregnancy, or for the treatment of NVP specifically, have not been conducted.

8. Nonpharmacological Therapies

In light of concerns about the teratogenic potential of pharmacological interventions to treat NVP, many women choose to use 'natural', nonpharmacological approaches. Although many are without safety concerns, most are of unproven effectiveness in both nonpregnant and pregnant populations.

8.1 Acupuncture/Acupressure

The practice of acupuncture originated in the Orient and has its basis in the idea that specific points on the body control certain bodily functions. Stimulation of the P6 (Neiguan) point, located 3 fingers breadth proximal to the wrist, has been used for thousands of years by acupuncturists to treat nausea and vomiting from a variety of causes (e.g. motion sickness, cancer chemotherapy).

Safety

There are no theoretical concerns about the safety of acupressure in pregnancy.

Effectiveness

There have been 7 published RCT of P6 stimulation (by acupressure or afferent stimulation) for treatment of NVP.[111-117] These trials were summarised in a quantitative overview,[17] which concluded that P6 acupressure significantly decreased 'persisting nausea' by at least 50%. However, methodological flaws (primarily, lack of blinding in these trials) led to the conclusion that confidence could not be placed in the demonstrated effectiveness of P6 acupressure.

8.2 Psychotherapy

Psychotherapy usually involves hypnosis and other positive reinforcements through subconscious meditation.

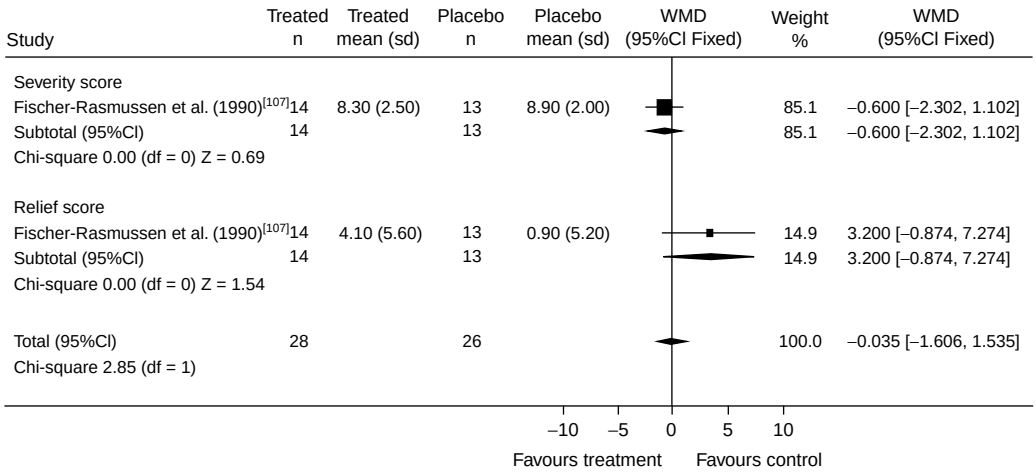

Fig. 8. Severity and relief NVP scores from a controlled effectiveness trial of ginger in women with hyperemesis gravidarum. **CI** = confidence interval; **df** = degrees of freedom; **n** = number of patients; **NVP** = nausea and vomiting of pregnancy; **sd** = standard deviation; **WMD** = weighted mean difference.

Safety

There are no theoretical concerns about the safety of psychotherapy in pregnancy.

Effectiveness

Two case series describe successful treatment of severe forms of NVP through hypnosis.[118,119] A prospective controlled study, using adjunctive psychotherapy in 10 patients with hyperemesis gravidarum, suggested benefit in combination with antiemetic medication.[120]

9. Ancillary Therapies

Ancillary therapies are used primarily to treat acid reflux that may arise as a result of vomiting. They have been shown to be effective in providing symptomatic relief in the nonpregnant population; no clinical trials have been published in pregnancy.

9.1 Antacids

Drugs of this class usually contain salts of magnesium, calcium or aluminum. They are used by up to 50% of pregnant women with gastric reflux conditions.[121] A case-control study revealed an increased risk for major malformations when antacids were grouped [i.e. 12/175 (cases) *vs* 24/911 (controls), OR = 2.24 (95% CI 1.31,3.83)],[60] although there were no significant differences with individual antacids. The overall consensus is that antacids are not human teratogens when used in recommended doses.[122-124]

9.2 H_2 Receptor Antagonists

This class of drugs includes cimetidine, ranitidine, famotidine, and nizatidine. Record linkage studies[18,125] examining exposure to cimetidine (n = 480 patients), ranitidine (n = 516), and famotidine (n = 33), have failed to report evidence in favour of teratogenicity. In the only prospective study on the topic,[126] no increase in major malformations was found following first trimester exposure to H_2 receptor antagonists [3/142 (2.1%) cases *vs* 5/143 (3/5%) controls; p = 0.55].

9.3 Proton Pump Inhibitors

Experience with omeprazole in human pregnancy is limited. A recent multicentre prospective cohort study of first trimester exposures did not detect an increased risk for malformations compared with disease-paired (DPC) and nonteratogenic controls (NTC) [4/101 (4.0%) omeprazole *vs* 3/109 (2.8%)

DPC; p = 0.71 and *vs* 2/98 (2.0%) NTC; p = 0.68].[127] Reproductive and developmental toxicology studies on lansoprazole are limited to animal data which failed to reveal teratogenicity.[128]

10. Conclusions

Management of any condition in pregnancy requires both the caregiver and patient to weigh both the risks and benefits of treatment. Since the thalidomide tragedy, the risks of drug therapy in general, and antiemetic therapy specifically, have been overestimated.[129] This comprehensive review of the literature has revealed that there are a number of pharmacological and nonpharmacological therapies available which have proven safety and effectiveness for treatment of NVP (table II).

Many drugs have proven not to be teratogenic to the developing fetus. The prototype is the doxylamine/pyridoxine±dicycloverine combination since it has been studied in the largest number of patients (≈200 000 first trimester exposures). However, as a delayed-release formulation, doxylamine/pyridoxine is only available in Canada; its component drugs are widely available elsewhere. Potential drawbacks are the lack of acute relief due to the delayed-release coating, as currently marketed, and the fact that doxylamine is a sedating antihistamine.

As a group, antihistamines and the phenothiazines have also failed to demonstrate teratogenic potential, although the number of exposed patients studied has been lower than with doxylamine/pyridoxine±dicycloverine.

Safety data are limited (although reassuring) for cisapride, trimethobenzamide, metoclopramide, droperidol and ondansetron. There are no human data for domperidone, granisetron and tropisetron.

The safety of high dose corticosteroids in pregnancy is being cautiously questioned. If possible, their use should be avoided if the pregnancy is less than 10 weeks gestation, which is the critical period for oral cleft formation.

Although cannabinoids are used in clinical practice for the treatment of chemotherapy-induced nausea and vomiting, the medicolegal implications of cannabinoids and their derivatives and the potential health risks of inhaled substances during pregnancy would preclude the potential benefits for treatment of NVP.

Table II. Summary of therapies available for the management of nausea and vomiting in pregnancy (NVP), according to safety and effectiveness

Recommended as first step[130] in countries where available	Doxylamine/pyridoxine[a]	2 tablets qhs, and 1 tablet in the morning and 1 tablet in the afternoon if needed
	± dimenhydrinate	50-100mg po q4-6h prn or 50-100mg po q6-8h prn (maximum 400 mg/day alone, or 200mg/day in combination with 4 tablets/day doxylamine/pyridoxine)
Also safe and effective	Phenothiazines[b]	
	e.g. Prochlorperazine	5-10mg po/IV q8h prn
	e.g. Promethazine	12.5-25mg po/IV q4-6h
Safe, may be effective	Pyridoxine (monotherapy)[c]	10-25mg po tid
	Ginger	250mg po q6h
	P6 acupressure/acupuncture e.g. Seabands®	Worn for 5-10 min q4-6h to continuously as much as possible
Probably safe, widely used for NVP	Metoclopramide	5-10mg po/IV q6h (maximum 0.5 mg/kg/day)
Probably safe, may be effective	Cisapride	5-10mg po q6-8h
Of unproven safety in first trimester of pregnancy, may be effective	Domperidone	10-20mg po q6-8h
	Ondansetron	8mg po/IV q12h
	Corticosteroids (prednisone, dexamethasone)	40-75 mg/day

a Available in Canada as Diclectin® (doxylamine 10mg/pyridoxine 10mg).

b Particularly for patients who require parenteral therapy.

c Additive effect of pyridoxine in presence of 4 tablets/day of Diclectin® is uncertain.

IV = intravenous; **po** = oral; **prn** = as required, according to circumstances; **qxh** = every x hours; **qhs** = at bedtime; **tid** =3 times daily.

Other pharmacological and nonpharmacological interventions reviewed here (i.e. dietary changes, pyridoxine and cyancobalamin, ginger, acupressure/acupuncture, and psychotherapy) appear not to have any safety concerns and may be attractive to the pregnant patient interested in more 'natural' therapy.

The decision about which management strategy to use should be based on data demonstrating safety *and* effectiveness shown in RCT. Although dietary and lifestyle changes can be tried, clear evidence of effectiveness is lacking and they should not be relied upon to have a clinical effect, and approaches with established safety and effectiveness should not be withheld.

The doxylamine/pyridoxine combination was and, in Canada, still is the primary source of treatment for NVP given the number of controlled trials conducted on the safety and effectiveness of the combination with or without dicycloverine. Effectiveness trials seem to suggest a dose-dependent effect of the combination, which the manufacturer currently recommends taking in doses of 40mg of doxylamine with 40mg of pyridoxine daily. Future trials should focus on a weight-adjusted dosing schedule.

Antihistamines other than doxylamine also appear to be effective for NVP. Dimenhydrinate has the advantages of being able to provide acute relief of nausea and vomiting (due to its rapid onset of action, as well as its availability as a suppository) and of being widely available. Sedation may be a problem for users of doxylamine or other antihistamines; this may limit their use, although this issue has not been addressed in most trials. In fact, studies that have examined sedation as an endpoint have not shown a trend towards an increase in drowsiness and sleepiness in the antihistamine-treated groups [i.e. 8/39 *vs* 4/38, RR = 1.79 (0.58,5.51)[40] and 8/40 *vs* 2/36, RR = 3.17 (95% CI 0.71,14.05)[45]].

Although pyridoxine is effective when combined with doxylamine±dicycloverine, trials to date have not demonstrated the effectiveness of pyridoxine alone when using treatment failure (i.e. usually cessation of vomiting) as the outcome measure, although nausea scores were significantly decreased. Other vitamins such as cyanocobalamin may also exhibit therapeutic effects.

Neither dicycloverine nor scopolamine, both anticholinergic agents, has proven to be effective in the management of NVP.

Phenothiazines are effective for severe NVP. Their parental administration has made them popular for the treatment of patients who are unable to take oral medication. As with antihistamines, sedation may be a problem. Although extrapyramidal adverse effects may occur in the mother, NVP is not commonly a problem near term. Hence, the risk of such symptoms in the newborn is not usually a consideration. Although domperidone, and particularly metoclopramide, are used for NVP in clinical practice, neither should be advocated for first-line use until agents with established safety and effectiveness have been tried and have failed.

Prokinetic agents other than metoclopramide (i.e. domperidone, cisapride) and ondansetron may have therapeutic roles to play. However, because of the lack of effectiveness data, their use for NVP cannot be advocated unless first line therapies have been tried and have failed.

Case series have suggested that corticosteroids are effective for NVP, however, effectiveness cannot be established without RCT. Hence, treatment of NVP with high dose corticosteroids may be used if more conventional therapies with proven safety and effectiveness have been tried and have failed, especially given the potentially small risk of oral clefts associated with first trimester exposure.

Ginger may prove to be useful for NVP and is worthy of future study. P6 stimulation for NVP shows promise, but effectiveness has not been clearly established. Insufficient data currently exist to regard psychotherapy as effective in the treatment of NVP.

Omeprazole should be used only for reflux oesophagitis when H_2 receptor antagonists have failed.

A limitation of our study is the fact that for both safety and effectiveness data, studies of agents acting at similar receptor sites (i.e. antihistamines and

phenothiazines) were pooled, thereby assuming that their pharmacological actions are similar. While this assumption may be the case for drugs acting to relieve NVP, it may not be true for drugs acting on the cellular level during fetal development. This rationale may help partially explain the heterogeneity found in safety studies for the antihistamines and phenothiazines. However, it must be noted that to date there is no evidence in humans that drugs within the same therapeutic class display different fetal safety profiles. Moreover, none of the individual antihistamine or phenothiazine studies had sufficient power to quantify a small magnitude of teratogenic risk and in the clinical setting when a decision on treating NVP with a particular drug class needs to made, the pooled analyses of risk provide a guideline for treatment decisions.

The best approach to treating NVP is unknown given the paucity of head-to-head comparisons for individual drugs. If success is not achieved with one agent, then another should be tried. When to treat a patient with NVP is probably as important an issue as what to use. Evidence suggests that quality of life may be impaired before severe physical symptoms appear.[1,2,19] It is hoped that by highlighting the fact that there are therapies with demonstrated safety and efficacy available for NVP, consideration will be given to offering them to women with either more mild to moderate physical symptoms, and/or impaired psychosocial functioning.

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