NAUSEA AND VOMITING OF PREGNANCY: MISPERCEPTION OF DRUG USE AND MAJOR ADVERSE EVENTS.

by

Paolo Mazzotta

A thesis submitted in conformity with the requirements for the degree of Master of Science
Graduate Department of Pharmacology
University of Toronto

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ABSTRACT

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AND MAJOR ADVERSE EVENTS.

Master of Science, June 1998
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This study investigated whether advice received regarding management of nausea and vomiting of pregnancy (NVP) affects risk perception of drug use in pregnancy. This study also investigated whether NVP is associated with elective termination of pregnancy. Women suffering or who had suffered from NVP voluntarily contacted an ‘NVP Healthline’ and were administered a questionnaire asking about their experience with NVP.

Women advised only to change their diet or lifestyle attributed an increased risk for major malformations with antiemetics for NVP (p = 0.001). Women advised to take antiemetic medication attributed no change in risk for major malformations with drugs for NVP (p = 0.002).

Sixty-six women reported elective termination of their pregnancy because of NVP. Case-control analysis identified 4 variables significantly associated with elective termination: previous elective termination, unplanned pregnancy, feelings of depression and lack of vitamin supplementation. Logistic regression analysis determined over 80% of the model could be explained by these 4 factors.
ACKNOWLEDGEMENTS

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<th>Description</th>
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<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
</tr>
<tr>
<td>CPP</td>
<td>Collaborative Perinatal Project</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>δ-9-THC</td>
<td>delta-9-tetrahydrocannabinol</td>
</tr>
<tr>
<td>DPC</td>
<td>disease-paired control</td>
</tr>
<tr>
<td>EGG</td>
<td>electrogastrogram</td>
</tr>
<tr>
<td>ER</td>
<td>emergency room</td>
</tr>
<tr>
<td>B</td>
<td>estimated coefficient</td>
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<tr>
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<td>5-hydroxytryptamine</td>
</tr>
<tr>
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<td>general practitioner</td>
</tr>
<tr>
<td>hCG</td>
<td>human chorionic gonadotropin</td>
</tr>
<tr>
<td>MM</td>
<td>Michigan Medicaid Study</td>
</tr>
<tr>
<td>NVP</td>
<td>nausea and vomiting of pregnancy</td>
</tr>
<tr>
<td>NTC</td>
<td>non-teratogen control</td>
</tr>
<tr>
<td>OB</td>
<td>obstetrician</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>OPCS</td>
<td>Office of Population Census and Statistics</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized control trial</td>
</tr>
<tr>
<td>RN</td>
<td>registered nurse</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SE</td>
<td>standard error</td>
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<tr>
<td>TA</td>
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1. Introduction

1.1. Statement of the Problem

Since the thalidomide disaster of the late 1950’s and early 1960’s, pharmacological interventions used to treat women suffering from nausea and vomiting of pregnancy (NVP) have been viewed with great trepidation. As a result, ‘morning sickness’ (as it is most commonly known) has been commonly treated with either dietary or lifestyle changes that have been derived empirically. Effective and safe pharmacological therapies have often been avoided; in fact, one of the drugs used in treating NVP, Bendectin®, was actually withdrawn from the world market because of unsubstantiated claims about teratogenicity and the inability of the manufacturer to pay litigation costs.

The Motherisk program, at the Hospital for Sick Children in Toronto, receives approximately 30 inquires each month regarding the safety and/or effectiveness of antiemetic medication for NVP. This given the fact that, unlike in the United States, Diclectin®, a drug indicated for the treatment of NVP in the Compendium of Pharmaceuticals and Specialties, is available to patients in Canada suffering from this disorder of pregnancy. Moreover, Motherisk has counseled a number of women who reported terminating their pregnancy because of the severity of their NVP. If pregnant women with NVP are not given evidence-based advice by their primary caregivers regarding the safety and effectiveness of various anti-emetics, it may negatively impact on the health and quality of life of these individuals. Moreover, factors related to NVP, such as severity of physical symptoms, lack of satisfactory treatment and reduced emotional and social function, may lead some women to terminate the pregnancy unnecessarily.
1.2. Purpose of Study

The purpose of this investigation was 1) to determine whether pregnant women in Canada and the United States are given evidence-based advice regarding pharmacological therapy to treat NVP and 2) how this advice may impact on the teratogenic risk perception of antiemetic use for NVP.

The purpose of this study was also to verify the initial impressions whether some women with NVP truly choose to terminate their pregnancy due to NVP. The basis for termination may be linked to physical symptoms of NVP, as well as social, emotional and occupational functioning in these patients.

1.3. Objectives

1. To document the appropriateness of management advice currently being given to women with NVP;

2. To determine how advice received for management of NVP may affect the teratogenic risk assessment attributed by women suffering from NVP to pharmacological interventions for their disease and the change in perception of risk after consultation from a source other than their primary caregiver;

3. To examine whether NVP is associated with therapeutic abortion;

4. To explore factors that may predict whether a woman affected by NVP will terminate a pregnancy.

1.4. Hypotheses

1. Women with NVP are not currently being given evidence-based advice about the benefits and risks of pharmacologic and nonpharmacologic treatment of NVP.

2. Misinformation regarding management of NVP may negatively affect the perception of risk of using anti-emetic medication during pregnancy.
3. Women with severe NVP may choose to terminate their pregnancy.

4. The decision to terminate a pregnancy may be based on the advice received from the primary care-giver, the characteristics of the patient and the severity of her NVP.
2. Background

In order to place into context the issues addressed in this investigation, it is important to first review the relevant clinical characteristics of NVP.

2.1. Epidemiology of NVP

Descriptions of NVP date back to writings from the second century AD\(^1\). Nausea and vomiting of pregnancy has been said to be 'statistically normal', because it afflicts up to 80% of pregnant women to greater or lesser degrees\(^2\). Approximately 50% of pregnant women have nausea and vomiting, whereas approximately 30% have only nausea\(^2\). Symptoms are usually self-limited to 7-12 weeks' gestation, although 9% of women continue to have symptoms beyond 20 weeks. Fewer than 1% of pregnant women develop 'hyperemesis gravidarum' characterized by severe physical symptoms and/or medical complications (e.g., dehydration, electrolyte imbalance) requiring admission to hospital\(^3\), although it has been documented to affect up to 4-5% of women suffering from NVP\(^4\). Based on data from multiparous patients, in approximately one third of women the symptoms of NVP will differ (i.e., severity or duration) in subsequent pregnancies\(^2\).

2.2. Etiology and Pathogenesis of NVP

The pathogenesis of NVP is poorly understood and etiologies abound\(^5\). This may be due, at least in part, to the fact that radiological and pharmacological investigations have been hampered by concerns about teratogenicity, especially during the first-trimester of pregnancy.

There is no proven role for gestational or other hormones. No correlation has been found between the severity of NVP and levels of human chorionic gonadotropin (hCG), despite the fact that hCG levels peak during the first-trimester, and conditions associated with high levels of hCG (e.g., molar pregnancy, multiple gestation) are associated with a higher prevalence of NVP. Neither estrogen nor 17-hydroxyprogesterone levels have been correlated with NVP, although a
correlation has been found with estradiol levels by some investigators but not by others. Raised thyroid hormone levels have been proposed as an etiologic factor, but not consistently observed. Nausea and vomiting of pregnancy has also been proposed to be due to blunted function of the autonomic nervous system, or dysregulation of gastric rhythms as measured by electrogastrograms (EGGs). Psychological factors, such as depression, anxiety, and eating disorders, have also been observed; however, it is not clear whether these preceded or resulted from the severe symptoms.

In summary, the etiology of NVP has not been established, and is likely to be multifactorial.

2.3. Diagnosis of NVP

NVP is a diagnosis of exclusion after history, physical and routine laboratory investigations have ruled out structural (gastrointestinal (e.g., obstruction) or central nervous system (e.g., space-occupying lesion)), hormonal (e.g., thyrotoxicosis), metabolic (e.g., renal failure), pharmacological (e.g., narcotics), or psychiatric (e.g., bulimia) causes of nausea or vomiting. Diagnosis of NVP is confirmed by symptoms which are self-limited, usually to the first and early second trimesters, but definitely to pregnancy itself.

2.4. Management of NVP

For a critical review regarding management of NVP, a search of the English and French literature was performed on MEDLINE from 1966 to July 1997, using the following key words: nausea, vomiting, emesis, hyperemesis gravidarum, morning sickness, pregnancy, pregnancy complications, treatment, efficacy, effectiveness, teratogens, placenta, embryo, fetus, maternal fetal exchange, drug-induced abnormalities, toxicology. The Pregnancy and Childbirth Module of Cochrane Database of Systematic Reviews was also searched for information regarding clinical trials on therapies to treat NVP. Other sources of information included personal files,
personal communication with various researchers and clinicians in the fields of pharmacology, toxicology, obstetrics and pediatrics, and spontaneous reports from pharmaceutical companies.

The choices of anti-emetic therapy in pregnancy are based on knowledge of physiological pathways, mediating nausea and vomiting, and drug effectiveness data from nonpregnant patients. Therefore, it is necessary to first review these physiological pathways and outline the variety of anti-emetics available over-the-counter or by prescription.

2.4.1. Physiological Pathways Mediating Nausea and Vomiting

The choice to treat nausea and vomiting in a nonpregnant patient is based on the variety of pathways involved in the pathophysiology of emesis and nausea. Thus, receptor antagonists (i.e., histamine, acetylcholine, dopamine and/or 5-hydroxytryptamine (5-HT₄) antagonists) in any or all of the following areas may have antiemetic potential: i) chemoreceptive trigger zone (which is richly innervated with receptors for dopamine, histamine, acetylcholine and serotonin), ii) vestibular apparatus (where cholinergic and histaminergic fibres are thought to be involved in transmission), iii) visceral afferents (e.g., dopamine receptors mediate motor reflexes in the stomach), and iv) vagal afferents (e.g., serotonin receptors (specifically 5-HT₄) are located in close proximity to enterochromaffin cells in the intestinal tract).

2.4.2. Safety and Effectiveness Data for Antiemetics Used In The Treatment of NVP

The majority of available anti-emetics are labelled by their manufacturers as contraindicated in pregnancy due in part to the lack of data on safety in human pregnancy. Although pre-marketing animal toxicology studies are performed by drug manufacturers, extrapolation to human pregnancy is often difficult. Therefore, it is typically only by observational studies of either inadvertent exposure in early pregnancy or treatment of life-threatening complications in pregnancy, that drug safety in pregnancy can be established. Such studies determine the overall rate of major malformations compared with the baseline risk (i.e.,
1%-5% of pregnancies), and the reported defects are reviewed to determine whether or not there is any discernible pattern. This literature will be reviewed for each anti-emetic drug and/or drug class.

Effectiveness for treatment of NVP is best established by randomized controlled studies of a drug vs. placebo or standard of care. Methodological difficulties inherent in case series are even greater when studying (what is usually) a self-limited illness like NVP; therefore, such literature, unless extremely compelling, will not be reviewed when addressing the issue of effectiveness of therapy for NVP.

2.4.2.1. Direct Acting Pharmacological Agents

2.4.2.1.1. Antihistamines

Although a large number of histamine (H₁) antagonists are available, very few have been shown to have antiemetic effects: cyclizine, dimenhydrinate, doxylamine, hydroxyzine, meclizine and promethazine.

Safety

A wide body of evidence suggests that the first generation antihistamines (e.g., dimenhydrinate, hydroxyzine, etc.) have no human teratogenic potential¹⁵. This point is highlighted by the prototype of this class of drugs, doxylamine, originally marketed in combination with pyridoxine and dicyclomine (as Bendectin® or Debendox®), and currently marketed in Canada as Diclectin®. The drug combination was first introduced in 1957 on the heels of the thalidomide tragedy. During the late 1960’s and 1970’s, thousands of claims were made concerning teratogenic effects of the medication. As a result, the combination was withdrawn from the world market by the manufacturer who could not pay the legal costs, even though epidemiological studies were not able to demonstrate an association between the drug and malformations. Two meta-analyses pooled data from all existing cohort and case control studies
on doxylamine/pyridoxine use in pregnancy. The first data from 17 studies published from 1963-1985 were analyzed; no association between Bendectin®/Debendox® exposure and congenital malformations were found (14,715 exposed, pooled odds ratio (OR) = 1.01 [0.66-1.55])^{16}. The second analyzed data from 16 studies published from 1963-1991 which documented 1,012 first- trimester exposures to Bendectin®/Debendox®^{17}. The pooled odds ratio was 0.95 [0.88,1.04], suggesting no association between the drug combination and major/minor malformations. Moreover, evidence from a recent meta-analysis confirms early reports that antihistamine use in pregnancy is not considered a risk to the fetus. Twenty-four controlled studies published from 1960-1991 on first-trimester exposures to various antihistamines failed to demonstrate an increased risk for major/minor malformations (OR = 0.76 [0.60,0.94])^{18}.

Effectiveness

A summary of 6 randomized control trials (RCTs) examining the effectiveness of antihistamines for NVP, not including doxylamine, is outlined in Figure 1. Four of the 6 studies demonstrated improvement in physical symptoms of NVP with the use of antihistamines compared with placebo^{19}^{20}^{21}^{22}, while 2 studies did not show improvement^{23}^{24}. Pooled data indicate that antihistamines are effective in reducing nausea in pregnant patients (OR = 0.12 [0.08,0.17]).

Doxylamine/pyridoxine

Two studies comparing doxylamine to placebo revealed effective response in the reduction of nausea (3/52 vs. 20/57, OR = 0.17 [0.07,0.44], 18/24 vs. 25/26, OR = 0.18 [0.04,0.87])^{25}^{26}. One study, though, did not find any significant difference between the combination and placebo (12/41 vs. 18/40, OR = 0.51 [0.21, 1.26])^{27}. However, when results of the three studies are pooled, there is a significant effect of the combination on the reduction of nausea as compared to placebo (33/117 vs. 63/123, OR = 0.28 [0.16,0.51])^{28}. 

8
In summary, antihistamine treatment of NVP is not associated with an increased risk for malformations and can be effective for the relief of nausea and vomiting. Unfortunately, adverse effects of antihistamines may limit their use. Although this issue has not been addressed in most trials, those that have examined sedation as an endpoint have shown a trend towards an increase in drowsiness and sleepiness in the antihistamine-treated group. 

Figure 1. Summary of Antihistamine Effectiveness Studies for NVP
2.4.2.1.2. Anticholinergics

Few anticholinergics are in use for the treatment of nausea and vomiting in the nonpregnant population; these include dicyclomine and scopolamine.

Dicyclomine

Dicyclomine is an anti-spasmodic agent indicated for the treatment of irritable bowel syndrome and related gastrointestinal dysfunctions.

Safety

A meta-analysis of Bendectin®/Debendox® failed to demonstrate an increased risk with the combination of dicyclomine/doxylamine/pyridoxine. In addition, in a prospective cohort study, no malformations were detected in women exposed to dicyclomine during the first-trimester as compared to controls (RR = 1.03 [0.82,1.30]).

Effectiveness

Dicyclomine failed to demonstrate independent or synergistic effectiveness in combination with doxylamine/pyridoxine for the treatment of NVP, resulting in the removal of the drug by the manufacturers from Bendectin®/Debendox®.

In summary, no teratogenic risk to the fetus has been demonstrated by dicyclomine. However, it has not proven to be efficacious in the management of NVP and, therefore, should not be considered a therapeutic option.

Scopolamine

Scopolamine is indicated for the treatment of motion sickness in nonpregnant patients. It is most widely used as a transdermal patch.

Safety

Teratogenicity studies are limited to two controlled observational studies: a prospective cohort study of 309 first-trimester exposures (RR = 1.05 [0.70,1.59]) and a record linkage study
of 27 first-trimester exposure (RR = 0.75 [0.11,5.16]). Neither study revealed an increased risk for malformations.

Effectiveness

No RCTs for treatment of NVP are available.

In summary, although safety data in human pregnancy are reassuring, their small numbers of exposed patients and the lack of effectiveness data for treatment of NVP would caution against the use of scopolamine for NVP.

2.4.2.1.3. Dopamine Antagonists

A number of dopamine antagonists have been used to treat NVP: phenothiazines (e.g., chlorpromazine, perphenazine, prochlorperazine, and trifluoperazine), metoclopramide and domperidone.

- Phenothiazines

Safety

Although anecdotal case reports associated phenothiazines with major malformations, the bulk of evidence suggests that, when used occasionally and in low dosage, there is no evidence of teratogenicity. Moreover, prospective and retrospective cohort studies of grouped phenothiazines have failed to demonstrate an increased risk for major malformations (pooled OR = 1.03 [0.87,1.23]). Supportive observational studies (i.e., prospective cohort, retrospective cohort, record linkage) are outlined in Table 1.

Extrapyramidal side effects may occur in the mother; however, NVP is not commonly a problem near term, so extrapyramidal symptoms in the newborn are not usually a consideration.
Table 1. Summary of Teratogenicity Studies - Phenothiazines.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Study</th>
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<th>Controls‡</th>
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<td>2.18</td>
<td>1.20,3.96</td>
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</tbody>
</table>

†malformations/no malformations - phenothiazine exposure; ‡malformations/no malformations - no drug exposure
**Effectiveness**

There have been 3 RCTs of various phenothiazines vs. placebo for treatment of (usually severe) NVP. These were published in a quantitative overview. In total, 43/203 patients randomized to a phenothiazine experienced NVP, compared with 132/195 randomized to placebo or no therapy; the pooled odds ratio (OR) = 0.15 [0.10,0.22] reflected a significant therapeutic effect.

In summary, the phenothiazines are widely accepted as safe and effective for treatment of NVP. Their parenteral route of administration has established a particular role for them in the treatment of patients unable to take medication by mouth.

- **Metoclopramide**

  Metoclopramide has not been extensively studied for treatment of NVP even though in many countries it is used extensively in clinical practice.

**Safety**

Studies of the teratogenic potential of the drug are limited. No malformations were reported among 4 first-trimester exposures. In a retrospective record linkage study, no increase in major malformations was reported (i.e., 10/192 (5.2%)) and no specific pattern of defects was detected. Therefore, the data do not support an association between the drug and congenital defects.

**Effectiveness**

No RCTs have been published to support the widespread use of metoclopramide for NVP.
• Domperidone

Safety

Domperidone was not teratogenic in animals in doses greater than 100 times the recommended human dose\(^{48}\). The only human data available are spontaneous reports to the drug manufacturer.

Effectiveness

No RCTs in pregnancy have been published.

In summary, although the biased nature of the safety data make their significance uncertain, domperidone cannot be advocated for use during pregnancy until more published information becomes available.

2.4.2.1.4. 5-HT\(_3\) Antagonists

This class of drugs have recently been introduced for the management of chemotherapy-induced nausea and vomiting. Ondansetron has widespread use in clinical settings, whereas granisetron and tropisetron are still undergoing clinical trials.

Ondansetron

Safety

Use of ondansetron in the first-trimester of pregnancy has been limited. No malformations were reported in three case reports\(^{49} 50 51\) or in the setting of a RCT of 15 patients exposed during the first-trimester (discussed below) (J.C. Morrison, personal communication, October 23, 1996).

Effectiveness

There is one RCT of intravenous ondansetron vs. promethazine for the treatment of severe NVP\(^{52}\). Ondansetron did not demonstrate any benefit over promethazine using the following outcome measures: severity of nausea, daily weight gain, days requiring
hospitalization, treatment failures and voluntary use of the drug. The lack of statistical differences between groups may have reflected low statistical power.

In summary, ondansetron cannot be advocated for use in pregnancy before other agents with established safety and effectiveness have been tried and failed.

2.4.2.1.5. Upper and Lower Gastrointestinal Tract Agents

Cisapride

Cisapride in a prokinetic agent that lacks central and peripheral antidopaminergic effects. It acts by enhancing acetylcholine release thereby increasing smooth muscle activity of the esophageal/gastric system.

Safety

The manufacturer of cisapride is aware of 6 cases of exposure during the first-trimester without detectable malformations53. In addition, a Prescription Event Monitoring program in the UK collected 12 cases of first-trimester exposure to cisapride; no malformations were detected44. A recent multicentre prospective controlled study of 88 first-trimester exposures to cisapride also failed to detect an increase in major malformations when compared to disease-paired and non-teratogen controls (i.e., 6.8% [cisapride] vs. 5.7% [DPC] p = 0.77, vs. 3.4% [NTC] p = 0.33)53.

Effectiveness

No RCT’s have been published in pregnancy.

In summary, cisapride cannot be advocated for use in pregnancy until further investigations are performed.

2.4.2.1.6. Corticosteroids

Severe NVP has been hypothesized to occur in part by adrenocortical insufficiency secondary to ACTH deficiency55. This, coupled with the successful use of steroid treatment for chemotherapy-induced emesis56, has increased awareness of the potential benefit of
corticosteroids to treat NVP. Steroids that have been proposed include cortisone, dexamethasone and prednisolone.

Safety

Although preliminary animal data suggested an increased risk for cleft palate, 6 cohort studies and one case-control study have failed to detect an increased risk for major malformations after use of steroids in pregnancy.

Effectiveness

In a number of case reports and case series the use of corticosteroids in patients suffering from hyperemesis gravidarum has been advocated. One trial comparing intramuscular ACTH to placebo in women suffering from hyperemesis gravidarum failed to reduce the severity of nausea and the number of subsequent re-admissions to hospital (0/16 patients, OR = 1.00 [0.13, 7.86])

In summary, corticosteroid treatment of NVP may be advocated if conventional management has been tried and failed.

2.4.2.2. Alternative Therapies

In light of the concerns about the teratogenic potential of pharmacological interventions to treat NVP, many women choose to use nonpharmacological approaches that are "natural". Although many are safe, most are also of unproven effectiveness in both nonpregnant and pregnant populations.

2.4.2.2.1. Dietary /Lifestyle changes

Traditionally, diet has been the mainstay of treatment for women suffering from NVP. Recommendations have included: eating small frequent meals, avoiding fatty foods, eating potato chips, and drinking cold, tart, or sweet beverages. Recent guidelines listed a number of foods that may appeal to women suffering from NVP
The safety of dietary recommendations has been presumed; however, a search of the medical literature has failed to reveal evidence-based research on the effectiveness of dietary treatment for NVP. Therefore, although dietary and lifestyle changes can be tried, they should not be quoted as proven to have a clinical effect, and approaches with established safety and effectiveness should not be withheld.

2.4.2.2.2. Pyridoxine (Vitamin B₆)

Pyridoxine is a water-soluble B-complex vitamin that is a necessary coenzyme in the metabolism of amino acids, carbohydrates and lipids.⁷⁰

Safety

Pyridoxine has proven not to be teratogenic in combination with doxylamine (see Bendectin®/Diclectin®/Debendox® data). In addition, a retrospective cohort study failed to link pyridoxine alone with an increase in major malformations compared with controls (18/458 vs. 34/911, respectively, RR = 1.05 [0.60,1.84])⁹⁹.

Effectiveness

Original placebo-controlled trials conducted by the manufacturers of Bendectin® determined that pyridoxine was effective for the reduction of NVP, although the pharmacologic action of pyridoxine is not fully understood.

Two RCTs using pyridoxine alone failed to help relieve symptoms of nausea and vomiting compared to placebo (pooled OR = 0.91[0.60,1.38])⁷¹. However, a randomized double-blind control trial of over 3000 women receiving multivitamins with B₆ or folic acid alone found a decreased incidence of hyperemesis gravidarum in women receiving multivitamins (3.0% vs. 6.6%)⁷².
In summary, pyridoxine alone or in combination with doxylamine does not pose a teratogenic risk to the fetus. Pyridoxine is effective when combined with doxylamine, although further investigations are needed to demonstrate the effectiveness of pyridoxine when used alone.

### 2.4.2.2.3. Ginger

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

**Safety**

Data on the safety of ginger in pregnancy are lacking, although it is commonly used in the diet of many cultures and is found in recommended doses within foodstuffs and ginger ale.

**Effectiveness**

A small crossover trial with placebo demonstrated that ginger tended to relieve nausea and vomiting in women suffering from hyperemesis gravidarum (4/23 reported NVP [ginger] vs. 19/23 reported NVP [placebo], OR = 0.08 [0.02,0.24])\(^4\).

In summary, ginger may prove to be useful for NVP and is worthy of future study.

### 2.4.2.2.4. 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 (pericardial) Neiguan point located three 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). It is widely accepted that the mechanism of action is mediated by endorphin release resulting in changes in physiology.

**Safety**

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

There have been 7 published randomized controlled trials of P6 stimulation (by acupressure or afferent stimulation) for treatment of NVP. These trials have been summarized in a quantitative overview, in which it was concluded that P6 acupressure significantly decreased “persisting nausea” by at least 50%. However, methodological flaws led to the conclusion that confidence could not be placed in the demonstrated effectiveness of P6 acupressure. Therefore, it remains unclear as to whether or not P6 stimulation is truly effective for NVP.

2.4.2.2.5. Psychotherapy

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

Safety

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

Effectiveness

Two case series exist indicating successful treatment of severe forms of NVP through hypnosis. A prospective controlled study, using adjunct psychotherapy in 10 patients suffering from hyperemesis gravidarum, suggested benefit in combination with anti-emetic medication.

In summary, insufficient data exist to regard this approach as an effective one to treat NVP.

2.4.2.2.6. Cannabinoids

Delta-9-tetrahydrocannabinol (δ-9-THC), the major pharmacological active constituent of cannabis, has been shown to relieve nausea and vomiting associated with cancer chemotherapy in a number of prospective placebo-controlled trials. In addition, 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 for the treatment of NVP have not been conducted. The medico-legal implications of cannabinoids and their derivatives, the fact that these products are not approved even for terminal AIDS patients and the potential health risks of inhaled substances during pregnancy would preclude the potential benefits for treatment of NVP.

2.4.2.3. Ancillary Therapies

This class of agents is primarily used to treat acid reflux that may arise as a result of vomiting. They act to neutralize gastric acidity (antacids), inhibit gastric acid and pepsin secretion from the stomach (H₂ antagonists), block the H⁺/K⁺-ATPase in the gastric lumen (proton pump inhibitors) or increase mucosal protection (misoprostol). They have shown to be effective in providing symptomatic relief in the nonpregnant population; however, no clinical trials in pregnancy have been published.

2.4.2.3.1. Antacids

Drugs of this class usually contain salts of magnesium, calcium, or aluminium. They are used by up to 50% of pregnant women suffering from gastric reflux conditions. A retrospective cohort study revealed an increased risk for major malformations when antacids were grouped (OR = 2.24 [1.31,3.83]) although there were no significant differences with individual antacids. Moreover, the bulk of evidence suggests that antacids are not human teratogens when used in recommended doses.

2.4.2.3.2. H₂ Antagonists

This class of drugs includes cimetidine, ranitidine, famotidine, and nizatidine. Neither postmarketing surveillance conducted by North American drug manufacturers (SB Dickson,
personal communication, Smith Kline & French Laboratories, 1986), anecdotal reports of
cimetidine (n=5) or ranitidine (n=5) exposures during the first-trimester, nor record linkage
studies\(^{92}\) (and the Michigan Medicaid Surveillance Study conducted from 1985-92\(^{31}\) examining
exposure to cimetidine (n=480 patients), ranitidine (N=516), and famotidine (N=33) have
reported evidence in favour of teratogenicity. In the only prospective study on the topic\(^{93}\), no
increase in major malformations was found following first-trimester exposure to H\(_2\)-blockers
(3/142 (2.1%) vs. 5/143 (3.5%) [controls], p=0.55; mean difference [95% CI] -1.4% [-5.2, +2.4]).

2.4.2.3.3. Proton Pump Inhibitors

Experience with omeprazole in human pregnancy is limited. Three malformations among
8 case reports of first-trimester exposure have been reported\(^{94} 95 96 97 98 99\), five of these
pregnancies had normal outcomes. In addition, a recent multicentre prospective cohort study did
not detect an increased risk for malformations compared to disease-paired and nonteratogen
control (unpublished data - Motherisk Program). Reproductive and developmental toxicology
studies on lansoprazole are limited to animal data which failed to reveal teratogenicity\(^{100}\).

In summary, there is currently insufficient information on safety in human pregnancy to
advocate the use of either omeprazole or lansoprazole.

2.4.2.3.4. Mucosal Protective Agent

Misoprostol is used as a gastroprotective agent, and could be used in conjunction with
corticosteroid treatment of NVP.

Misoprostol is contraindicated in pregnancy due to its potential uterotonic effects leading
to vaginal bleeding and miscarriage, as well as premature labour. However, not all women
exposed to misoprostol will experience contractility of uterine muscles and these pregnancies
may continue to viability.
Human data are limited to 18 retrospective case reports and 1 prospective cohort study of 20 exposed pregnancies. All reports described cases with Möbius syndrome (congenital facial paralysis with or without limb defects) in mothers using misoprostol to induce abortion. Two recent reports attempted to quantify the fetal risk. A multicentre case-control study determined that a significant number of infants with Möbius syndrome had been exposed to misoprostol during the first-trimester compared with nonteratogen controls (44/94 vs. 4/121, OR = 25.7 [8.3,89.4]; however, a prospective cohort failed to reveal an increase for major or minor malformations between misoprostol-exposed mothers and non-exposed controls (2.9% vs, 2.5% for major anomalies; RR = 1.19 [0.17,8.23]).

In summary, misoprostol may increase the risk of the rare Möbius syndrome. Given this concern and the established uterotonic effect of the drug, misoprostol should not be used for NVP.

2.4.2.4. Summary of Safety and Effectiveness Studies for Antiemetics in Pregnancy

Comprehensive review of the literature has revealed that there are a number of pharmacological and non-pharmacological therapies available which have proven safety and effectiveness for treatment of NVP.

Many drugs have proven not to be teratogenic to the developing fetus. The prototype is the doxylamine/pyridoxine combination which is currently marketed in Canada as Diclectin®. It has been studied in the largest number of patients (~200,000). However, the drug is not currently available in other countries, may cause drowsiness, and is long-acting, thereby preventing it from providing acute relief. Other antihistamines (such as dimenhydrinate) and the phenothiazines (as a group) have also failed to demonstrate teratogenic potential, although the number of exposed patients studied has been lower. Dimenhydrinate has the advantage of being able to provide acute relief. Parenteral administration of phenothiazines has made them popular for treatment of
patients who are unable to take oral medication; sedation and extrapyramidal effects may minimize their usefulness. The non-pharmacological interventions reviewed here appear to be safe and may be attractive to the pregnant patient interested in more “natural” therapy.

Ultimately, the decision about which management strategy to use should be based on data demonstrating safety and effectiveness demonstrated in RCT's. Evidence from small randomized placebo-controlled trials have shown that all of the following are effective for treatment of varying degrees of NVP: Bendectin/Diclectin (doxylamine, pyridoxine ± dicyclomine), antihistamine (H₁) blockers, phenothiazines (as a group), P6 acupressure, and ginger. Case series have (variably) suggested that corticosteroids, prokinetic agents, and ondansetron may have therapeutic roles to play; however, their fetal safety is far from established and their use for NVP cannot be advocated unless first line therapies have been tried and failed.

What is the best treatment for NVP? At this point, it is impossible to isolate one therapy that will effectively treat morning sickness, primarily because (with the exception of the intravenous ondansetron vs. promethazine trial previously mentioned) there are no head-to-head trials comparing the various medications discussed. In addition, all trials published to date have used only the physical symptoms of NVP as outcome measures. Firstly, this approach ignores the fact that the relationship between the occurrence/severity of nausea/vomiting and the distress caused by that nausea/vomiting is not predictable¹⁸. This approach may also miss not only therapeutic effects of potential importance to patients (e.g., the ability to work), but also adverse effects that might make therapy less desirable to patients (e.g., drowsiness from antihistaminic anti-emetics). Clinicians should choose from among the therapies with proven safety and effectiveness. If success is not achieved with one, then another should be tried. Therapies with limited data on safety should be tried only if other approaches have failed and after discussion of the uncertainties with the patient.
2.5. Impact of NVP on the Lives of Women

Traditionally, the severity of NVP has been measured by the degree of physical symptoms alone. There has been very little study of the impact of NVP on other aspects of the lives of patients, such as emotional well-being or function within the home. There is some evidence to suggest that NVP is associated with adverse effects on social and occupational function.

O'Brien et al\textsuperscript{109} documented, among a cohort of 147 pregnant women with NVP (who booked with one of three obstetric or midwifery practices), that 41 (29\%) experienced symptoms severe enough to force them to alter their daily activities. Among a subset of 27 patients who were interviewed in detail, effects on family, social, and/or occupational function were reported by all women, regardless of whether their physical symptoms were mild (n=14 subjects), moderate (n=8), or severe (n=5).

Two other reports have described changes in occupational function (both inside and outside the home) associated with NVP. One population-based cohort study, which enrolled 363 women with NVP, documented that 35\% of the 57\% of these women, who worked outside the home, spent a mean of 62 hours away from paid work\textsuperscript{2}. Based on the population of England and Wales and their number of live births, these figures represent 8.6 million hours of paid employment lost per year. This same study also found that 26\% of women reported time lost from housework. Another cohort study (of consecutively booking antenatal patients) identified 500 women with NVP, and documented that a quarter of the 64\% who worked outside the home reported time off paid work\textsuperscript{3}; in addition, 25\% of the 500 patients reported a mean of 8 hours lost from household tasks. These reports emphasize the importance of NVP from a societal perspective, given that over half of women now work outside the home and that work inside the home entails care of young children and older family members.
2.6. Perception of Teratogenic Risk in a Pregnant Population

Since the discovery that the placenta does not impede the passage of exogenous agents to the fetus, increased efforts in the area of developmental toxicology have assisted in revealing a number of potentially harmful pharmacologic agents. As a result, the growth in public awareness has been coupled with serious concerns regarding treatment of pregnant women with medications.

Koren et al\textsuperscript{110} reported the perception of risk in patients attending the Motherisk clinic in Toronto. Eighty women, exposed to both teratogenic and nonteratogenic agents, were asked to indicate on a visual analogue scale their own risk and the risk in the general population for major malformations. Women exposed to agents not considered teratogenic reported their risk to be 24%, which is approximately the rate of malformations for \textit{in utero} exposure to thalidomide\textsuperscript{111}. After consultation on their specific drug, the women’s perception decreased to 14%. This result emphasizes the notion that the effect of thalidomide on the general population has not disappeared after a 30 year period. In addition, although the risk perception remained above the actual baseline risk of 1% to 5% in the general population, the results indicate how accurate and reassuring advice concerning environmental exposures during pregnancy can change the perception in a positive manner.

Mastroiacovo et al\textsuperscript{112}, as part of the reproductive counselling service, The Telefono Rosso, focused on diagnostic radiation exposure during pregnancy. A cohort of 50 women who received radiation levels not associated with an increased risk reported consultation with their physician. Thirty-seven women were advised that their exposure represented a high-risk to the pregnancy and 12 women were advised to terminate. In addition, Mastroiacovo, et al\textsuperscript{113} in a cohort of 2,318 women exposed to nonteratogenic agents found that 104 strongly considered termination of pregnancy, but after consultation with the Telefono Rosso only 26 underwent termination. These data reveal that apprehension of physicians to provide clear, evidence-based
consultation regarding their patient’s situation can perpetuate misperception of risk to any exposure and may lead to an unnecessary termination of an otherwise healthy pregnancy.

2.7. Abortion and NVP

2.7.1. Spontaneous Case Reports

The following reports were obtained through the Motherisk Program telephone service.

Case 1

A woman in her late 20s, residing in the United States, was pregnant with her third child in March 1993. She was suffering from NVP similar to her previous two pregnancies. She presented with serious medical complications (i.e., itching, skin peeling and jaundice). During her pregnancy, she reported feeling as if she was “poisoned”. She tried using alternative remedies (e.g., Indian herbs, meditation, hypnotherapy) but none helped. She lost a total of 15 pounds. At 6 weeks gestation, she had a therapeutic abortion.

Case 2

A Quebec woman, in her early 30s, became pregnant in 1993. She reported that her pregnancy was unplanned. She has severe vomiting and attempted to alleviate her symptoms with numerous products (e.g., ginger, spirulina, modified diet). None of these remedies worked. Her physician advised her that there was nothing she could do about the nausea and vomiting. At 3 months gestation, she had a therapeutic termination because she “could no longer endure the nausea and vomiting”.

2.7.2. Medical Literature - NVP and Elective Termination

A search of the medical literature revealed one case report that described an association between severe NVP (i.e., hyperemesis gravidarum) and therapeutic abortions. A search of non-peer reviewed journals revealed case reports of elective termination and NVP.
2.7.3. Population-Based Statistics

Population-based statistics are most appropriate for determining the natural history of a disease. Because such statistics were not available for Ontario, relevant data from England and Wales were obtained from the Office of Population Censuses and Statistics (OPCS), UK. For the years 1979-1992 (for which relevant data were available), the number of legal abortions for both ‘excessive vomiting in pregnancy’ (ICD code 643) and all ‘maternal medical’ indications was sought from the OPCS, UK (Personal communication, Abortion Statistics, IPSC, London, UK, November, 1995). The incidence was expressed as the number of legal abortions for NVP per i) 100,000 legal abortions, and ii) 100,000 maternities (mothers delivered of live or stillborn infants (at >24 weeks’ gestation)), and iii) percent (%) legal abortions for maternal indications.

Table 2 shows that in England and Wales between 1979 and 1992, there were 25 to 59 cases per year of legal abortion for ICD code 643. This corresponds to a median [range] annual incidence of termination for ‘excessive vomiting in pregnancy’ of 25.7 [15.6,46.6] per 100,000 legal abortions, and 6.0 [3.7,9.5] per 100,000 maternities, and 97% [60%, 100%] of all terminations for maternal indications. Since 1979, the rate of termination for NVP has fallen relative to all legal abortions (p=0.0001, R^2=0.71); however, there was no significant change from 1984 onwards (p=0.53, R^2=0.06 relative to all terminations). No data were available with which to interpret this finding further.
Table 2. Legal Abortions for 'Excessive Vomiting in Pregnancy' (ICD code 643) to Residents of England and Wales Over the Study Period 1979-1992.

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<th>Year</th>
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<th>per 100,000 maternities</th>
<th>% legal abortions for maternal medical disease</th>
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2.8. Summary of Objectives and Hypotheses

Misperception of drug use in pregnancy has been demonstrated with a number of pharmacologic agents. In some cases, it has led to an unnecessary termination of pregnancy. Nausea and vomiting of pregnancy is a condition that can be treated, if necessary, with safe and effective medications. However, pregnant women may not be advised to treat their condition because of fear of major birth defects. Moreover, NVP and its effect on social, emotional and occupational functioning may affect a woman’s decision to terminate her pregnancy. Therefore, this study will document whether women are receiving evidenced-based information regarding management of their NVP. Furthermore, it will determine whether advice received, with respect to antiemetic medication to treat NVP, affects perception of risk. Finally, it will investigate whether NVP is associated with elective termination of pregnancy and, if so, determine what factors may affect a woman’s decision to have a therapeutic abortion.
3. Methods

3.1. Subjects

From February 1996 to August 1997, announcements on radio programs and in Canadian and American women’s magazines and newspapers advertised the Hospital for Sick Children’s interest in hearing from women with previous or current NVP. Women were invited to call a ‘NVP Healthline’ (Appendix D). The project was approved by the Research Ethics Board of the Hospital for Sick Children in January 1996.

Women who called the NVP Healthline were informed of the Motherisk Program’s interest in learning more about NVP. Eligible callers were chosen based on the following criteria:

Inclusion criteria:
1. Current or past pregnancy;
2. Recurrent nausea and/or vomiting not attributable to a cause other than pregnancy.

Exclusion criteria:
1. Severe NVP that would preclude a telephone interview;
2. Nausea and/or vomiting due to a condition(s) other than pregnancy;
3. Inadequate cognitive skills and/or knowledge of English/French to allow or permit a telephone interview.

3.2. Baseline Data Collection

Eligible callers were asked for their permission to undergo a detailed, 20-minute telephone interview. Verbal consent to participate in the study was obtained. Interviews were conducted by bilingual individuals informed about NVP and pregnancy in general. Semi-structured data collection forms (Appendix A and Appendix B) were used to collect the following information: i) maternal demographics, ii) severity of physical symptoms of NVP
(including details of admissions to hospital), iii) advice received (and from whom) about anti-emetic medication and other treatments for NVP, iv) actual use of drugs or other therapy for NVP, v) other (concurrent) drug/physical exposures, vi) impact of symptoms of NVP on emotional well-being (i.e., depression, emotional support from partner, concerns about NVP and/or anti-emetic therapy harming the baby, likelihood of having another pregnancy, consideration of pregnancy termination), vii) impact of symptoms of NVP on social functioning (i.e., time lost from household tasks, time lost from paid work, relationship with partner, effect on partner’s day-to-day life), and viii) pre-counselling views on the risk of anti-emetic medication on the likelihood of having a baby with a major birth defect. Open-ended questions about the impact of NVP on emotional and social functioning were also included.

3.3. Interventions/Maneuver

Each woman was informed that she had a 1% to 5% chance of having a baby with a major birth defect, even if she took no medication for her NVP. She was also informed that i) no anti-emetic medication (other than thalidomide) has been proven to cause birth defects, and ii) Diclectin® (doxylamine/pyridoxine) is the only drug in Canada labelled specifically for treatment of NVP, and that this labelling came about only after the Government of Canada reviewed all available information. Further reproductive risk counselling was provided at the caller’s request.

After the initial interview was completed, the interviewer asked the caller for her permission to be contacted at approximately 20 weeks’ gestation for a 20-minute telephone follow-up interview (Appendix C). The purpose of this interview was: 1) to determine the women’s views on the risk of anti-emetic drug use during pregnancy, 2) to further characterize symptoms (and their resolution/persistence) in the population studied, and 3) to document drug or other therapies used for NVP. The opportunity was provided for further risk counselling at the patient’s request.
3.4. **Statistical Analyses**

3.4.1. **Teratogenic Risk Perception and Advice Analysis**

Risk perception before and after consultation was compared by the McNemar test (non-parametric) for two related proportions. Advice received was compared to risk perception by chi-squared with continuity correction (Fisher's exact test was employed for expected values less than 5). Association between advice and risk perception was analyzed by the correlation coefficient, Phi ($\phi$), for nominal data. For all tests, the level of statistical significance was set at 5%, with a 95% confidence interval.

3.4.2. **Elective Termination Analysis**

Proportions were compared by chi-squared with continuity correction. Fisher’s exact test was employed for expected values less than 5. Continuous variables were compared by student t test. Association between abortion and significant variables was analyzed by the correlation coefficient Phi ($\phi$) for nominal data or Pearson correlation coefficient for continuous variables. For all tests, the level of statistical significance was adjusted to 0.1% with a 99.9% confidence interval, to account for multiple comparisons.

Logistic regression (enter method) was used to determine predictors for abortion due to NVP.
4. Results

4.1. Prospective Study - Advice and Teratogenic Risk Perception

4.1.1. Baseline Maternal Characteristics of Study Participants

From January to August, 1997, 667 women suffering from NVP at the time of interview contacted the Healthline. From this group of patients, 372 were at or beyond 20 weeks gestation and were excluded from the analysis. The remainder 295 patients were under 20 weeks gestation and enrolled in the study. From this cohort, 35 women were lost to follow-up at the 20-week return call, leaving 260 patients under 20 weeks gestation who were prospectively collected through the Healthline as the final group for analysis.

Maternal demographics for these women are outlined in Table 3. Just over half of the callers identified Canada as their place of residence, while the remainder identified the United States of America as their place of residence. Over two-fifths of the respondents reported the source of information on the NVP Healthline as “other” which included posters in physicians offices, radio programs and word of mouth from friends or family members. The mean age of the respondents was 30 years. The median gravidity, parity, and previous spontaneous and therapeutic abortions of the study participants were 2, 1, 0 and 0, respectively. Eleven patients identified a birth defect in a previous pregnancy, representing an incidence of 4.8% in this population. Under three-quarters of the women reported that the pregnancy was planned. Two-thirds were being cared for by an obstetrician, while very few were seeing a midwife/registered nurse. Over two-thirds of the women reported working outside of the home environment. Socioeconomic status of the study participants was determined by the Blishen socioeconomic index for the total Canadian labour force, based on the 1981 Census data117. This index is specific for females in the workplace and incorporates income level and education level for determination of status. Scores range from 4.23 (representing poor socioeconomic status) to
101.32 (representing excellent socioeconomic status). The mean score for socioeconomic status of the study participants was 44.9.
Table 3. Baseline Maternal Demographics and Pregnancy Characteristics

<table>
<thead>
<tr>
<th>Place of Residence (n=260)</th>
<th>USA</th>
<th>121 (46.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Canada</td>
<td>139 (53.5%)</td>
</tr>
<tr>
<td>Source of Information (n=256)</td>
<td>Magazine</td>
<td>94 (36.2%)</td>
</tr>
<tr>
<td></td>
<td>Television</td>
<td>40 (15.4%)</td>
</tr>
<tr>
<td></td>
<td>Newspaper</td>
<td>9  (3.5%)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>113 (43.5%)</td>
</tr>
<tr>
<td>Maternal Age-1st call (n=259)</td>
<td>years ± SD (range)</td>
<td>29.78 ± 5.14 (17-43)</td>
</tr>
<tr>
<td>Gestational Age 1st call (n=254)</td>
<td>weeks ± SD (range)</td>
<td>12.17 ± 3.24 (4-14)</td>
</tr>
<tr>
<td>Gravidity (n=260)</td>
<td>median (range)</td>
<td>2 (1-8)</td>
</tr>
<tr>
<td>Parity (n=260)</td>
<td>median (range)</td>
<td>1 (0-6)</td>
</tr>
<tr>
<td>Spontaneous Abortion (n=260)</td>
<td>median (range)</td>
<td>0 (0-5)</td>
</tr>
<tr>
<td>Therapeutic Abortion (n=260)</td>
<td>median (range)</td>
<td>0 (0-2)</td>
</tr>
<tr>
<td>Previous defects (n=167)</td>
<td>11 (4.2%)</td>
<td></td>
</tr>
<tr>
<td>Planned pregnancy (n=256)</td>
<td>188 (72.3%)</td>
<td></td>
</tr>
<tr>
<td>Singleton pregnancy (n=260)</td>
<td>253 (97.3%)</td>
<td></td>
</tr>
<tr>
<td>Primagravida (n=260)</td>
<td>68 (26.2%)</td>
<td></td>
</tr>
<tr>
<td>Caregiver (n=260)</td>
<td>family practitioner</td>
<td>92 (35.4%)</td>
</tr>
<tr>
<td></td>
<td>obstetrician</td>
<td>154 (59.2%)</td>
</tr>
<tr>
<td></td>
<td>midwife/RN</td>
<td>11 (4.2%)</td>
</tr>
<tr>
<td></td>
<td>none as of yet</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>Occupation (n=260)</td>
<td>outside the home</td>
<td>167 (64.2%)</td>
</tr>
<tr>
<td></td>
<td>socioeconomic (n=140)†</td>
<td>44.9 ± 14.3 (4.2-79.6)</td>
</tr>
</tbody>
</table>

†based on Blishen's index for occupations in Canada\textsuperscript{118}
Table 4 lists the drugs used in this population therapeutically for medical conditions not related to NVP. Although one quarter of the study participants reported use of medications, 73 products are listed because some patients were taking more than one drug. None of the drugs listed are considered teratogenic.

Table 4. Medications Used for Medical Conditions Other Than NVP

<table>
<thead>
<tr>
<th>Medications for other conditions</th>
<th>n=259</th>
<th>69 (26.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td>Indication</td>
<td>Number of patients (n=73)</td>
</tr>
<tr>
<td>acetaminophen</td>
<td>headaches/migraine/cold/pains</td>
<td>33</td>
</tr>
<tr>
<td>propranolol, ibuprofen, ketorolac</td>
<td>migraine, headaches</td>
<td>3</td>
</tr>
<tr>
<td>salbutamol, budesonide,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>beclomethasone, cetirizine,</td>
<td>asthma</td>
<td>11</td>
</tr>
<tr>
<td>triamcinolone, albuterol,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nedocromil sodium, salmeterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>simethicone</td>
<td>anti-flatulent</td>
<td>1</td>
</tr>
<tr>
<td>Ornade®, Robitussin®</td>
<td>cough</td>
<td>1</td>
</tr>
<tr>
<td>penicillin</td>
<td>infection</td>
<td>2</td>
</tr>
<tr>
<td>antibiotic, not specified</td>
<td>throat infection</td>
<td>2</td>
</tr>
<tr>
<td>antibiotic, not specified</td>
<td>urinary tract infection</td>
<td>3</td>
</tr>
<tr>
<td>nitrofurantoin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>erythromycin</td>
<td>bronchitis</td>
<td>1</td>
</tr>
<tr>
<td>clindamycin</td>
<td>acne</td>
<td>1</td>
</tr>
<tr>
<td>psyllium hydrophilic mucilloid</td>
<td>constipation</td>
<td>1</td>
</tr>
<tr>
<td>nasal spray, diphenhydramine</td>
<td>allergies</td>
<td>2</td>
</tr>
<tr>
<td>Drug</td>
<td>Condition</td>
<td>Notes</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>progesterone</td>
<td>maintain pregnancy</td>
<td>1</td>
</tr>
<tr>
<td>amoxicillin</td>
<td>upper respiratory infection</td>
<td>1</td>
</tr>
<tr>
<td>aspirin</td>
<td>not specified</td>
<td>1</td>
</tr>
<tr>
<td>levothyroxine</td>
<td>hypothyroidism</td>
<td>1</td>
</tr>
<tr>
<td>Sudafed®</td>
<td>reduce ptylism</td>
<td>1</td>
</tr>
<tr>
<td>sennosides/docusate sodium</td>
<td>constipation</td>
<td>1</td>
</tr>
<tr>
<td>heparin</td>
<td>anti-coagulant</td>
<td>1</td>
</tr>
<tr>
<td>insulin</td>
<td>insulin dependent diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Cotazyme®</td>
<td>enzymes for pancreas</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 5 summarizes the severity of symptoms in these patients. On average the physical symptoms of NVP appeared in the sixth week of gestation. Although a large majority reported severe nausea prior to treatment with anti-emetic medication, only 20% experienced severe vomiting. Two-thirds of the women reported weight loss with a mean of 3.5 kilograms.

In terms of emotional well-being, an almost equal number of patients reported depression always/most of the time and rarely/never. The vast majority felt emotional support by their partner (91.9%). Thirty-one patients indicated that they considered termination of the pregnancy because of the NVP, giving an incidence rate in this population of 11.9%.

Although over two-thirds of the women reported time lost from paid employment, only one-third reported obtaining sick leave (i.e., paid time off). Just under half the patients indicated that their NVP had an adverse effect on their relationship with their partner, while over half felt that the NVP had an adverse effect on their partner’s day-to-day life.
Table 5: Baseline Severity of NVP According to Physical Symptoms, and Emotional and Social Function.

**Severity of physical symptoms of NVP**

<table>
<thead>
<tr>
<th></th>
<th>weeks ± SD (range)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of symptoms (n=258)</td>
<td></td>
<td>5.6 ± 1.7 (2-14)</td>
</tr>
<tr>
<td>Resolution of NVP (n=139)</td>
<td></td>
<td>16.9 ± 3.1 (10-29)</td>
</tr>
<tr>
<td>Nausea (n=260)</td>
<td>mild (0-1 episodes/day)</td>
<td>15 (5.8%)</td>
</tr>
<tr>
<td></td>
<td>moderate (2-5 episodes/day)</td>
<td>41 (15.8%)</td>
</tr>
<tr>
<td></td>
<td>severe (&gt;5 episodes/day)</td>
<td>204 (78.5%)</td>
</tr>
<tr>
<td>Vomiting (n=260)</td>
<td>mild (0-1 episodes/day)</td>
<td>103 (39.6%)</td>
</tr>
<tr>
<td></td>
<td>moderate (2-5 episodes/day)</td>
<td>89 (34.2%)</td>
</tr>
<tr>
<td></td>
<td>severe (&gt;5 episodes/day)</td>
<td>68 (26.2%)</td>
</tr>
<tr>
<td>Most bothersome (n=256)</td>
<td>nausea</td>
<td>140 (53.8%)</td>
</tr>
<tr>
<td></td>
<td>vomiting</td>
<td>19 (7.3%)</td>
</tr>
<tr>
<td></td>
<td>both</td>
<td>97 (37.3%)</td>
</tr>
<tr>
<td>Weight loss (n=258)</td>
<td>yes</td>
<td>155 (59.6%)</td>
</tr>
<tr>
<td></td>
<td>kg ± SD (range) (n=151)</td>
<td>3.6 ± 2.7 (0.4-13.6)</td>
</tr>
<tr>
<td>Hospital/ER visits (n=260)</td>
<td>yes</td>
<td>47 (18.1%)</td>
</tr>
<tr>
<td></td>
<td>once</td>
<td>28 (59.6%)</td>
</tr>
<tr>
<td></td>
<td>more than once</td>
<td>19 (40.4%)</td>
</tr>
</tbody>
</table>
### Table 5 (continued). *Impact of NVP on emotional well-being*

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Feelings of depression about NVP (n=257)</strong></td>
<td>always/most of the time</td>
<td>94 (36.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>some of the time</td>
<td>67 (25.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rarely/never</td>
<td>95 (36.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Emotional support by partner (n=258)</strong></td>
<td>yes</td>
<td>239 (91.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Consider TA because of NVP (n=257)</strong></td>
<td>yes</td>
<td>31 (11.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Concerns about NVP harming baby (n=259)</strong></td>
<td>more likely</td>
<td>135 (51.9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>unchanged</td>
<td>102 (39.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>less likely</td>
<td>22 (8.5%)</td>
<td></td>
</tr>
</tbody>
</table>

**Impact of NVP on social functioning**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time lost - paid employment (n=162)</strong></td>
<td>yes</td>
<td>127 (78.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hours ± SD (range)</td>
<td>52.1 ± 83.1 (1-480)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sick leave (n=120)</td>
<td>82 (31.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse effect on relationship (n=257)</strong></td>
<td>yes</td>
<td>126 (48.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>AE on partner's day-to-day life (n=259)</strong></td>
<td>yes</td>
<td>143 (55.0%)</td>
<td></td>
</tr>
</tbody>
</table>
Table 6 summarizes the women's report of their caregivers advice regarding management of their NVP. One hundred and thirty-three women reported receiving a single piece of advice, whereas 89 women received multiple options. Of those who received one recommendation, two-thirds were advised to use anti-emetic medication, while one quarter were advised to change their diet or lifestyle and a small percentage were told there was nothing to alleviate the NVP (12.8%).

In terms of pharmacologic recommendations, over half the women, all of which were residing in Canada, were advised to use only the doxylamine/pyridoxine combination (i.e., Diclectin®), while 10 women were informed to use doxylamine/pyridoxine in combination with other antiemetic medication. The most common phenothiazine recommended was promethazine (22 women). A small number of women were advised to use dimenhydrinate (4.8%) and pyridoxine alone (10.9%).

Table 6. Advice Received by Women with NVP from their Caregivers.

<table>
<thead>
<tr>
<th>Discussed NVP with caregiver (n=222)</th>
<th>85.4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single advice given by caregiver (n=133)</td>
<td>nothing/NVP will resolve 17 (12.8%)</td>
</tr>
<tr>
<td></td>
<td>change diet/lifestyle 32 (24.1%)</td>
</tr>
<tr>
<td></td>
<td>take medication 82 (61.6%)</td>
</tr>
<tr>
<td></td>
<td>use non-pharm. therapy 0</td>
</tr>
<tr>
<td></td>
<td>missing data 2 (1.5%)</td>
</tr>
<tr>
<td>Multiple advice given by caregiver (n=89)</td>
<td>nothing/NVP will resolve +</td>
</tr>
<tr>
<td></td>
<td>change diet/lifestyle 22 (24.7%)</td>
</tr>
<tr>
<td></td>
<td>nothing/NVP will resolve +</td>
</tr>
<tr>
<td></td>
<td>take medication 5 (5.6%)</td>
</tr>
<tr>
<td></td>
<td>use non-pharm. therapy 1 (1.1%)</td>
</tr>
<tr>
<td>Recommendations</td>
<td>Count (Percentage)</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>change diet/lifestyle +</td>
<td></td>
</tr>
<tr>
<td>take medication</td>
<td>54 (60.7%)</td>
</tr>
<tr>
<td>change diet/lifestyle +</td>
<td></td>
</tr>
<tr>
<td>use non-pharm. therapy</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td>nothing/NVP will resolve +</td>
<td></td>
</tr>
<tr>
<td>change diet/lifestyle +</td>
<td></td>
</tr>
<tr>
<td>take medication</td>
<td>5 (5.6%)</td>
</tr>
</tbody>
</table>

**Drug recommendations - single therapy**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>doxylamine/pyridoxine</td>
<td>79 (54.5%)</td>
</tr>
<tr>
<td>dimenhydrinate</td>
<td>7 (4.8%)</td>
</tr>
<tr>
<td>promethazine</td>
<td>22 (15.2%)</td>
</tr>
<tr>
<td>other</td>
<td>37 (25.5%)</td>
</tr>
</tbody>
</table>

**Drug recommendations - multiple therapy**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>doxylamine/pyridoxine +</td>
<td></td>
</tr>
<tr>
<td>dimenhydrinate</td>
<td>8 (53.3%)</td>
</tr>
<tr>
<td>doxylamine/pyridoxine + other</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>dimenhydrinate + other</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>promethazine + other</td>
<td>4 (26.7%)</td>
</tr>
</tbody>
</table>

**Vitamin supplements recommended**

<table>
<thead>
<tr>
<th>Vitamin Name</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>prenatal/multivitamin</td>
<td>90 (89.1%)</td>
</tr>
<tr>
<td>vitamin B6</td>
<td>11 (10.9%)</td>
</tr>
</tbody>
</table>
Other medications recommended for NVP are listed in Table 7. The majority of the medications listed below were identified by women residing in the United States. Doxylamine (Unisom® in the USA) is listed in combination with pyridoxine not as the Diclectin® formulation, rather as a preparation made specifically by pharmacists in the United States for the treatment of NVP.

Table 7. Other Recommendations to Treat NVP

<table>
<thead>
<tr>
<th>Anti-emetic recommendations</th>
<th>Number of patients (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emetrol® (glucose, fructose, phosphate)</td>
<td>7</td>
</tr>
<tr>
<td>compazine</td>
<td>4</td>
</tr>
<tr>
<td>doxylamine/pyridoxine</td>
<td>4</td>
</tr>
<tr>
<td>trimethobenzamide</td>
<td>4</td>
</tr>
<tr>
<td>doxylamine</td>
<td>3</td>
</tr>
<tr>
<td>metoclopramide</td>
<td>3</td>
</tr>
<tr>
<td>amitriptyline</td>
<td>1</td>
</tr>
<tr>
<td>chlorpromazine</td>
<td>1</td>
</tr>
<tr>
<td>Sudafed®/pyridoxine</td>
<td>1</td>
</tr>
<tr>
<td>diphenhydramine</td>
<td>1</td>
</tr>
<tr>
<td>ginger root</td>
<td>1</td>
</tr>
</tbody>
</table>
Figure 2. Antiemetic Treatments Used by Study Participants (n=239)

Figure 2 outlines the number of various anti-emetic medications used by this population of women. Although 146 women used at least one anti-emetic treatment for their NVP, a total of 239 pharmacological agents were used by the study participants. The study participants were administered some of the treatments in a hospital or emergency room setting.
Figure 3 lists various alternative therapies used in combination with anti-emetic medication. Ancillary therapies included antacids (i.e., calcium carbonate, magnesium hydroxide, aluminum hydroxide) and H₂-blockers (i.e., ranitidine, cimetidine), non-drug anti-emetics included acupressure/acupuncture and herbal products other than ginger or red raspberry tea.
Table 8 summarizes the reported effect of the various anti-emetic medications used by the study participants. Over half the women felt better after administration of medication for NVP, while few reported feeling worse for reasons such as increased nausea (ginger), drowsiness (doxylamine/pyridoxine) and extrapyramidal effects (phenothiazines).

Table 8. Effect of Starting Antiemetic Medication Used by the Study Participants

<table>
<thead>
<tr>
<th>Antiemetic</th>
<th>better</th>
<th>same</th>
<th>worse</th>
<th>missing data</th>
</tr>
</thead>
<tbody>
<tr>
<td>doxylamine/pyridoxine</td>
<td>50</td>
<td>22</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>promethazine</td>
<td>22</td>
<td>10</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>dimenhydrinate</td>
<td>19</td>
<td>12</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>pyridoxine</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>ginger</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>doxylamine</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>prochlorperazine</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ginger root tea</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>red raspberry tea</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>metoclopramide</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>trimethobenzamide</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ondansetron</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>chlorpromazine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>clemastine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>amitriptyline</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>cannabis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Totals 125 (52.3%) 68 (28.5%) 7 (2.9%) 39 (16.3%)
4.1.2. Teratogenic Risk Perception and Intervention

Table 9 outlines the perception of teratogenic risk attributed to anti-emetics for NVP in the cohort of patients contacting the healthline.

At the initial call, all women responded to the question posed regarding the teratogenic risk of anti-emetic use during their pregnancy. Over three-quarters of the women reported that drug use for NVP was more likely to increase their baby's risk for malformations, while one-third attributed no teratogenic risk to the fetus.

At the 20-week gestation follow-up, a statistically significant drop was seen in the "more likely teratogenic risk" category (65.8% vs. 42.3%, p < 0.05) concurrent with a statistically significant increase in the "unchanged teratogenic risk" category (32.7% vs. 51.9%, p < 0.05). Stratification of the respondents into those using anti-emetic medication at the initial call and those not using anti-emetics at the initial call produced similar trends (Table 10 and Table 11, respectively).

Table 9. Teratogenic Risk Potential of NVP Treatments Before and After Consultation

<table>
<thead>
<tr>
<th>Teratogenic Risk</th>
<th>Initial Call (n=260)</th>
<th>Follow-up (n=258)</th>
<th>( \chi^2 )</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>more likely</td>
<td>171 (65.8%)</td>
<td>110 (42.3%)</td>
<td>43.51</td>
<td>0.000</td>
</tr>
<tr>
<td>unchanged</td>
<td>85 (32.7%)</td>
<td>135 (51.9%)</td>
<td>33.33</td>
<td>0.000</td>
</tr>
<tr>
<td>less likely</td>
<td>4 (1.5%)</td>
<td>13 (5.0%)</td>
<td>0.049</td>
<td></td>
</tr>
</tbody>
</table>

*McNemar test (non-parametric) for 2 related samples
†significance p < 0.05
Table 10. Teratogenic Risk Potential of NVP Treatments Before and After Consultation For Patients Who Received Anti-emetic Medication.

<table>
<thead>
<tr>
<th>Teratogenic Risk</th>
<th>Initial Call (n=146)</th>
<th>Follow-up (n=145)</th>
<th>$\chi^2*$</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>more likely</td>
<td>80 (54.8%)</td>
<td>45 (30.8%)</td>
<td>24.75</td>
<td>0.000</td>
</tr>
<tr>
<td>unchanged</td>
<td>65 (44.5%)</td>
<td>94 (64.4%)</td>
<td>17.42</td>
<td>0.000</td>
</tr>
<tr>
<td>less likely</td>
<td>1 (0.7%)</td>
<td>6 (4.1%)</td>
<td>0.344</td>
<td>0.125</td>
</tr>
</tbody>
</table>

*McNemar test (non-parametric) for 2 related samples
†significance p < 0.05

Table 11. Teratogenic Risk Potential of NVP Treatments Before and After Consultation For Patients Not Receiving Anti-emetic Medication.

<table>
<thead>
<tr>
<th>Teratogenic Risk</th>
<th>Initial Call (n=114)</th>
<th>Follow-up (n=113)</th>
<th>$\chi^2*$</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>more likely</td>
<td>91 (79.8%)</td>
<td>65 (57.0%)</td>
<td>17.36</td>
<td>0.000</td>
</tr>
<tr>
<td>unchanged</td>
<td>20 (17.5%)</td>
<td>41 (36.0%)</td>
<td>14.70</td>
<td>0.000</td>
</tr>
<tr>
<td>less likely</td>
<td>3 (2.6%)</td>
<td>7 (6.1%)</td>
<td>0.344</td>
<td></td>
</tr>
</tbody>
</table>

*McNemar test (non-parametric) for 2 related samples
†significance p < 0.05
4.1.3. Advice vs. Teratogenic Risk Perception

Table 12 summarizes the difference in risk perception in the population based on the advice received. Although the risk assessment was not significantly different when advice was to do nothing to treat NVP, both advice to change diet/lifestyle and to use anti-emetic medication produced statistically significant results. The trends for each, however, differed: advice to change diet/lifestyle was significantly associated with an increased risk perception ($\phi = 0.23$, $p = 0.001$), whereas recommendation to use anti-emetic medication was significantly associated with no change in risk for major malformations ($\phi = 0.22$, $p = 0.001$).

Table 12. Cross-tabulation of Advice Received Compared to Perception of Risk

<table>
<thead>
<tr>
<th>Advice</th>
<th>Increased risk</th>
<th>Unchanged risk</th>
<th>$\chi^2$*</th>
<th>$p^\dagger$</th>
<th>$\phi$</th>
<th>$p^\dagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nothing/will resolve (n=17)</td>
<td>11 (64.7%)</td>
<td>6 (35.3%)</td>
<td>0.000</td>
<td>1.00</td>
<td>0.006</td>
<td>0.933</td>
</tr>
<tr>
<td>Change diet/lifestyle (n=50)</td>
<td>42 (84.0%)</td>
<td>8 (16.0%)</td>
<td>10.39</td>
<td>0.001</td>
<td>0.230</td>
<td>0.001</td>
</tr>
<tr>
<td>Use medication (n=146)</td>
<td>64 (43.8%)</td>
<td>82 (56.2%)</td>
<td>10.07</td>
<td>0.002</td>
<td>-0.225</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Chi-squared with continuity correction
†significance $p < 0.05$
4.2. Data on Elective Termination

4.2.1. Case-Control Study

From February 1996 through to December 1996, 2,693 retrospective cases were collected through the healthline. Ninety-one women reported terminating their pregnancy as a result of the severity of their NVP, giving an incidence in this population of 3.4%. Twenty-five of the 91 women did not wish to discuss the termination and were excluded from analysis leaving 66 women who completed the intake questionnaire. For the purposes of analysis, four of the women reported more than one elective termination because of NVP. Therefore, their terminations were treated as individual pregnancies.

The cases of elective termination were matched to controls consisting of women who called regarding a past pregnancy in which they suffered from NVP. Controls were obtained in a sequential fashion based on the day of intake into the study of the women who reported a termination. If no eligible matches were found for the same day, the day before and after were scanned for potential matches. This process was done up to one month before and after the initial intake date. The cases were matched for severity of vomiting (based on a scale of mild (0-1 episodes/day), moderate (2-5 episodes/day) and severe (>5 episodes/day)), age (± 3 years), and year of pregnancy (± 2 years).
Figure 4 illustrates a breakdown of the years in which the respondents reported their therapeutic abortions. Over 60% of the callers had an elective termination during the 1990s, whereas 30% occurred during the 1980s, and just under 10% were reported to occur during the 1970s.
The following tables summarize the case-control analysis of 70 pregnancies that ended in an elective termination because of NVP compared to 70 pregnancies affected by NVP that did not end in an elective termination.

Table 13 summarizes baseline maternal and fetal characteristics of women who terminated their pregnancies and those who continued to term. Statistical significance was achieved with parity, planned pregnancy and the obstetrician providing obstetric care: women who continued to term were more likely to have more live births (1.34 vs. 2.23, \( p=0.0001 \)), plan their pregnancy (21 vs. 53, \( p=0.0001, \text{OR}=0.14 \ [0.04,0.51] \)) and have an obstetrician care for them during their pregnancy (32 vs. 53, \( p=0.0005, \text{OR}=0.27 \ [0.08,0.91] \)). However, the mean gestational age of the women who reported terminating the pregnancy was 10 weeks. Since the majority of obstetricians do not see pregnant patients until they are 12 weeks gestation, this difference in obstetric care can be explained, and therefore will not be included as a predictor for termination.
Table 13. Characteristics of Women Who Aborted Their Pregnancy and Also Suffered From NVP Compared to Those of Controls.

*General Pregnancy Information*

<table>
<thead>
<tr>
<th>Pregnancy Parameter</th>
<th>Abortion (n=70)</th>
<th>No Abortion (n=70)</th>
<th>p†</th>
<th>OR [99.9% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Place of residence - USA</td>
<td>10</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>58</td>
<td>54</td>
<td>0.31</td>
<td>0.58 [0.13,2.52]</td>
</tr>
<tr>
<td>Previous defects</td>
<td>2</td>
<td>4</td>
<td>0.44‖</td>
<td>0.49 [0.03,8.87]</td>
</tr>
<tr>
<td>Gravidity</td>
<td>3.1 ± 1.4</td>
<td>2.8 ± 1.7</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>(1-8)</td>
<td>(1-11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td>1.3 ± 1.0</td>
<td>2.2 ± 1.1</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>(0-3)</td>
<td>(1-8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous parity</td>
<td>0.7 ± 0.9</td>
<td>0.6 ± 1.0</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>(0-3)</td>
<td>(0-5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous Abortion</td>
<td>0.3 ± 0.7</td>
<td>0.4 ± 0.9</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>(0-3)</td>
<td>(0-5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous TA</td>
<td>16</td>
<td>2</td>
<td>0.001</td>
<td>10.07 [2.22,45.73]</td>
</tr>
<tr>
<td>Socioeconomic Score‡</td>
<td>44.9 ± 14.7</td>
<td>45.2 ± 19.2</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>(22.1-78.3)</td>
<td>(4.2-101.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planned pregnancy</td>
<td>21</td>
<td>53</td>
<td>0.0001</td>
<td>0.14 [0.04,0.51]</td>
</tr>
<tr>
<td>Caregiver - GP</td>
<td>34</td>
<td>17</td>
<td>0.005</td>
<td>2.94 [0.88,9.86]</td>
</tr>
<tr>
<td>OB/GYN</td>
<td>32</td>
<td>53</td>
<td>0.0005</td>
<td>0.27 [0.08,0.91]</td>
</tr>
<tr>
<td>Midwife/RN</td>
<td>2</td>
<td>0</td>
<td>0.50‖</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2</td>
<td>0</td>
<td>0.50‖</td>
<td></td>
</tr>
<tr>
<td>Parameter</td>
<td>Value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age at time of abortion (weeks)</td>
<td>10.2 ± 3.1 (5-18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age at time of birth (weeks)</td>
<td>39.9 ± 1.9 (32-42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth Weight (g)</td>
<td>3435.7 ± 558.8 (1846.5-5000)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†significance p < 0.001, ‡based on Blishen’s index for occupations in Canada

¶ Fisher’s exact test (2-tailed)
In Table 14, characteristic of baseline severity of NVP yielded one statistically significant result; depression always/most of the time because of the NVP (47 vs. 30, \( p=0.0016 \), OR=3.41 [0.99,11.70]).

Table 14. Severity of NVP by Physical Symptoms, and Emotional and Social Functioning.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Abortion</th>
<th>No Abortion</th>
<th>( \chi^2 )</th>
<th>( p^+ )</th>
<th>[99.9% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- mild</td>
<td>1</td>
<td>0</td>
<td>0.00</td>
<td>1.00|</td>
<td></td>
</tr>
<tr>
<td>- moderate</td>
<td>0</td>
<td>6</td>
<td>3.50</td>
<td>0.026|</td>
<td></td>
</tr>
<tr>
<td>- severe</td>
<td>69</td>
<td>64</td>
<td>1.71</td>
<td>0.110|</td>
<td>6.47 [0.18,236.69]</td>
</tr>
<tr>
<td>Weight Loss (kg)</td>
<td>5.9 ± 3.7</td>
<td>7.7 ± 4.1</td>
<td></td>
<td>0.027</td>
<td></td>
</tr>
<tr>
<td>Hospitalization - yes</td>
<td>24</td>
<td>37</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- no</td>
<td>46</td>
<td>31</td>
<td>4.88</td>
<td>0.027</td>
<td>0.45 [0.14,1.41]</td>
</tr>
<tr>
<td>Freq hospital - once</td>
<td>10</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- &gt; once</td>
<td>14</td>
<td>20</td>
<td>0.004</td>
<td>0.95</td>
<td>0.79 [0.14,4.48]</td>
</tr>
<tr>
<td># medications used</td>
<td>31</td>
<td>19</td>
<td>3.76</td>
<td>0.05</td>
<td>2.13 [0.65,6.99]</td>
</tr>
<tr>
<td>Depression - always/most</td>
<td>47</td>
<td>30</td>
<td>9.95</td>
<td>0.0016</td>
<td>3.41 [0.99,11.70]</td>
</tr>
<tr>
<td>some times</td>
<td>4</td>
<td>14</td>
<td>4.75</td>
<td>0.029</td>
<td>0.25 [0.04,1.80]</td>
</tr>
<tr>
<td>rarely/never</td>
<td>13</td>
<td>23</td>
<td>2.56</td>
<td>0.11</td>
<td>0.49 [0.13,1.84]</td>
</tr>
<tr>
<td>Occupation - outside</td>
<td>47</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- not outside</td>
<td>23</td>
<td>21</td>
<td>0.03</td>
<td>0.85</td>
<td>0.88 [0.26,2.90]</td>
</tr>
<tr>
<td>Lost work time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- yes</td>
<td>38</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>9</td>
<td>7</td>
<td>0.02</td>
<td>0.89</td>
<td>0.79 [0.12,5.06]</td>
</tr>
<tr>
<td></td>
<td>yes</td>
<td>no</td>
<td>χ²</td>
<td>p</td>
<td>OR</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Affect relationship</td>
<td>42</td>
<td>28</td>
<td>6.82</td>
<td>0.009</td>
<td>2.67</td>
</tr>
<tr>
<td>Partner support</td>
<td>43</td>
<td>58</td>
<td>5.24</td>
<td>0.02</td>
<td>0.37</td>
</tr>
<tr>
<td>Meds risks</td>
<td>39</td>
<td>36</td>
<td>0.87</td>
<td>0.35</td>
<td>1.47</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>30</td>
<td>3.21</td>
<td>0.073</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>4</td>
<td>1.15</td>
<td>0.28</td>
<td>2.36</td>
</tr>
<tr>
<td>NVP risks</td>
<td>39</td>
<td>45</td>
<td>0.11</td>
<td>0.74</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>13</td>
<td>0.58</td>
<td>0.44</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>11</td>
<td>1.66</td>
<td>0.20</td>
<td>1.91</td>
</tr>
<tr>
<td>More Child</td>
<td>15</td>
<td>15</td>
<td>0.05</td>
<td>0.95</td>
<td>1.06</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>23</td>
<td>5.11</td>
<td>0.02</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>30</td>
<td>3.38</td>
<td>0.07</td>
<td>2.03</td>
</tr>
</tbody>
</table>

†significance p < 0.001

†Fisher exact test (2-tailed)
Table 15 summarizes the advice received regarding management of NVP and the medication used specifically for NVP and other conditions during the pregnancy. Although all 70 of the women who did not terminate their pregnancy received advice from their caregiver, only 56 of the women who aborted the pregnancy reported receiving advice regarding their NVP. Statistical significance was achieved only with vitamin use; a smaller number of women who aborted the pregnancy reported using prenatal or multivitamins during the pregnancy (9 vs. 41, p=0.0001, OR=0.10 [0.03,0.43]).
Table 15. Advice Received for Treatment of NVP - Pharmacological, Nonpharmacological.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Abortion</th>
<th>No Abortion</th>
<th>$\chi^2$</th>
<th>p†</th>
<th>[99.9% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>One piece of advice received</td>
<td>43</td>
<td>40</td>
<td>4.50</td>
<td>0.03</td>
<td>2.48 [0.67,9.19]</td>
</tr>
<tr>
<td>nothing/will go away</td>
<td>10</td>
<td>11</td>
<td>0.00</td>
<td>1.00</td>
<td>0.89 [0.19,4.25]</td>
</tr>
<tr>
<td>change diet/lifestyle</td>
<td>8</td>
<td>10</td>
<td>0.06</td>
<td>0.80</td>
<td>0.77 [0.15,4.12]</td>
</tr>
<tr>
<td>use medication</td>
<td>21</td>
<td>16</td>
<td>0.59</td>
<td>0.44</td>
<td>1.45 [0.41,5.15]</td>
</tr>
<tr>
<td>use non-drug remedies</td>
<td>4</td>
<td>3</td>
<td>0.00</td>
<td>1.00</td>
<td>1.35 [0.10,17.81]</td>
</tr>
<tr>
<td>&gt; one piece of advice received</td>
<td>13</td>
<td>30</td>
<td>4.50</td>
<td>0.03</td>
<td>0.40 [0.11,1.49]</td>
</tr>
<tr>
<td>nothing/change diet</td>
<td>3</td>
<td>8</td>
<td>0.02</td>
<td>1.00</td>
<td>0.83 [0.06,10.64]</td>
</tr>
<tr>
<td>change diet/use meds.</td>
<td>5</td>
<td>19</td>
<td>1.38</td>
<td>0.18</td>
<td>0.36 [0.04,3.44]</td>
</tr>
<tr>
<td>Meds for NVP - doxylamine/vit B₆</td>
<td>13</td>
<td>16</td>
<td>0.17</td>
<td>0.68</td>
<td>0.77 [0.19,3.05]</td>
</tr>
<tr>
<td>dimenhydrinate</td>
<td>28</td>
<td>28</td>
<td>0.03</td>
<td>0.86</td>
<td>1.00 [0.32,3.11]</td>
</tr>
<tr>
<td>phenothiazines</td>
<td>5</td>
<td>9</td>
<td>0.71</td>
<td>0.40</td>
<td>0.52 [0.08,3.58]</td>
</tr>
<tr>
<td>herbal products</td>
<td>16</td>
<td>14</td>
<td>0.04</td>
<td>0.84</td>
<td>1.19 [0.30,4.61]</td>
</tr>
<tr>
<td>other</td>
<td>6</td>
<td>8</td>
<td>0.05</td>
<td>0.82</td>
<td>0.75 [0.12,4.88]</td>
</tr>
<tr>
<td>Vitamins</td>
<td>9</td>
<td>41</td>
<td>29.90</td>
<td>0.0001</td>
<td>0.10 [0.03,0.43]</td>
</tr>
<tr>
<td>Minerals</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1.00</td>
<td>2.03 [0.03,118.73]</td>
</tr>
<tr>
<td>Ancillary Therapies</td>
<td>6</td>
<td>20</td>
<td>7.98</td>
<td>0.005</td>
<td>0.23 [0.04,1.22]</td>
</tr>
<tr>
<td>Meds other conditions</td>
<td>9</td>
<td>17</td>
<td>2.31</td>
<td>0.13</td>
<td>0.46 [0.10,2.04]</td>
</tr>
</tbody>
</table>

†significance p < 0.001

¶Fisher exact test (2-tailed)
4.2.2. Multi-variant Analysis of Case-Control Study - Logistic Regression

The univariant analysis conducted comparing those women who aborted the pregnancy because of NVP to controls yielded 4 variables that were statistically significant at the 99.9% confidence interval. The variables and their respective correlation coefficients with significance are listed in Table 16. All 4 variables were used to conduct the multi-variant analysis to determine what specific variables would best predict the model for abortion.

Table 16. Correlation Coefficients for Factors Significantly Associated with Abortion.

<table>
<thead>
<tr>
<th>Factor</th>
<th>$\phi$</th>
<th>$p^\dagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td>previous elective termination</td>
<td>0.299</td>
<td>0.000</td>
</tr>
<tr>
<td>planned pregnancy</td>
<td>-0.452</td>
<td>0.000</td>
</tr>
<tr>
<td>always/most of the time depressed</td>
<td>0.291</td>
<td>0.001</td>
</tr>
<tr>
<td>use of vitamin supplementation during pregnancy</td>
<td>-0.477</td>
<td>0.000</td>
</tr>
</tbody>
</table>

$^\dagger$significance $p < 0.001$

The variables to be analyzed are all nominal in nature with a dichotomous value of 'yes' or 'no'. Therefore, a logistic regression model was employed. The results of the regression analysis are summarized in Table 17 and Table 18.

The total number of cases included for analysis totaled 140. However, 13 cases were rejected prior to the regression because of missing data, leaving 127 cases for the final regression analysis (65 abortion and 62 non-abortion).

Table 17 contains the parameter estimates for the logistic regression model: the estimated coefficients for each variable (B) with each respective standard error (SE) and significance. Three out of the 4 variables entered were statistically significant, with a $p$ value greater than 0.05.
Table 17. Variable Predictors of Regression Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>previous elective termination</td>
<td>-1.60</td>
<td>0.89</td>
<td>0.0715</td>
</tr>
<tr>
<td>planned pregnancy</td>
<td>-2.04</td>
<td>0.50</td>
<td>0.0000</td>
</tr>
<tr>
<td>always/most of the time depressed</td>
<td>1.20</td>
<td>0.50</td>
<td>0.0171</td>
</tr>
<tr>
<td>use of vitamin supplementation during pregnancy</td>
<td>-2.40</td>
<td>0.55</td>
<td>0.0000</td>
</tr>
<tr>
<td>Constant</td>
<td>5.49</td>
<td>1.38</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table 18 represents the classification table comparing predicted to observed outcomes for the case-control. Fifty-one patients (83.61%) who reported aborting the pregnancy were correctly predicted by the model to abort. Similarly, 52 women (78.79%) who did not abort the pregnancy were correctly predicted to not abort. A total of 24 women were misclassified—10 women who did abort and 14 who did not. Overall, 81.10% of the 70 women who aborted the pregnancy were correctly classified.

Table 18. Model for Independent Variables That Best Predicts Patients Who Abort Because of NVP - Logistic Regression Enter Method.

<table>
<thead>
<tr>
<th>Observed</th>
<th>Abort</th>
<th>Not Abort</th>
<th>Percent correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abort</td>
<td>51</td>
<td>10</td>
<td>83.61%</td>
</tr>
<tr>
<td>Not Abort</td>
<td>14</td>
<td>52</td>
<td>78.79%</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>81.10%</td>
</tr>
</tbody>
</table>
Although the classification table reveals the proportion of women correctly predicted by the model, it does not reveal the distribution of the estimated probabilities for the women who did and did not abort. Figure 5 represents a histogram of estimated probabilities of the cases. The two groups appear to cluster towards their respective ends of the plot. However, there are 3 abortion cases with estimated probabilities of greater than 0.75 and an equal number of non-abortion cases with estimated probability of less than 0.25.

**Figure 5. Histogram of observed groups and predicted probabilities**

<table>
<thead>
<tr>
<th>Predicted</th>
<th>Prob:</th>
<th>Group:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>.25</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>.5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>.75</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Predicted Probability is of Membership for 2.00
The Cut Value is .50
Symbols: 1 - elective termination
2 - no elective termination
Each symbol represents 1.25 cases based on probability distribution.

The logistic regression equation for the population being studied is as follows:

\[
\text{Probability (abortion due to NVP)} = \frac{1}{1 + e^{-d}}
\]

where \( d = 5.49 - 1.60(\text{previous elective termination}) - 2.04(\text{planned pregnancy}) + 1.20(\text{always/most of the time depressed}) - 2.40(\text{use of vitamin supplementation}) \)
5. Discussion

5.1. Prospective Patients Suffering from NVP - Quality of Medical Advice

The population of pregnant women collected for investigation were similar to what is expected in women of child-bearing age in North American society today: the 50th percentiles for age, gravidity and parity were 30 years, 2 and 1, respectively. The rate of previous defects also falls within the expected rate of 1-5% in the general population. Given that the average gestational age of the participants was 12 weeks, it was not surprising that two-thirds of the women reported an obstetrician as their primary caregiver.

In terms of the NVP, the data collected were also found to be similar to those documented: the 50th percentile for onset of symptoms was 6 weeks gestation and for resolution of NVP was 16 weeks gestation. However, the women who contacted the Healthline presented with more severe nausea and vomiting than the average in the population. Therefore, conclusions drawn regarding this cohort of patients should be directed towards the more severe end of the spectrum.

The data did identify a number of issues also raised by others regarding the effects of NVP on the quality of life. For example, over 60% of the women reported some degree of depression because of the NVP and 50% were concerned that their NVP would impact negatively on the health of their child. Moreover, 12% of patients considered termination of their pregnancy because of the severity of their NVP. This possibly reflects the severe nature of the disease in this population. In terms of lifestyle changes, 78% reported some time lost from outside employment, which is higher than previously reported in a similar study, although the mean number of hours lost was quite similar (52 vs. 62). This probably can be attributed to the severer nature of the condition in the group studied here.

Although almost half the women felt that the NVP adversely affected the relationship with their partner, over 90% felt support by their partner. This seeming contradiction can
possibly be explained by the nonspecific nature of the question. Support from a partner can be interpreted as financial, emotional, intimate or, all three.

The current study demonstrates that caregivers have not reached a consensus regarding advice for the treatment for NVP. Although in this cohort, the majority of women reported being told to use anti-emetic medication, a substantial number of women continued not to receive advice regarding specific strategies for the management of their NVP. For example, in Canada, Diclectin® is available and indicated for the treatment of NVP. Moreover, there was a wide variety of anti-emetics recommended in general, some of which are clearly not considered standard therapy, for example amitriptyline. Furthermore, not all the women responded favourably to treatment with medication. What is more concerning is that, based on the reported nausea in this group, the women who contacted the Healthline were at the severe end of the spectrum in terms of their physical symptoms. It is these women that require the most attention and should be offered treatment.

In general, the women in this cohort considered that anti-emetics used to treat NVP would increase the risk for major malformations, whether they used medication or not. The perception of teratogenic risk was hypothesized to be related to advice received from their major caregiver. In this study, statistical analysis showed that women who were advised to take medication by their primary caregiver were proportionally less likely to attribute an increased risk for major malformations as compared to those not told to use medication. Overall, those who were advised to change their diet or lifestyle were more likely to consider anti-emetic medication as a teratogenic risk to the fetus. These results are not surprising given that increased awareness of safety issues concerning medication use in pregnancy would be expected to reduce anxiety, as shown by Koren110 and Mastroiacovo112. Moreover, the additional supportive advice received from the Healthline regarding anti-emetic management of NVP suggested effective counselling, based on the reduced numbers women who considered drug therapy for NVP to
increase the risk for major malformations. However, it must be noted that perception of teratogenic risk may not be entirely attributed to the caregivers direct advice. Women may have their own predetermined opinion of teratogenic risk in pregnancy and their anxiety towards use of medication during pregnancy may determine what advice a caregiver will provide regarding management of NVP. The methodology of the study cannot address this issue directly, and it is necessary in the future to incorporate such observations into the study protocol.

We hypothesized that an additional reason for the increased risk-perception of anti-emetic therapy (not tested in this investigation) may be related, in part, to the thalidomide tragedy itself. Thalidomide was the first drug to be labelled as a human teratogen and was indicated for the relief of morning sickness. The net result of the thalidomide experience was increased scrutiny of anti-emetic drugs with potential benefits, such as Bendectin®/Diclectin®. In fact, even up to 1989, the Canadian media reported Diclectin® to be "another thalidomide". The effect of these reports on potentially beneficial drugs for NVP continue to be felt in the medical community and the public at large.
5.2. Abortion Data

It was the anecdotal experience of “Motherisk” that NVP may be associated with elective termination of pregnancies. The case-control investigation was able to uncover a number of determinants which may be associated with abortion due to NVP.

In this study, the women who aborted were treated no differently than their matched controls for severity of their NVP. Moreover, the method of treatment was what is expected in general practice (i.e., Bendectin®/Diclectin®, dimenhydrinate, phenothiazines). This is an encouraging result, given that one of our primary concerns with women terminating a pregnancy was inappropriate recommendations regarding treatment of their NVP. However, less than half of the women who reported termination actually used antiemetic medication. Therefore, they did not exhaust the therapeutic options prior to deciding to terminate the pregnancy and, although not significantly different than their matched controls, would indicate a need to increase management of these patients with either pharmacologic and/or non-pharmacologic interventions.

Women who decided to abort their pregnancy were significantly more depressed than those who had similar severity but did not terminate. This indicates an urgent need to increase psychosocial support to these women and to refer those suffering from depression to professional help. None of the women in the abortion group identified previous history of depression or use of anti-depressant medication. However, given that the result was significantly associated with depression, it is possible that the women who aborted may be affected by their NVP more than normal. Psychological factors have been previously documented\[12 \, 13\] which may partial explain the results obtained.

The issue of vitamin supplementation is of interest. In this study, vitamin use had the most significant correlation of all the factors analyzed (r=0.48). Use of vitamin supplementation during pregnancy as a protective effect against abortion may indicate a better informed subgroup which may be supported better in many other ways. Alternatively, these data agree with a recent
published observation by Czeizel et al\textsuperscript{73}, that women randomized to receive vitamins (for the prevention of neural tube defects) were less likely to have severe or moderate forms of NVP than those not receiving vitamins. This may represent the pharmacologic effects of vitamin B\textsubscript{6} alone or vitamin B\textsubscript{6} deficiency corrected by such supplementation.
6. Limitations of Study

6.1. Prospective Data

Although the respondents, collected prospectively through the Healthline, were able to respond accurately to the questionnaire since they were currently suffering from NVP, the study was not population-based, but rather a cohort of women who were motivated to answer an ad or respond to a radio advertisement. Therefore, this may bias the sample collected toward women with more severe symptoms. This was indeed the case. However, the fact that a number of these women reported they were advised not to use any anti-emetic medication despite the severity of their symptoms lends further towards to notion that women may not be receiving adequate advice.

Another limitation of the study is that the documented advice was from the callers recollection only and not validated by the caregivers as to their advice. In this way, the women may have remembered only what they felt was important. However, the interviewers were prompted by each of the categories listed and, therefore, it is unlikely that the woman would not have disclosed information provided by her caregiver. Moreover, caregivers, especially physicians, are considered to be experts in their field and it is highly likely that women will act on what they are recommended.

Finally, the study is qualitative, with no specific laboratory analysis or physical examination result with which diagnosis and severity could be confirmed. However, we sought women with NVP, and “…it is assumed that participants in qualitative samples have relevant information about the phenomena of interest so that it can be examined ‘where it is found to exist’”.

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6.2. Case-Control Study

The cases of elective termination of pregnancy collected through the Healthline were not linked to medical records; therefore, neither the diagnosis of NVP nor other potential reasons for pregnancy termination could be confirmed. However, it must be acknowledged that the women did not list medical indications as their reason for choosing abortion, and that NVP (which has been long regarded to have a strong psychological component), cannot be assumed to be a more socially acceptable indication for abortion than personal choice.

The case-control data were retrospectively ascertained and therefore are subject to recall bias. However, given that NVP is a common experience for pregnant women and choosing to terminate a pregnancy would be a significant decision, it is not unreasonable to assume that that aspect of their pregnancy would remain in their memory. Moreover, given the rarity of elective termination because of NVP, a case-control design is best suited to revealing factors that may influence a woman to terminate a pregnancy.

The regression analysis is a useful tool for identifying predictors for various outcomes. In this study factors pertaining to physical symptoms and their effects on quality of life (such as emotional, social and occupational functioning) were attempted to be identified. The model is specific only for those outcomes deemed significant through application of statistical methods. Other variables not tested in this case-control study may also contribute to women undergoing abortion of their pregnancy because of NVP. Therefore, the conclusions are specific for the population collected until they can be reproduced in other centres.
7. Conclusions

Management of any condition in pregnancy requires that both the care-giver and the patient weigh the risks and benefits of any treatment. Unfortunately, after the thalidomide tragedy, the risks of drug therapy in general, and anti-emetic therapy specifically, have been overestimated. A comprehensive review of the literature has revealed that there are a number of pharmacological and nonpharmaceutical measures available that have proven safety and effectiveness for treatment of NVP. However, intervention using these therapies may be delayed until severe physical symptoms appear.

This investigation would suggest that there is still misperception, by patients and health professionals alike, about the risks of anti-emetic medication. Firstly, thalidomide would have been identified as a major teratogen at the pre-marketing stages of drug development if evaluated by today's testing standards. Secondly, Diclectin® (currently marketed only in Canada) has been proven not to be a teratogen, and other anti-emetics in common use (e.g., dimenhydrinate) are not known to be teratogenic. Therefore, consideration should be given to offer pharmacologic treatment to women before severe physical symptoms appear.

In this investigation it was also determined that NVP is associated (albeit uncommonly) with legal abortions. The study identified a number of factors that may contribute to the decision to terminate the pregnancy, which included an unplanned pregnancy, severity of depression regarding the NVP and lack of vitamin supplementation. Although psychosocial issues were not shown to be significant factors in the decision to terminate, because of the small sample these differences may not have been detected. Therefore, future study is warranted into the impact of NVP on a woman's life and how this impact may be associated with elective termination of pregnancy.

A large educational effort based on evidence-based management is needed among health professionals and patients to optimize management and eradicate misinformation about NVP.
Women with severe forms of NVP may benefit from specialized services focusing on their physical, as well as their psycho-social needs.
REFERENCES


Richards ID. A retrospective enquiry into possible teratogenic effects of drugs in pregnancy. IN: Drugs and teratology development. 1971:441-55.


APPENDIX A - Prospective Questionnaire Intake Form (English and French)
NVP QUESTIONNAIRE

REAL TIME INTAKE

Date of Follow-up __________________________
(d/m/y)

How did you hear about this healthline?
________________________________________

Patient No. ________________________________
Date of Interview (d/m/yr) ____________________
Interviewer ________________________________

I. GENERAL INFORMATION

Name ________________________________ Date of Birth (d/m/yr) __________________________
Street Address __________________________ City/Province ______________________________
Telephone (H) ____________________________ (W) ________________________________
G ___ P ___ SA ___ TA ___ Birth Defects? 〇 No 〇 Yes (specify)____________________
LMP (d/m/yr) ______________________________ Was this a planned pregnancy? 〇 No 〇 Yes

• Who is providing your obstetric care? 〇 Family Doctor 〇 Obstetrician
  〇 Midwife

II. SEVERITY OF NVP

• When did your NVP start? (d/m/yr) __________________________

• When did your NVP stop? (d/m/yr) __________________________

• Before taking medication, how often did you have nausea?
  No. of times per day __________

• Before taking medication, how often did you vomit?
  No. of times per day __________

• What bothered you most? 〇 Nausea 〇 Vomiting

• Have you discussed your NVP with your caregiver? 〇 No 〇 Yes

  If no, explain why:
If yes, what did he/she advise you (choose more than one)?

- There is nothing he/she can do,
- Your nausea and vomiting will go away on their own
- You should change your diet (e.g. eat small meals, bland food)
- You should take medication but only after the first trimester of pregnancy
- You should take medication (please specify drugs)
  - Gravol® (Dimenhydrinate)
  - Diclectin® (Doxylamine/pyridoxine)
  - Vitamin (please specify) ________________________________
  - Other (please specify drugs) ________________________________

Have you used any of the following to treat your NVP? - e.g. prescription or OTC drugs, herbal remedies, acupuncture

- No — Why not?
  - Nothing has been recommended to you
  - You are worried that medications will cause birth defects
  - Other (please specify) ________________________________

- Yes (Please specify below in Table)

Did you have any medical conditions as a consequence of your NVP (e.g. blood in vomit)?

- No
- Yes

Did you injure yourself in consequence of your NVP? (e.g.: faint, fall?)

- No
- Yes

Did you have to see a doctor because of the seriousness of injury(ies) and/or medical conditions? (as mentioned in question above).

- No
- Yes

Have you lost weight?

- No
- Yes ___________________ kg/lb

Have you been admitted to hospital and/or had emergency room visits for NVP?

- No
- Yes —> admit ER both
  - How many times? ______
  - When (d/m/yr)?:

Did you receive treatment there?

- No
- Yes —> How many days? ____________________
• What treatment did you receive there?
  ○ IV fluids
  ○ Medications for vomiting:
    ○ Graviol
    ○ Metoclopramide
    ○ Diclectin
    ○ Other
    ○ Phenothiazines

• Were there any medical complications due to treatment?
  ○ No
  ○ Yes (please specify): 

III. TREATMENT/MEDICATIONS

ANTIEMETIC DRUGS (including those taken in hospital)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Start date (d/m/yr)</th>
<th>Stop date (d/m/yr)</th>
<th>Dosage (dose, frequency)</th>
<th>Effect of starting the medication</th>
<th>By whose advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td>○ Very much better</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ Slightly better</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ About the same</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ Slightly worse</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ Very much worse</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ ongoing</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
<td>○ Very much better</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ Slightly better</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ About the same</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ Slightly worse</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ Very much worse</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ ongoing</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td></td>
<td></td>
<td>○ Very much better</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ Slightly better</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ About the same</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ Slightly worse</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ Very much worse</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ ongoing</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td></td>
<td></td>
<td>○ Very much better</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ Slightly better</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ About the same</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ Slightly worse</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ Very much worse</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>○ ongoing</td>
<td></td>
</tr>
</tbody>
</table>
For our records, have you taken any other medications, or have you had conditions not treated with medications?

☐ No  ☐ Yes (please specify)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Start date (d/m/yr)</th>
<th>Stop date (d/m/yr)</th>
<th>Dosage (dose, frequency)</th>
<th>Indication</th>
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IV. PSYCHOSOCIAL COMPLICATIONS

- Have you felt depressed about your NVP?

  ☐ Always  ☐ Most of the time  ☐ Some of the time  ☐ Rarely  ☐ Never

  Specify:

- Occupation?  ☐ Unemployed
  ☐ Inside the home (please specify) __________________________
  ☐ Outside the home (please specify) __________________________

- If you work inside the home, have you lost time from your household tasks because of NVP?

  ☐ No  ☐ Yes ______________________ hr or days (so far)
• If you are outside the home, have you lost time from work because of NVP?
  
  O No
  O Yes ____________________ hrs or days (so far)

• If you stopped working, did you obtain a sick leave?  O No  O Yes

• Do you think your NVP has adversely affected your relationship with your partner?
  O No             Explain:
  O Yes

• Do you feel supported by your partner (eg. emotionally)?  O No
  O Yes

• Does your NVP affect your partner's day-to-day life?  O No
  O Yes

V. WOMEN'S VIEW ON RISK OF DRUGS VS. NVP

• Given that you have taken these medications, OR If you were advised to use NVP medication,
  do you think you are more likely to have a baby with a major birth defect, less likely to have a
  baby with a major birth defect, or do you think that your risk is unchanged?

  O Much more likely  O Slightly more likely  O Unchanged  O Slightly less likely
  O Much less likely

• Do you feel that NVP has a chance of affecting your baby in an adverse way?

  O Much more likely  O Slightly more likely  O Unchanged  O Slightly less likely
  O Much less likely

• Have you ever considered terminating your pregnancy because of your NVP?
  O No  O Yes --->  What changed your mind?
  O Your doctor advised against elective termination
  O Your family/friends advised against elective termination
  O You received effective treatment for your symptoms
  O Other (please specify):

• Given that you have had NVP in this pregnancy, would you be more likely to have another
  child, less likely to have another child, or would your thinking be unchanged?

  O Much more likely  O Slightly more likely  O Unchanged  O Slightly less likely
  O Much less likely
VI. COUNSELLING

Diclectin® is the only drug in Canada labeled specifically for treatment of nausea and vomiting in pregnancy. This means that the Government of Canada has reviewed the available information and considers Diclectin® to be safe for use by pregnant women.

Random allocation to saying:

| We should emphasize to you that every young, healthy woman has a 1-5% chance of having a baby with a major birth defect. However, your chance is not changed by taking Diclectin. |
| OR |
| Every young, healthy woman has a 95-99% chance of having a normal baby, and your chance is not changed by taking Diclectin. |

Other information provided/advice:

• We would like to contact you again at approximately 20 weeks of pregnancy to find out how you are doing. May we have your permission to do so? ☐ No ☐ Yes
QUESTIONNAIRE NVG
FORMULAIRE

Comment avez-vous entendu parler de cette recherche? ________________

Patient No. ________________
Date de l'entrevue (j/m/a) ________________
Interviewer ________________

I. Information Générale

Nom _____________________________ Date de Naissance (j/m/a) ________________
Adresse ___________________________ Ville/Province _____________________________
Téléphone (Residence) _______________ (Travail) ________________________________

G _ P _ SA _ TA _ Malformation? _ Non _ Oui (specifiéz) ________________

- La date de vos dernières menstruations (j/m/a) ________________
- Est-ce qu'il s'agit d'une grossesse planifiée? _ Non _ Oui
- Qui vous suit durant votre grossesse? _ Médecin de famille _ Obstétricien
  _ Sage-femme

Sévérité de vos NVG

- Quand vos nausées et vomissements ont-ils commencés?
  (j/m/a) __________________________
- Quand vos nausées et vomissements ont-ils disparu?
  (j/m/a) __________________________

- Avant de prendre ce médicament, à quelle fréquence avez-vous eu des nausées?
  Nombre de fois par jour ___________
- Avant de prendre ce médicament, à quelle fréquence avez-vous eu des vomissements?
  Nombre de fois par jour ___________

- Qu'est-ce qui vous dérangeait le plus? _ Nausées _ Vomissements

- En avez-vous parlé à la personne qui vous suit durant votre grossesse? _ Non _ Oui

  Si non, pourquoi?:

89
Si oui, qu’est-ce qu’il vous a suggéré de faire (si nécessaire, choisir plus d’une réponse)?

- Il n’y a rien à faire
- Vos nausées et vomissements vont passer tout seuls
- Changez votre diète (e.g. mangé moins, diète légère)
- Vous allez pouvoir prendre un médicament seulement après le premier trimestre
- Vous pouvez prendre ce médicament (veuillez spécifier le médicament)
  - Gravol® (Dimenhydrinate)
  - Diclectin® (Doxylamine/pyridoxine)
  - Vitamin (spécifiez) ____________________________
  - Autre (spécifiez le(s) médicament(s)) ________________

- Avez vous reçu d’autre traitements pour NVG? (e.g. prescription ou médicament sans prescription, homeopathie, acupuncture)
  - Non – Pourquoi?  Rien ne m’a été recommandé
  - Vous aviez peur que le médicament cause des malformations
  - Autre (veuillez spécifier) _______________________

- Oui (S.V.P. spécifiez dans le tableau “Médicament pour NVG”)

- Est-ce que vous avez eu des problèmes de santé causés par les NVG (e.g. saignement des conjonctives)?
  - Non  Oui

- Est-ce que vous vous êtes blessée à la suite de vos NVG? (e.g. : chute, perte de conscience?)
  - Non  Oui

- Est-ce que vous avez besoin de consulter un médecin en raison de vos blessures ou de vos problèmes de santé ? (Tel que mentionne dans la question précédente).
  - Non  Oui

- Avez vous perdu du poids?  Non
  - Oui ____________________ kg/lb

- Est-ce que vous avez été admise à l’hôpital ou à l’urgence en raison des NVG?
  - Non
  - Oui --->  Admise  Urgence  Les deux

  Combien de fois? ______
  Quand? (Mentionner les dates d’entrée et de sortie de l’hôpital):
• Est-ce que vous avez été traitée?
  ○ Non
  ○ Oui ---> Combien de jours? ____________________________

• Quel traitement avez-vous reçu?
  ○ Sérums - intraveineuses
  ○ Médicaments pour les vomissements:
    ○ Gravol
    ○ Metoclopramide
    ○ Diclectin
    ○ Autre ____________
    ○ Phenothiazines

• Est-ce que vous avez eu des complications causées par le traitement?
  ○ Non
  ○ Oui (S.V.P. specifiez):

III. Traitement/Médicament

MEDICAMENT POUR NVG-(Inclure tous les médicaments, même ceux donnés à l'hôpital)

<table>
<thead>
<tr>
<th>Nom du Médicament</th>
<th>Débuté (j/m/a)</th>
<th>Arrêté (j/m/a)</th>
<th>Dose et fréquence</th>
<th>Le médicament a-t-il amélioré votre condition</th>
<th>Selon l'avis de qui</th>
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<td>○ Amélioré</td>
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<td>○ N'a rien changé</td>
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</table>
Pour compléter nos dossiers, avez-vous pris d'autres médicaments, où avez d'autres problèmes santé non traité par des médicament?

- Non  - Oui (spécifiez)

<table>
<thead>
<tr>
<th>Nom du médicament</th>
<th>Débuté (j/m/a)</th>
<th>Arrêté (j/m/a)</th>
<th>Dose et indication</th>
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<td>en cours</td>
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<td>en cours</td>
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<tr>
<td>3.</td>
<td></td>
<td></td>
<td>en cours</td>
</tr>
</tbody>
</table>

Complications psychosociales

- Est-ce que vous vous sentez déprimée a cause de vos NVG?
  - Toujours
  - La plupart de temps
  - Quelquefois
  - Rarement
  - Jamais

  Specifiez:

- Est-ce que vous avez un emploi?
  - Sans emploi
  - A la maison (spécifiez)
  - A l'extérieur (spécifiez)

- Si vous demeurez à la maison, est-ce que vos NVG vous ont empeche de faire vos activités quotidiennes?
  - Non
  - Oui heures ou journees (jusqu’a aujourd’hui)

- Si vous travaillez à l'extérieur, avez-vous eu a vous absenter du travail a cause de vos NVG?
  - Non
  - Oui heures ou journees (jusqu’a aujourd’hui)

- Si vous avez dû arrêté de travailler, avez-vous reçu un retrait preventif paye?
  - Non  - Oui
• Est-ce que vous pensez que cela a affecté votre relation avec votre conjoint?
  
  O Non
  O Oui

Expliquez:

• Est-ce que vous vous sentez appuyée par votre conjoint?
  
  O Non
  O Oui

• Est-ce que vos NVG ont affecté le routine quotidienne de votre conjoint?
  
  O Non
  O Oui

V. Opinion de la mère sur les risques du médicament dans les NVG

• Considérant que vous avez pris médicament pour NVG, OUI
  Si vous deviez prendre des médicaments pour NVG,

  Pensez-vous que vous avez plus de chance ou moins de chance ou aucune chance d’avoir un bébé avec une malformation?

  O Plus de chances
  O Un peu plus de chances
  O Mêmes chances
  O Moins de chances
  O Aucune chance

• Est-ce que vous pensez que vos NVG ont des chances d’affecter votre bébé?

  O Plus de chances
  O Un peu de chances
  O Mêmes chances
  O Moins de chances
  O Aucune chance

• Bien que je sais que cela est un sujet délicat, vous savez peut-être que l’avortement est légal au Canada, est-ce que vous avez déjà considéré vous faire avorter à cause de vos NVG?

  O Non
  O Oui — Qu’est-ce qui a changé votre opinion?
  O Votre médecin vous l’a déconseillé
  O Votre famille/amie vous l’a déconseillé
  O Vous avez recu un traitement efficace
  O Autre (S.V.P. spécifiez):

• Étant donné que vous avez des NVG durant cette grossesse, est-ce que vous pensez que vous avez plus de chance d’avoir un autre enfant ou moins de chances ou cela ne fait aucune différence?

  O Plus de chance
  O Un peu plus de chance
  O Aucune différence
  O Moins de chance
  O Aucune chance
VI. "Counseling"

Le médicament Diclectin est le seul médicament prescrit spécialement pour le traitement des NVG au Canada. Cela veut dire que le gouvernement a vérifié toutes les informations disponibles et considère Diclectin sécuritaire durant la grossesse.

Saviez-vous que pour toutes les femmes enceintes, même celles en pleine santé, il y a un risque de 1 à 5% qu'elle donne naissance à un enfant avec une malformation. Ce risque ne change pas en utilisant Diclectin.

OU

Chaque femme en pleine santé a de 95 à 99% de chances d'avoir un enfant en santé et cette proportion n'est pas diminuée en utilisant Diclectin.

Autres conseils:

Nous aimerions vous rappeler vers la vingtième semaine de votre grossesse pour savoir comment vous allez. Est-ce qu'on peut le faire? O Non O Oui
APPENDIX B - Retrospective Questionnaire Intake Form
(English and French)
NVP QUESTIONNAIRE

How did you hear about this healthline?

Patient No. __________________________
Date of Interview (d/m/yr) ____________
Interviewer _________________________

I. GENERAL INFORMATION

Name ____________________________ Date of Birth (d/m/yr) _______________________
Street Address ____________________ City/Province _____________________________
Telephone (H) ______________________ (W) ________________________________
G ___ P ___ SA ___ TA ___ Birth Defects? O No O Yes (specify) ________________

- Was this a planned pregnancy? O No O Yes

- Who provided your obstetric care? O Family Doctor O Obstetrician
  O Midwife

If we may ask, how did your pregnancy end:

O LIVE BIRTH:

- Gestational age at birth ______________ weeks (if applicable)

- Did the child have to stay in the hospital for special care?
  O No
  O Yes ---> For how long ________________________________

- Intensive care?
  O No
  O Yes ---> For how long ________________________________

- What was your child's weight at birth? ______ pounds _____ oz
  ______ Kg ______ g

O Miscarriage/Stillbirth at ________________________________ weeks

O ELECTIVE ABORTION at ________________________________ weeks
  * If so, why (e.g. NVP, health):
  * Was the choice of abortion
    O Yours
    O My MD suggested abortion because of concern to my health
    O I went to abortion clinic without my MD knowing
    O My MD suggested abortion as per my request
    O Other (please specify) ________________________________
II. SEVERITY OF NVP

• When did your NVP start? (d/m/yr) ____________________________

• When did your NVP Stop? (d/m/yr) ______________________________

• Before taking medication, how often did you have nausea?
  No. of times per day __________

• Before taking medication, how often did you vomit?
  No. of times per day __________

• What bothered you most?  ☐ Nausea  ☐ Vomiting

• Did you discuss your NVP with your caregiver?  ☐ No ☐ Yes
  If no, explain why ________________________________

  If yes, what did he/she advise you (choose more than one)?

  ☐ There is nothing he/she can do,
  ☐ Your nausea and vomiting will go away on their own
  ☐ You should change your diet (e.g. eat small meals, bland food)
  ☐ You should take medication but only after the first trimester of pregnancy
  ☐ You should take medication (please specify drugs)
    ☐ Gravitol® (Dimenhydrinate)
    ☐ Diclectin® (Doxylamine/pyridoxine)
    ☐ Vitamin (please specify ____________________________
    ☐ Other (please specify drugs) ____________________________

• Did you use any of the following to treat your NVP? - e.g. prescription or OTC drugs, herbal remedies, acupuncture

  ☐ No -- Why not?  ☐ Nothing has been recommended to you
  ☐ You are worried that medications will cause birth defects
  ☐ Other (please specify):

  ☐ Yes (Please specify below in Table)

• Did you have any medical conditions as a consequence of your NVP (e.g. blood in vomit)?

  ☐ No  ☐ Yes
Did you injure yourself in consequence of your NVP? (e.g. faint, fall?)

- No  - Yes

Did you have to see a doctor because of the seriousness of injury(ies) and/or medical conditions? (as mentioned in question above).

- No  - Yes

Did you lose weight?

- No
- Yes ________________ kg/lb

Were you admitted to hospital and/or had emergency room visits for NVP?

- No
- Yes --> admit  ER  both
  How many times: ______
  When? (d/m/yr):

Did you receive treatment there?

- No
- Yes --> How many days?

What treatment did you receive there?

- IV fluids
- Medications for vomiting:
  - Gravol
  - Diclectin
  - Phenothiazines
  - Metoclopramide
  - Other __________

Were there any medical complications due to treatment?

- No
- Yes (please specify):
### III. TREATMENT/MEDICATIONS

**ANTIEMETIC DRUGS** (including those taken in hospital)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Start date (d/m/yr)</th>
<th>Stop date (d/m/yr)</th>
<th>Dosage (dose, frequency)</th>
<th>Effect of starting the medication</th>
<th>By whose advice</th>
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<td>Very much better</td>
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<td>Slightly better</td>
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<td>About the same</td>
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<td>Slightly worse</td>
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<td>Very much worse</td>
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| 2.        |                     |                    |                          | Very much better                 |                 |
|           |                     |                    |                          | Slightly better                  |                 |
|           |                     |                    |                          | About the same                   |                 |
|           |                     |                    |                          | Slightly worse                   |                 |
|           |                     |                    |                          | Very much worse                  |                 |
|           | ongoing             |                    |                          |                                  |                 |

| 3.        |                     |                    |                          | Very much better                 |                 |
|           |                     |                    |                          | Slightly better                  |                 |
|           |                     |                    |                          | About the same                   |                 |
|           |                     |                    |                          | Slightly worse                   |                 |
|           |                     |                    |                          | Very much worse                  |                 |
|           | ongoing             |                    |                          |                                  |                 |

For our records, did you take any other medications, or did you have any conditions not treated with medications?

- [ ] No
- [ ] Yes (please specify)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Start date (d/m/yr)</th>
<th>Stop date (d/m/yr)</th>
<th>Dosage (dose, frequency)</th>
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| 2.        |                     |                    |                          |            |
|           | ongoing             |                    |                          |            |

| 3.        |                     |                    |                          |            |
|           | ongoing             |                    |                          |            |
IV. PSYCHOSOCIAL COMPLICATIONS

• Did you feel depressed about your NVP?
  ○ Always
  ○ Most of the time
  ○ Some of the time
  ○ Rarely
  ○ Never

  Specify:

• Occupation?  ○ Unemployed
  ○ Inside the home (please specify) ________________________________
  ○ Outside the home (please specify) ________________________________

• If you worked inside the home, did you lose time from your household tasks because of NVP?
  ○ No
  ○ Yes __________________________ hr or days

• If you worked outside the home, did you lose time from work because of NVP?
  ○ No
  ○ Yes __________________________ hrs or days

• If you stopped working, did you obtain a sick leave?  ○ No  ○ Yes

• Do you think your NVP adversely affected your relationship with your partner?
  ○ No  
  ○ Yes  
  Explain:

• Did you feel supported by your partner (eg. emotionally)?  ○ No  ○ Yes

• Did your NVP affect your partner’s day-to-day life?  ○ No  ○ Yes
V. WOMEN'S VIEW ON RISK OF DRUGS VS. NVP

• Given that you have taken these medications, OR If you were advised to use NVP medication, do you think you are more likely to have a baby with a major birth defect, less likely to have a baby with a major birth defect, or do you think that your risk is unchanged?

  OA Much more likely  OA Slightly more likely  OA Unchanged  OA Slightly less likely  OA Much less likely

• Do you feel that NVP had a chance of affecting your baby in an adverse way?

  OA Much more likely  OA Slightly more likely  OA Unchanged  OA Slightly less likely  OA Much less likely

• Did you ever consider terminating your pregnancy because of your NVP?
  OA No  OA Yes —> What changed your mind?
  OA Your doctor advised against elective termination
  OA Your family/friends advised against elective termination
  OA You received effective treatment for your symptoms
  OA Other (please specify) ____________________________

• Given that you have had NVP in this pregnancy, would you be more likely to have another child, less likely to have another child, or would your thinking be unchanged?

  OA Much more likely  OA Slightly more likely  OA Unchanged  OA Slightly less likely  OA Much less likely

VI. COUNSELLING

Diclectin® is the only drug in Canada labeled specifically for treatment of nausea and vomiting in pregnancy. This means that the Government of Canada has reviewed the available information and considers Diclectin® to be safe for use by pregnant women.

Random allocation to saying:

We should emphasize to you that every young, healthy woman has a 1-5% chance of having a baby with a major birth defect. However, your chance is not changed by taking Diclectin.

OR

Every young, healthy woman has a 95-99% chance of having a normal baby, and your chance is not changed by taking Diclectin.

Other information provided/advice:
QUESTIONNAIRE NVG FORMULAIRE

RETROSPECTIF

Date du suivi ________________
(j/m/a)

Comment avez-vous entendu parler de cette recherche? ________________

Patient No. _______________________
Date de l’entrevue (j/m/a) ____________
Interviewer _______________________

I. Information Générale

Nom ____________________________ Date de Naissance (j/m/a) ________________

Adresse ___________________________ Ville/Province _______________________

Téléphone (Maison) ________________ (Travail) ____________________________

G ___ P ___ SA ___ TA ___ Malformation? ☐ Non ☐ Oui (spécifiez) ________________

• Est-ce qu’il s’agissait d’une grossesse planifiée? ☐ Non ☐ Oui

• Qui vous suivait durant votre grossesse? ☐ Medecin de famille ☐ Obstétricien
☐ Sage-femme

• Est-ce que vous avez complété votre grossesse? ☐ Oui ☐ Non

• Si oui: Combien de semaines de grossesse ________________ semaines

Quel était le poids de votre enfant à la naissance? _______ livres ______ onces

_______ kg _____ g

Est-ce que votre enfant a été hospitalisé plus longtemps que la normale?

☐ Non
☐ Oui, combien de temps? ________________________________

Soins intensifs? ☐ Non
☐ Oui, combien de temps ? ________________________________

• Si non: Comment ça s’est terminé:

☐ Fausse Couche - Combien de semaines __________
☐ Mort-Né - Combien de semaines _________________
☐ Avortement - Quand ___________________________
☐ Raison? ☐ NVG

☐ Problème avec le bébé
☐ Autre (spécifiez) ________________________________
Le choix de l'avortement a été: O Le vôtre
  O De votre médecin parce qu'il était inquiet de votre santé
  O J'ai été dans une clinique d'avortement sans que mon médecin le sache
  O Je lui ai demandé
  O Autre (spécifiez) ____________________________

II. Sévérité de vos NVG

• Quand vos nausées et vomissements avaient-ils commencés?
  (j/m/a) ____________________________

• Quand vos nausées et vomissements avaient-ils disparu?
  (j/m/a) ____________________________

• Avez-vous pris des médicaments pour vos nausées?  O Non  O Oui

• Avant de prendre ce médicament, a quelle fréquence avez-vous eu des nausées?
  Nombre de fois par jour ________

• Avant de prendre ce médicament, a quelle fréquence avez-vous eu des vomissements?
  Nombre de fois par jour ________

• Qu’est-ce qui vous dérangeait le plus?  O Nausées  O Vomissements

• En avez-vous parlé à la personne qui vous suivait durant votre grossesse?
  O Non, pourquoi? ____________________________

  O Oui, qu’est-ce qu’il vous avait suggéré de faire (si nécessaire, choisir plus d’une réponse)?
    O Il n’y a rien à faire
    O Vos nausées et vomissements vont passer tout seuls
    O Changez votre diète (e.g. mangé moins, diète légère)
    O Vous allez pouvoir prendre un médicament seulement après le premier trimestre
    O Vous pouvez prendre ce médicament (veuillez spécifier le médicament)
      O Gravoj® (Dimenhydrinate)
      O Diclectin® (Doxylamine/pyridoxine)
      O Vitamin (spécifiez) ____________________________
      O Autre (spécifiez le(s) médicament(s)):
• Avez-vous reçu d'autres traitements pour NVG? (e.g. prescription ou médicament sans prescription, homeopathie, acuponcture)
  • Non — Pourquoi?  • Rien ne m’a été recommandé
  • Vous aviez peur que le médicament cause des malformations
  • Autre (veuillez spécifier) __________________________
  • Oui (S.V.P. spécifiez dans le tableau "Médicament pour NVG")

• Est-ce que vous avez eu des problèmes de santé causés par les NVG (e.g. saignement)?
  • Non  • Oui

• Est-ce que vous avez été blessée suite à vos NVG? (e.g. : chute, perte de conscience?)
  • Non  • Oui

• Est-ce que vous avez eu besoin de consulter un médecin en raison de vos blessures ou de vos problèmes de santé ? (Tel que mentionné dans la question précédente).
  • No  • Yes

• Avez-vous perdu du poids?  • Non
  • Oui __________________________ kg/lb

• Est-ce que vous avez été admise à l'hôpital ou à l'urgence en raison des NVG?
  • Non
  • Oui —>  • Admise  • Urgence  • Les deux
    Combien de fois? ______
    Quand? (Mentionner les dates d'entrée et de sortie de l'hôpital):

• Est-ce que vous avez été traitée?  • Non
  • Oui —> Combien de jours:

• Quel traitement avez-vous reçu?
  • Sérum - intraveineuse
  • Médicament pour les vomissements
    • Gravol
    •Diclectin
    •Phenothiazines
    • Metoclopramide
    • Autre __________________________
• Est-ce que vous avez eu des complications causées par le traitement?
  
  O Non  
  O Oui, spécifiez:

III. Traitement/Médicament

MEDICAMENT POUR NVG-(Inclure tous les médicaments, même ceux donnés à l'hôpital)

<table>
<thead>
<tr>
<th>Nom du Médicament</th>
<th>Débuté (j/m/a)</th>
<th>Arrêté (j/m/a)</th>
<th>Dose et fréquence</th>
<th>Le médicament a-t-il amélioré votre condition</th>
<th>Selon l'avis de qui</th>
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</table>
Pour compléter nos dossiers, avez-vous pris d'autres médicaments, où avez d'autres problèmes santé non traité par des médicament?

- Non
- Oui (spéciﬁez)

<table>
<thead>
<tr>
<th>Nom du médicament</th>
<th>Débuté</th>
<th>Arrêté</th>
<th>Dose et fréquence</th>
<th>Indication</th>
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</table>

IV. Complications psychosociales

- Est-ce que vous vous sentiez déprimée à cause de vos NVG?
  - Toujours
  - La plus part du temps
  - Quelquefois
  - Rarement
  - Jamais

- Spécifiez:

- Est-ce que vous aviez un emploi?
  - Sans emploi
  - A la maison (spéciﬁez)
  - A l’extérieur (spéciﬁez)

- Si vous étiez à la maison, est-ce que vos NVG vous ont empêché de faire vos activités quotidiennes?
  - Non
  - Oui heures ou journées
• Si vous travailliez à l’extérieur, avez-vous eu à vous absenter du travail à cause de vos NVG?
  
  O Non
  O Oui _________________ heures ou journées

• Si vous avez arrêté de travailler, avez-vous eu un retrait préventif payé?  O  Non  O  Oui

• Est-ce que vous pensez que cela a affecté votre relation avec votre conjoint?
  
  O Non
  O Oui  Expliquez:

• Est-ce que vous vous sentiez appuyée par votre conjoint?  O  Non
  
  O Oui

• Est-ce que vos NVG ont affecté le quotidien de votre conjoint?  O  Non
  
  O Oui

V. Opinion de la mère sur les risques du médicament dans les NVG

• Considérant que vous ayez pris ce médicament, OU Si vous deviez prendre des médicaments, pensez-vous que vous aviez plus de chance, moins de chance ou aucune chance d’avoir un bébé avec une malformation?
  
  O Plus de chances  O Un peu plus de chances  O Memes chances  O Moins de chances
  O Aucune chance

• Est-ce que vous pensez que vos NVG ont eu des chances d’affecter votre bébé?
  
  O Plus de chances  O Un peu de chances  O Memes chances  O Moins de chances
  O Aucune chance

• Bien que je sais que cela est un sujet délicat, vous savez peut-être que l’avortement est légal au Canada, est-ce que vous avez déjà considéré vous faire avorter à cause de vos NVG?
  
  O Non
  O Oui ---> Qu’est-ce qui a changé votre opinion?
  O Votre médecin vous l’a déconseillé
  O Votre famille/amie vous l’a déconseillé
  O Vous avez reçu un traitement efficace
  O Autre (S.V.P. spécifiez):
Etant donné que vous avez eu des NVG durant cette grossesse, est-ce que vous pensez que vous avez plus de chance d'avoir un autre enfant ou moins de chances ou cela ne fait aucune différence?

○ Plus de chance ○ Un peu plus de chance ○ Aucune différence ○ Moins de chance ○ Aucune chance

VI. “Counseling”

Le médicament Diclectin est le seul médicament prescrit spécialement pour le traitement des NVG au Canada. Cela veut dire que le gouvernement a vérifié toutes les informations disponibles et considère Diclectin sécuritaire durant la grossesse.

Saviez-vous que pour toutes les femmes enceinte, même celles en pleine santé, il y a un risque de 1 à 5% qu'elle donne naissance à un enfant avec une malformation. Ce risque ne change pas en utilisant Diclectin.

OU

Chaque femme en pleine santé a de 95 à 99% de chances d'avoir un enfant en santé et cette proportion n'est pas diminuée en utilisant Diclectin.

Autres conseils:
APPENDIX C - Twenty week Gestation Follow-up Questionnaire Intake Form (English and French)
NVP QUESTIONNAIRE

20 WKS PREGNANT

Patient No. ____________________________
Date of Interview (d/m/yr) ____________________
Interviewer _____________________________

I. GENERAL INFORMATION

Name ____________________________ Date of Birth (d/m/yr) ____________________
Street Address ____________________________ City/Province ____________________________
Telephone (H) ____________________________ (W) ____________________________

- Are you currently pregnant?
  □ Yes
  □ No —> If we may ask, how your pregnancy end?
    □ Miscarriage at __________ weeks
    □ Stillbirth at __________ weeks
    □ Elective termination at __________ weeks
  - If so, why (eg. NVP, health):
  - Was the choice of abortion:
    □ Yours
    □ My MD suggested abortion because of concern to my health
    □ I went to abortion clinic without my MD knowing
    □ My MD suggested abortion as per my request
    □ Other (please specify):

- Who is providing/provided your obstetric care?
  □ Family Doctor  □ Obstetrician
  □ Midwife

II. SEVERITY OF NVP

- Has your NVP stopped?
  □ No
  □ Yes ____________(d/m/yr)

- When your symptoms were at their worst, how often did you have nausea?
  □ Always
  □ Most of the time
  □ Some of the time
  □ Rarely
  □ Never

- When your symptoms were at their worst, how often did you vomit?
  No. of times per day ____________
Have you discussed your NVP with your caregiver?  

- No  
- Yes

If no, explain why:

If yes, what did he/she advise you?

- There is nothing he/she can do
- Your nausea and vomiting will go away on their own
- You should change your diet (e.g. eat small meals, bland food)
- You should take medication but only after the first trimester of pregnancy
- You should take medication (please specify drugs)
  - Gravol® (Dimenhydrinate)
  - Diclectin® (Doxylamine/pyridoxine)
  - Vitamin (please specify _____________________________)
  - Other (please specify drugs) ____________________________

Were you treated for NVP? (e.g. prescription or OTC drugs, herbal remedies, acupuncture)

- No, why not?  
  - Nothing was recommended to you
  - You are worried that medications would cause birth defects
  - Other (please specify):

- Yes (Please specify in chart below)

Did you have any medical conditions as a consequence of your NVP (e.g. bleeding eye)?

- No  
- Yes

Did you injure yourself in consequence of your NVP? (e.g.: faint, fall?)

- No  
- Yes

Did you have to see a doctor because of the seriousness of injury(ies) and/or medical conditions? (as mentioned in question above).

- No  
- Yes

Did you lose weight because of NVP?

- No
- Yes ____________________________ kg/lb

Have you been admitted to hospital and/or had emergency room visits for NVP?

- No
- Yes --->  
  - admit  
  - ER  
  - both

How many times? _______
When (d/m/yr):
Did you receive treatment there?

- No
- Yes —> How many days?:

What treatment did you receive there?
- IV fluids
- Medications for vomiting:
  - Gravol
  - Diclectin
  - Phenothiazines
  - Metoclopramide
  - Other ____________

Were there any medical complications due to treatment?

- No
- Yes (please specify):

### III. TREATMENT/MEDICATIONS

**ANTIEMETIC DRUGS** (Please specify drugs, including those taken in hospital)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Start date (d/m/yr)</th>
<th>Stop date (d/m/yr)</th>
<th>Dosage (dose, frequency)</th>
<th>Effect of starting the medication</th>
<th>By whose advice</th>
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For our records, have you taken any other medications?

- No
- Yes (please specify)

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<tr>
<th>Drug Name</th>
<th>Start date (d/m/yr)</th>
<th>Stop date (d/m/yr)</th>
<th>Dosage (dose, frequency)</th>
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IV. PSYCHOSOCIAL COMPLICATIONS

- Have you felt depressed about your NVP?
  - Always
  - Most of the time
  - Some of the time
  - Rarely
  - Never
  - Specify:

- Do you work inside or outside of the home?
  - Inside the home
  - Outside the home

- If you work inside the home, have you lost time from your household tasks because of NVP?
  - No
  - Yes ____________________ hr or days (so far)

- If you are outside the home, have you lost time from work because of NVP?
  - No
  - Yes ____________________ hr or days (so far)
• If you stopped working, did you obtain a "preventive withdrawal" (or sick leave)?
  ○ No ○ Yes

• Do you think your NVP has adversely affected your relationship with your partner?
  ○ No ○ Yes
  Explain:

• Do you feel supported by your partner (eg. emotionally)?
  ○ No ○ Yes

• Does your NVP affect your partner's day-to-day life?
  ○ No ○ Yes

V. WOMEN'S VIEW ON RISK OF DRUGS VS. NVP

• *Given* that you took these medications, OR *If* you were advised to use NVP medication,
  do you think you are *more likely* to have a baby with a major birth defect, *less likely* to have a baby
  with a major birth defect, or do you think that your risk is *unchanged*?
  ○ Much more likely ○ Slightly more likely ○ Unchanged ○ Slightly less likely
  ○ Much less likely

• Do you feel that NVP has a chance of affecting your baby in an adverse way?
  ○ Much more likely ○ Slightly more likely ○ Unchanged ○ Slightly less likely
  ○ Much less likely

• Elective termination of pregnancy is now widely available to women in Canada.
  Because of your NVP, did you ever consider terminating the pregnancy?
  ○ No ○ Yes--->
     What changed your mind?
  ○ Your doctor advised against elective termination
  ○ Your family/friends advised against elective termination
  ○ You received effective treatment for your symptoms
  ○ Other (please specify):
Given that you had NVP in this pregnancy, would you be more likely to have another child, less likely to have another child, or would your thinking be unchanged?

- Much more likely
- Slightly more likely
- Unchanged
- Slightly less likely
- Much less likely

Other information provided/advice:
QUESTIONNAIRE NVG
FORMULAIRE

20 SEMAINES

Patient No. ___________________________
Date de l' entrevue (j/m/a) _______________
Interviewer ___________________________

I. Information Générale

Nom ________________________________ Date de Naissance (j/m/a) ________________
Adresse ______________________________ Ville/Province ___________________________
Téléphone (Maison) ____________________ (Travail) ________________________________

Est-ce que vous êtes présentement enceinte?

☐ Oui
☐ Non --> Pourquoi:

☐ Fausse-couche - Combien de semaines ___________________________
☐ Mort-Né - Combien de semaines ___________________________
☐ Avortement - Combien de semaines ___________________________

Pourquoi (e.g. NVG, problèmes avec le bébé):

• Le choix de l'avortement a été:

☐ Le vôtre
☐ De votre médecin parce qu’il était inquiet de votre santé
☐ J’ai été dans une clinique d’avortement sans que mon médecin le sache
☐ Je lui ai demandé
☐ Autre (specifiez):

Qui vous suit durant votre grossesse?

☐ Medecin de famille ☐ Obstétricien
☐ Sage-femme

II. Sévérité de vos NVG

• Est-ce que vous avez encore des NVG?

☐ Non
☐ Oui __________________ (j/m/a)

Avant de prendre ce médicament, à quelle fréquence avez-vous eu des nausées?

☐ Toujours
☐ La plupart du temps
☐ Quelquefois
☐ Rarement
☐ Jamais

Avant de prendre ce médicament, à quelle fréquence avez-vous eu des vomissements?

Nombre de fois par jour _________
• En avez-vous parlé à la personne qui vous suivait durant votre grossesse?  O  Non  O  Oui

  Si non, pourquoi?:
  Si oui, qu’est-ce qu’il vous avait suggéré de faire?
  O  Il n’y a rien à faire
  O  Vos nausées et vomissements vont passer tout seuls
  O  Changez votre diète (e.g. mangez moins, diète légère)
  O  Vous allez pouvoir prendre un médicamente seulement après le premier trimestre
  O  Vous pouvez prendre ce médicamente (veuillez spécifier le médicamente)
      O  Gravol® (Dimenhydrinate)
      O  Diclectin® (Doxylamine/pyridoxine)
      O  Vitamine (specifiez) ________________________________
      O  Autre (specifiez le(s) medicament(s)) ________________________________

• Avez vous reçu un traitement? (e.g. prescription ou medicament sans prescription, homeopathie, acuponcture)
  O  Non -- Pourquoi?  O  Rien ne m’a été recommandé
      O  Vous aviez peur que le médicamente cause des malformations
      O  Autres (veuillez specifier):

  O  Oui (S.V.P. specifiez dans le tableau “Medicament pour NVG”)

• Est-ce que vous avez eu des problèmes de santé causés par les NVG (e.g. saignement des conjonctives)?
  O  Non  O  Oui

• Est-ce que vous avez été blessée suite à vos NVG? (e.g.: chute, perte de conscience?)
  O  Non  O  Oui

• Est-ce que vous avez eu besoin de consulter un médecin en raison de vos blessures ou de vos problèmes de santé? (Tel que mentionne dans la question precedente).
  O  Non  O  Oui

• Avez vous perdu du poids?
  O  Non
  O  Oui _________________ kg/lb

• Est-ce que vous avez été admise à l’hôpital ou à l’urgence en raison des NVG?
  O  Non
  O  Oui ---> O  Admise  O  Urgence  O  Les deux
      Combien de fois? ______
      Quand (j/m/a)?:
• Est-ce que vous avez été traitée?
  O Non
  O Oui —> Combien de jours?:

• Quel traitement avez-vous reçu?
  O Sérum - intraveineuse
  O Médicament pour les vomissements
    O Gravol
    O Diclectin
    O Metoclopramide
    O Autre ____________
    O Phenothiazines

• Est-ce que vous avez eu des complications causées par le traitement?
  O Non
  O Oui (S.V.P. spécifiez):

III. Traitement/Médicament

**MEDICAMENT POUR NVG**-(Inclure tous les médicaments, même ceux donnés à l'hôpital)

<table>
<thead>
<tr>
<th>Nom du Médicament</th>
<th>Débuté (j/m/a)</th>
<th>Arrêté (j/m/a)</th>
<th>Dose et fréquence</th>
<th>Le médicament a-t-il améliore votre condition</th>
<th>Selon l’avis de qui</th>
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</thead>
<tbody>
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<td>O Beaucoup détérioré</td>
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</table>
Pour compléter nos dossiers, avez-vous pris d'autres médicaments, ou avez vous eu d'autres problèmes santé non traité par des médicaments?

- Non  
- Oui (spécifiez)

<table>
<thead>
<tr>
<th>Nom du médicament</th>
<th>Débuté (j/m/a)</th>
<th>Arreté (j/m/a)</th>
<th>Dose et fréquence</th>
<th>Indication</th>
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</tbody>
</table>

IV. Complications psychosociales

- Est-ce que vous vous sentez déprimée à cause de vos NVG?
  - Toujours
  - La plus part du temps
  - Quelquefois
  - Rarement
  - Jamais
  - Specifiez:

- Est-ce que vous avez un emploi?
  - A la maison
  - A l'extérieur

- Si vous demeurez à la maison, est-ce que vos NVG vous ont empêché de faire vos activités quotidiennes?
  - Non
  - Oui heures ou journées (jusqu’à aujourd’hui)

- Si vous travaillez à l’extérieur, avez-vous eu à vous absenter du travail à cause de vos NVG?
  - Non
  - Oui heures ou journées (jusqu’à aujourd’hui)
• Si vous avez dû arrêté de travailler, avez-vous eu un retrait préventif payé?  ○ Non  ○ Oui

• Est-ce que vous pensez que vos NVG ont affecté votre relation avec votre conjoint?
  ○ Non  ○ Oui  Expliqué

• Est-ce que vous vous sentez appuyée par votre conjoint?  ○ Non  ○ Oui

• Est-ce que vos NVG ont affecté le quotidien de votre conjoint?  ○ Non  ○ Oui

V. Opinion de la mère sur les risques du médicament dans les NVG

• Considérant que vous ayez pris ce médicament, OU Si vous deviez prendre des médicaments, pensez-vous que vous ayez plus de chance, moins de chance ou aucune chance d’avoir un bébé avec une malformation?
  ○ Plus de chances  ○ Un peu plus de chances  ○ Mêmes chances  ○ Moins de chances  ○ Aucune chance

• Est-ce que vous pensez que vos NVG ont des chances d’affecter votre bébé?
  ○ Plus de chances  ○ Un peu de chances  ○ Mêmes chances  ○ Moins de chances  ○ Aucune chance

• Bien que le sujet est délicat, vous savez peut-être que l’avortement est légal au Canada, vous avez déjà considéré vous faire avorter a cause de vos NVG?
  ○ Non  ○ Oui —> Qu’est-ce qui a changé votre opinion?
    ○ Votre médecin vous l’a déconseillé
    ○ Votre famille/amie vous l’a déconseillé
    ○ Vous avez reçu un traitement efficace
    ○ Autre (S.V.P. spécifiez):
Étant donné que vous avez des NVG durant cette grossesse, est-ce que vous pensez avoir plus de chance d’avoir un autre enfant ou moins de chances ou cela ne fait aucune différence?

☐ Plus de chance  ☐ Un peu plus de chance  ☐ Aucune différence  ☐ Moins de chance  ☐ Aucune chance

Autres information/conseils:
APPENDIX D - Advertisement for Nausea and Vomiting in Pregnancy Healthline (English and French)
We need your story...

A research group at the Hospital for Sick Children in Toronto is looking for women who have experienced or who are now experiencing health problems caused by nausea and vomiting during their pregnancy. This includes women who have had an abortion due to these complications. The aim of this research is to try to understand the consequences of these problems. Your personal experience is very important to us.

Please call in confidence at 1-800-436-8477.
Un groupe de recherche de l'Hôpital pour les Enfants Malades de Toronto désire recueillir le témoignage de femmes qui ont déjà eu ou qui ont présenlement des problèmes de santé occasionnés par les nausées et les vomissements de la grossesse, ou qui ont même déjà eu un avortement suite à ces complications. Le but de cette recherche est d'étudier et d'essayer de comprendre les conséquences reliées à ces problèmes. Votre expérience personnelle est très importante pour nous. Les données recueillies seront traitées de façon confidentielle.

Veuillez téléphoner au 1-800-436-8477
Nous vous répondrons en français