INVESTIGATING SOURCES OF VARIABILITY IN PHARMACOLOGICAL RESPONSE TO NAUSEA AND VOMITING OF PREGNANCY

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy.
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ABSTRACT

Investigating Sources of Variability in Pharmacological Response to Nausea and Vomiting of Pregnancy

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Nausea and vomiting of pregnancy (NVP) is the most common medical condition in pregnancy, and, unfortunately, variability exists among pregnant women in the therapeutic effect of anti-emetics as well as in factors that can exacerbate NVP. Identifying and managing these sources of variability will result in significant improvements in the quality of life of pregnant woman. This dissertation addressed clinical pharmacology strategies in managing NVP by focusing on three predominant areas of variability.

The first challenge addressed in this dissertation was women with pre-existing gastrointestinal (GI) conditions and adherence and tolerability to prenatal multivitamin supplementation. To identify the role of iron in reducing adherence and increasing NVP and GI symptoms, two separate studies were conducted. In the first study, women randomized to a prenatal multivitamin supplementation with higher iron content experienced more adverse GI effects and increased severity of NVP symptoms. In the second study, after discontinuing iron-containing prenatal multivitamins, two-thirds of
women in a prospective cohort reported improvement in their NVP symptoms which was corroborated with validated scales to quantify NVP severity.

The second challenge addressed in this dissertation was the effect of heartburn and acid reflux on the severity of NVP. In a controlled, prospective study, women experiencing heartburn and acid reflux experienced greater severity of NVP compared to women with no GI symptoms. Furthermore, treatment of heartburn and acid reflux with acid-reducing pharmacotherapy was associated with a reduction in GI symptoms and NVP severity. Therefore, histamine 2 blockers or proton pump inhibitors, which do not appear to be associated with increased fetal risks, should be administered when required.

The third clinical pharmacology challenge addressed in this dissertation was to determine the pharmacokinetic variability of the active ingredients of Diclectin®, first-line pharmacotherapy for the treatment of NVP. Large variability was observed in the area under the curve for both active metabolites: a 6.5-fold difference for pyridoxal-5’-phosphate and a 2.1-fold difference for doxylamine. Whether these pharmacokinetic differences contribute to suboptimal efficacy remains to be determined.

In conclusion, based on the results presented in this dissertation, several improvements in clinical pharmacology strategies can be made to enhance management of NVP.
DEDICATION

I will always be indebted to my fiancée, Arjun Balasingham, for his unwavering faith in me, encouraging me to pursue my dreams. Thank you for being the voice of reason in trying times, and providing me with a shoulder to cry on in times of need.

And to Kittu, thank you for teaching me to stop and smell the roses, and to always appreciate the good things in life, no matter how big or small.

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Although these acknowledgements are not sufficient to fully reflect my gratitude, I hope the following people understand the depth of my appreciation that I am unable to accurately express in writing.

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<td>5-HT&lt;sub&gt;3&lt;/sub&gt;</td>
<td>5-hydroxy-tryptamine&lt;sub&gt;3&lt;/sub&gt; receptor</td>
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<tr>
<td>ACOG</td>
<td>American College of Obstetrics and Gynecology</td>
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<tr>
<td>AUC</td>
<td>area under the curve</td>
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<td>RF</td>
<td>acid reflux</td>
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<td>CI</td>
<td>confidence interval</td>
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<td>DRI</td>
<td>dietary reference intake</td>
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<td>DMT1</td>
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<td>Dcytb</td>
<td>duodenal cytochrome B</td>
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<td>D&lt;sub&gt;2&lt;/sub&gt;</td>
<td>dopamine 2 receptor</td>
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<td>DOX</td>
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<td>k&lt;sub&gt;el&lt;/sub&gt;</td>
<td>elimination rate constant</td>
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<td>gastrointestinal</td>
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<td>gastrointestinal tract</td>
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<td>gastroesophageal reflux disorders</td>
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<td>gastrointestinal symptom rating scale</td>
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<td><em>H. pylori</em></td>
<td><em>Helicobacter pylori</em></td>
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<td>HG</td>
<td><em>hyperemesis gravidarum</em></td>
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<td>IDA</td>
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<td>proton pump inhibitors</td>
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<td>SOGC</td>
<td>Society of Obstetricians and Gynecologists of Canada</td>
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<td>WB</td>
<td>Well-being</td>
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CHAPTER ONE

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INTRODUCTION
1.1 INTRODUCTION

Nausea and vomiting of pregnancy (NVP) is the most common medical condition in pregnancy, affecting 80% of pregnant women\(^1\). Typically, 50% of women experience both nausea and vomiting, whereas, approximately 25% experience nausea alone\(^2\). Different theories have been proposed to explain the existence of NVP; however, the mechanism(s) remain to be elucidated. Regardless of the mechanism(s), the physical, psychological and financial impact of NVP can be devastating, especially when left unmanaged\(^3\). Management of NVP can range from dietary strategies and other non-pharmacological to pharmacological therapy\(^4\); however, women and healthcare providers may hesitate in commencing anti-emetic pharmacotherapy due to perceived fetal risks.

When considering pharmacotherapy in pregnancy, determining potential fetal risks is an absolute necessity. Every pregnancy is associated with baseline risks; for example, the prevalence of major congenital malformations in the general population is 1% to 3\(^%\)\(^5\). Following the thalidomide disaster, a common misperception is that all medicinal or pharmacological therapies in pregnancy can result in fetal abnormalities\(^5\). Unfortunately, this view can often result in negative maternal consequences. Certain maternal medical conditions, when left untreated in pregnancy, are associated with pregnancy complications and increased fetal risks above the baseline risks\(^5\). Similarly, certain medical conditions, such as gastrointestinal (GI) conditions and thyroid or other metabolic disorders, are associated with increased severity of NVP\(^6,7\); therefore, these
conditions should be effectively treated using the appropriate therapy especially if the maternal benefits outweigh the potential fetal risks.

The importance of providing evidence-based information regarding the fetal safety of medications and other exposures in pregnancy cannot be stressed enough. The study of teratology, or abnormal fetal development, has allowed for drastic improvements in the treatment of pregnant women by providing healthcare providers with evidence-based information\(^5\). Teratogen information services such as the Motherisk Program located at the Hospital for Sick Children in Toronto are invaluable as they evaluate the quality of scientific literature and provide accurate fetal safety information to optimize maternal and fetal health throughout pregnancy.

In the context of NVP, any untreated medical conditions should be addressed and treated with appropriate therapy\(^8\). Therapy with anti-emetics, either non-pharmacological or pharmacological, should be initiated depending on the severity of NVP\(^4\). Unfortunately, although protocols and guidelines are available from obstetrical societies such as the Society of Obstetrics and Gynecologists of Canada (SOGC) and the American College of Obstetrics and Gynecology (ACOG), they are often not adhered to. Furthermore, there is variability among pregnant women in the therapeutic effect of anti-emetics as well as in factors that can exacerbate NVP. Further research is required to identify these areas of variability in order to improve management of NVP.

Unfortunately, although NVP is the most common medical condition in pregnancy, and its physical, psychosocial and financial impacts can be quite significant, limited research is conducted in this area. Non-pharmacological and pharmacological
strategies are available to help manage symptoms of NVP; however, as mentioned above, variability exists among pregnant women that may result in ineffective management by these strategies. The importance of studying and addressing these sources of variability cannot be over-stated as proper management will result in significant improvements in the quality of life of pregnant woman suffering with this debilitating condition.

This dissertation examined clinical pharmacology strategies in managing NVP by focusing on three key areas of variability. The first clinical pharmacology challenge is women with pre-existing GI conditions or symptoms and adherence and tolerability to prenatal multivitamin supplementation. Women with pre-existing GI conditions have reported difficulty with adherence as prenatal multivitamin supplementation appears to exacerbate their GI symptoms and NVP\textsuperscript{9,10}. Iron supplements are associated with adverse GI effects such as heartburn, stomach pain, constipation and nausea\textsuperscript{11}; prenatal multivitamin supplements contain at least 27 mg of elemental iron\textsuperscript{12}; therefore, it is plausible that the iron content causes intolerability. As a result of these adverse effects, pregnant women with pre-existing GI conditions or symptoms may be at greater risk for reduced adherence to prenatal multivitamin supplementation recommendations.

Prenatal multivitamin supplementation, however, is recommended as supplementation provides both the mother and fetus with the appropriate vitamins and minerals required to maintain a healthy pregnancy\textsuperscript{13}. Importantly, folic-acid containing multivitamins are associated with decreased risks of congenital malformations and certain pediatric cancers\textsuperscript{14,15}. Specifically, folic acid also provides protection against
neural tube defects as folate plays an essential role in cell division\textsuperscript{16}. Undoubtedly, there are many maternal and fetal benefits of adhering to prenatal multivitamins; however, due to the adverse effects, many pregnant women, especially those with pre-existing GI conditions may not be able to adhere to prenatal vitamin recommendations, and hence, will not receive the necessary nutrients for pregnancy\textsuperscript{10,17}. Improving maternal and fetal health will require improving adherence to prenatal multivitamin supplementation; therefore, identifying the role of iron with respect to tolerability to prenatal multivitamin supplementation requires further research.

The second clinical pharmacology challenge this dissertation addressed involves examining the role of GI conditions and acid-reducing pharmacotherapy on the severity of NVP. In pregnancy the prevalence of gastroesophageal reflux disorders (GERD) ranges from 40\% to 85\%\textsuperscript{7,18}. Although the onset and severity of GERD and related GI symptoms vary in pregnancy, it is biologically plausible that these GI disturbances may result in increased severity of NVP\textsuperscript{19,20}. Such mechanisms, if they exist, would suggest that typical anti-emetics would not be successful in managing NVP resulting from GI symptoms, instead, in theory, acid-reducing pharmacotherapy would be required. Further research is required to determine whether GI symptoms such as heartburn and acid reflux increase the severity of NVP; if so, it is necessary to determine whether acid-reducing pharmacotherapy reduces the severity of NVP.

The most commonly used acid-reducing pharmacotherapy for acid-related disorders in the non-pregnant population are the histamine 2 (H2) blockers and the proton pump inhibitors (PPIs). The use of H2 blockers and PPIs may be limited in
pregnancy as, often, pregnant women and healthcare professionals are wary of commencing pharmacotherapy due to fears of fetal risks. Retrospective and prospective cohort studies are available regarding the fetal safety of these two classes of medications in pregnancy; however, each study is relatively small\textsuperscript{21-31}. Conducting a literature search to identify all studies examining the fetal safety of H2 blockers and PPIs would allow for merger of all the pregnancy exposure data, and hence, a more accurate depiction of any potential fetal risks in pregnancy. Accurate fetal safety information regarding the use of H2 blockers and PPIs in pregnancy is required to dispel fears of taking these medications to treat acid-related disorders in pregnancy.

As there is very large variability in the severity of NVP, and in its response to pharmacotherapy, the third clinical pharmacology challenge this dissertation addressed is the pharmacokinetics of doxylamine succinate and pyridoxine hydrochloride after Diclectin\textsuperscript{®} administration. Diclectin\textsuperscript{®} is the pharmacotherapy of choice for the treatment of NVP in Canada as it is approved by Health Canada for use in pregnancy\textsuperscript{32,33}. This anti-emetic is composed of two ingredients: doxylamine succinate and pyridoxine hydrochloride, which is converted to its active metabolite, pyridoxal-5'-phosphate (PLP). Although it is an effective anti-emetic\textsuperscript{32}, Diclectin\textsuperscript{®} is formulated to be delayed-release, and hence, there is great opportunity for variability with respect to its onset of action. Furthermore, there is also variability with respect to its extent therapeutic effect among pregnant women with NVP. Reliable data are required to determine the variability in the pharmacokinetic parameters of both active ingredients in order to counsel pregnant
women on the use of this anti-emetic. This pharmacokinetic data may provide more accurate guidelines on dosing of Diclectin® to ensure maximum efficacy.

Nausea and vomiting of pregnancy can be a very debilitating condition, and effective management is essential. This dissertation examined the aforementioned sources of variability in the clinical pharmacological management of NVP to allow optimization of both maternal and fetal health.
1.2 STATEMENT OF THE PROBLEM

Nausea and vomiting of pregnancy is experienced by the majority of pregnant women; however, effective management is still lacking partially due to large individual variability in symptoms and response to therapy. Although several anti-emetics are available, and are not associated with fetal risks in pregnancy, they may not be sufficient or even appropriate for every woman depending on the severity of her NVP and comorbidities such as GI conditions. Women with pre-existing GI conditions may have less than optimal adherence to iron-containing prenatal multivitamins due to increased GI side effects, including nausea. This decreased adherence, in turn, may result in adverse pregnancy outcomes and nutritional deficiencies. Additionally, if women experiencing GI conditions experience increased severity of NVP, treatment with acid-reducing pharmacotherapy may alleviate both symptoms of acid and NVP. Anti-emetics, specifically the combination of doxylamine succinate and pyridoxine hydrochloride, are widely used in Canada to manage NVP symptoms; however, in order to provide a dosing regimen to maximize efficacy, the variability in pharmacokinetics of these two ingredients found in Diclectin® must be addressed.
**1.3 RATIONALE**

Nausea and vomiting of pregnancy can result in a variety of negative physical, emotional and financial effects including malnutrition, dehydration and reduced quality of life. Considering the prevalence, duration and potential severity of NVP, management should commence at first signs of symptoms, if not before. Unfortunately, not all women are managed effectively due to inter-individual variability and lack of knowledge by both healthcare professionals and patients. Once these gaps in knowledge are identified, more effective evidence-based management of NVP can be implemented.

1) Women experiencing NVP have reported decreased adherence to prenatal multivitamin supplementation due to GI side effects. Based on the vitamins and minerals and their individual side effect profiles, iron is the most likely culprit as it is associated with adverse GI effects such as stomach pain, nausea, vomiting and constipation. Furthermore, in pregnant women with pre-existing GI conditions, side effects may be exacerbated resulting in poor adherence to prenatal multivitamin supplements. These supplements, however, are recommended in pregnancy as they provide both the mother and fetus with the appropriate nutrients for a healthy pregnancy. Further research is required regarding the effects of iron-containing prenatal multivitamins on adherence and tolerability to improve supplementation.

2) Gastrointestinal conditions and symptoms can cause nausea and vomiting in the non-pregnant population. Studies have demonstrated that changes in gastric motility and dysrhythmias occur in women experiencing NVP; similarly, these gastric
disturbances have also been reported in women with increasing circulating female hormones experiencing GI symptoms. The possibility exists, therefore, that in pregnant women already experiencing NVP, there may be increased severity of symptoms. If confirmed, acid-reducing pharmacotherapy may be beneficial in reducing the severity of NVP in women experiencing GI conditions or symptoms.

3) Diclectin® is the anti-emetic of choice during pregnancy, and although NVP can be managed using this pharmacotherapy, this delayed-release formulation requires dosing adjustments. Pharmacokinetic analysis of the active ingredients, doxylamine and pyridoxal-5'-phosphate, will provide more accurate data regarding potential variability in the onset, extent and duration of action of this delayed-release preparation. Pharmacokinetic analysis will provide accurate data on which to base dosing schedules for Diclectin®, and therefore, will allow for optimization of anti-emetic activity.

By addressing the aforementioned gaps in knowledge, this research will allow for better management of NVP, and hence, improved maternal and fetal health.
The overall goal of this dissertation was to address unrecognized sources of variability in the pharmacotherapy of NVP. The objectives of the seven studies presented in this dissertation are as follows:

**Study 1**: Adherence and tolerability of iron-containing prenatal multivitamins in women with pre-existing gastrointestinal conditions

**Objective**: To determine the effect of iron content on the adherence and tolerability of prenatal multivitamins in women with pre-existing GI conditions

**Study 2**: The effectiveness of discontinuing iron-containing prenatal multivitamin supplements on the severity of nausea and vomiting of pregnancy

**Objective**: To determine the effectiveness of discontinuing iron-containing prenatal multivitamins in reducing the severity of NVP

**Study 3**: The effect of heartburn and acid reflux on the severity of nausea and vomiting of pregnancy

**Objective**: To determine the effect of heartburn and acid reflux on the severity of NVP

**Study 4**: The effect of acid-reducing pharmacotherapy on the severity of nausea and vomiting of pregnancy

**Objective**: To determine the effect of acid-reducing pharmacotherapy on the severity of NVP

**Study 5**: The safety of histamine 2 (H2) blockers in pregnancy: a meta-analysis

**Objective**: To determine the fetal safety of H2 blockers in pregnancy

**Study 6**: The safety of proton pump inhibitors (PPIs) in pregnancy: a meta-analysis
Objective: To determine the fetal safety of PPIs in pregnancy

Study 7: Pharmacokinetics of doxylamine and pyridoxal-5’-phosphate after Diclectin® administration

Objective: To determine the pharmacokinetics of doxylamine and pyridoxal-5’-phosphate after single dose Diclectin® administration
1.5 RESEARCH HYPOTHESES

The hypotheses of the seven studies presented in this dissertation are as follows:

**Study 1:** Adherence and tolerability of iron-containing prenatal multivitamins in women with pre-existing gastrointestinal conditions

**Hypothesis:** Prenatal multivitamin supplements with lower iron content will improve adherence and tolerability in women with pre-existing GI conditions

**Study 2:** The effectiveness of discontinuing iron-containing prenatal multivitamin supplements on the severity of nausea and vomiting of pregnancy

**Hypothesis:** Discontinuing iron-containing prenatal multivitamins will reduce the severity of NVP

**Study 3:** The effect of heartburn and acid reflux on the severity of nausea and vomiting of pregnancy

**Hypothesis:** Pregnant women experiencing heartburn and acid reflux will have increased severity of NVP

**Study 4:** The effect of acid-reducing pharmacotherapy on the severity of nausea and vomiting of pregnancy

**Hypothesis:** Acid-reducing pharmacotherapy will reduce the severity of NVP in pregnant women experiencing heartburn and/or acid reflux

**Study 5:** The safety of histamine 2 (H2) blockers in pregnancy: a meta-analysis

**Hypothesis:** The use of H2 blockers in the first trimester of pregnancy is not associated with an increased risk for congenital malformations

**Study 6:** The safety of proton pump inhibitors (PPIs) in pregnancy: a meta-analysis
**Hypothesis:** The use of PPIs in the first trimester of pregnancy is not associated with an increased risk for congenital malformations

**Study 7:** Pharmacokinetics of doxylamine and pyridoxal-5’-phosphate after Diclectin® administration

**Hypothesis:** The pharmacokinetics of doxylamine and pyridoxal-5’-phosphate after single dose Diclectin® administration will vary
CHAPTER TWO

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LITERATURE REVIEW
2.1 PREFACE

The following chapter is a literature review that will provide the background information required to understand the gaps in knowledge, research goals and studies discussed in this dissertation. The main topics reviewed include nausea and vomiting of pregnancy, gastrointestinal symptoms in pregnancy, nutritional requirements in pregnancy, iron in pregnancy and vitamin B6 in pregnancy.

As this dissertation is in the alternate format, each published study will have its own Background, Methods, Results and Discussion sections.
2.2.1 Clinical Presentation of NVP

Nausea and vomiting of pregnancy is the most common medical condition affecting up to 80% of pregnant women\(^2\). The onset of symptoms is typically between 4 to 6 weeks of pregnancy; symptoms progressively worsen and peak between 7 to 9 weeks\(^1\). For the majority of pregnant women, NVP symptoms subside between 12 to 16 weeks of pregnancy; however, 20% of women may continue to experience NVP throughout pregnancy\(^1\).

The primary symptoms of NVP include nausea, vomiting, gagging and dry heaving. Approximately 50% of women suffer from both nausea and vomiting and 25% experience nausea alone\(^1,2\). These symptoms are not limited to a specific time of day, as was thought with “morning sickness”, but may occur at any time of the day, or last from morning to evening and throughout the night\(^1,2,34\). In a study involving 160 pregnant women, 74% reported NVP symptoms, of whom, only 1.8% experienced “morning sickness”, whereas, 80% experienced NVP throughout the day\(^34\).

Women experiencing NVP may also experience other symptoms as well. These secondary symptoms can include sialorrhea, or excessive saliva production, a bitter or metallic taste in the mouth, a heightened sense of smell, and GI disturbances, including increased bloating, gas, belching or indigestion, which often result in food aversions and difficulty eating\(^3,4\). Treatment of these symptoms is important for effective management of NVP as these symptoms may increase the severity of NVP.
The severity of NVP symptoms ranges from mild to severe whether one is experiencing nausea alone or vomiting as well. The most severe form is hyperemesis gravidarum (HG) affecting 1-3% of women who are experiencing NVP\textsuperscript{35}. Hyperemesis gravidarum is characterized by severe and persistent nausea and vomiting that may result in dehydration, vitamin and mineral deficiencies, and the loss of more than 5% of initial body weight\textsuperscript{35}. As a result, many women experiencing HG are often hospitalized to restore fluids and nutrients with an average stay of 4 days per patient\textsuperscript{6}.

Hyperemesis gravidarum has been found to occur more frequently in adolescent females\textsuperscript{36}, females with increased body weight\textsuperscript{36}, females with multiple gestations\textsuperscript{36}, when there has been a history of HG in previous pregnancies\textsuperscript{36}, and in women with chronic Helicobacter pylori (H. pylori) infection\textsuperscript{37-39}. Other risk factors have been suggested as well, and it is important to identify these risk factors in order to effectively manage this condition.

2.2.2 Etiology of NVP

Currently, the etiology of NVP remains unknown; however, various explanations have been proposed. One explanation is that NVP protects the fetus by causing pregnant women to be aversive to foods and other potential toxicants and/or physically expel potentially teratogenic and abortifacient substances, for example, aversion to caffeinated beverages and alcohol\textsuperscript{40,41}. In support of this theory, NVP symptoms occur in the first trimester when embryonic organogenesis is most susceptible to chemical disruption\textsuperscript{40,41}. Additionally, studies have demonstrated that women who experience NVP are significantly less likely to experience spontaneous abortions than women who
do not experience NVP\textsuperscript{40,42}. This “maternal and embryonic protection” hypothesis takes into account primary symptoms of nausea and vomiting, as well as secondary symptoms such as heightened olfaction, that may be related to increasing hormone levels\textsuperscript{42}.

Nausea and vomiting of pregnancy has been hypothesized to be of hormonal nature due to the markedly changing levels of human chorionic gonadotrophic hormone\textsuperscript{43}, estrogen\textsuperscript{44}, and progesterone\textsuperscript{44} that reflect a similar pattern during the first trimester when NVP occurs, peaks and diminishes. Although a causal relationship linking hormones and NVP remains to be conclusively established, hormonal changes may worsen the symptoms of NVP as higher levels of human chorionic gonadotrophic hormone in multiple pregnancies, or lower estradiol levels in lower parity consistently are associated with increased symptoms of NVP\textsuperscript{6,45}. Other hormonal imbalances are thought to be associated with NVP as well, for example, women with thyroid disorders, such as hyperthyroidism, have been found to be more prone to experiencing NVP with more severe symptoms\textsuperscript{6,45}.

Psychosocial theories have been proposed to explain NVP symptoms. The basis of this aforementioned hypothesis is that women with severe NVP are transforming psychosocial distress into physical symptoms either through a conversion disorder or conditioning\textsuperscript{46}. Support for this notion is provided by studies that have demonstrated the effectiveness of hypnosis for the treatment of NVP\textsuperscript{46,47}, and studies that have found an association between the presence of psychological co-morbidities and severe NVP\textsuperscript{48,49}. 
Other research has suggested that changes within the gastrointestinal tract such as gastric dysrhythmia or gastroparesis are responsible for NVP\textsuperscript{7,50}. In non-pregnant patients, abnormalities in gastric neural activity and smooth muscle function are associated with nausea and vomiting\textsuperscript{50}. These same abnormalities have been observed in pregnant women leading to the hypothesis that these changes may be the cause of NVP\textsuperscript{7}. Research also shows that women with either pre-existing gastrointestinal symptoms such as constipation, acid reflux, and heartburn, or pre-existing gastrointestinal conditions such as ulcerative colitis, Crohn’s disease, Celiac disease, or irritable bowel syndrome, are susceptible to more intense symptoms of NVP\textsuperscript{7,50,51}.

Irrespective of the exact mechanism, there is a vomiting centre located in the medulla which receives chemoreceptor or mechanoreceptor signaling from various parts of the body (Figure 1.1). The stomach and small intestine send both chemoreceptor and mechanoreceptor signals; whereas, higher cortical areas of the brain and the chemoreceptor trigger zone send chemoreceptor signals to the vomiting centre\textsuperscript{52,53}. The vomiting centre, in turn, coordinates sympathetic and parasympathetic responses to initiate emesis\textsuperscript{52,54}. Sympathetic responses include sweating, pallor, increased respiration and heart rate and dilatation of pupils; parasympathetic responses include profuse salivation, pronounced motility of the esophagus, stomach, and duodenum, and relaxation of the esophageal sphincters\textsuperscript{52}. 
Figure 2.1 Nausea and vomiting is induced by the vomiting centre in the medulla

2.2.3 Aggravating Factors of NVP

A plethora of additional factors have also been identified to aggravate NVP. Both increased maternal age at conception and gravidity have also been positively associated with increased severity of NVP\(^5\). Recent studies have demonstrated that the use of prenatal multivitamin supplementation aggravates or may even initiate symptoms of NVP; however, additional studies are required to determine the effects on adherence and tolerability\(^9\). Certain medical conditions may also exacerbate NVP symptoms. For instance, women suffering from metabolic disorders have been shown to have more severe symptoms of NVP\(^6,45\). Additionally, migraines, motion sickness and other vestibular conditions are associated with increased severity of NVP\(^6,56,57\). Viral and bacterial infections in pregnancy are associated with increased NVP symptoms; in fact, in women with HG, numerous studies have found a higher prevalence of \textit{H. pylori} infection\(^37-39\). Gastrointestinal conditions and symptoms can, in theory, worsen NVP
symptoms; however, no prospective study has been conducted to confirm this hypothesis. Further studies are required to identify aggravating factors in order to improve overall management of NVP.

2.2.4 Impact of NVP

Nausea and vomiting of pregnancy can substantially reduce a woman’s quality of life and her ability to function, especially when under-treated or untreated. In fact, 55% of women suffering from NVP report feeling frustrated, helpless, resentful and depressed. Studies have documented that women’s social life and family life are negatively affected by NVP with approximately half of women with NVP reporting negative effects on their marital relationships due to NVP. In some cases, women have electively terminated their pregnancy due to severe NVP and its impact: in a study of 3201 pregnant women experiencing NVP, 108 terminated their pregnancy because of NVP and 413 considered termination.

In addition to these psychosocial issues, NVP can result in increased socioeconomic costs. A recent Canadian study estimated that the societal cost per woman-week of untreated NVP, in Canadian dollars is $132, $355, and $653 for women with mild, moderate, and severe NVP, respectively. Similarly, studies conducted in Great Britain and the United States have estimated that pregnant women experiencing NVP lose an average of 62 hours and 64 hours of paid work, respectively.

2.2.5 Quantifying the Severity of NVP Symptoms

The impact of NVP largely depends on the severity of symptoms. Pregnant women can perceive their symptoms to be mild, moderate, or severe, or even variable
depending on their pattern of symptoms. These self-reports are useful in determining the impact of NVP on a woman’s quality of life; however, they only provide qualitative data. In order to quantify the severity of NVP symptoms, scales have been created such as the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) scale.

The PUQE scoring system is based on the gold-standard, validated Rhodes’ Scale of Nausea, Vomiting and Retching. From the lengthy 8-item Rhodes’ Scale, several short versions containing only 3 to 4 items were created. Scores from the newly created scales were compared to scores from the Rhodes’ Scale. Based on the strongest correlation (r=0.904, p<0.0001) the new PUQE scoring system was developed based on the number of vomiting episodes, the number of retching episodes and the hours of nausea in a 12 hour period. Recently, however, the original PUQE scoring system has been modified to quantify the same NVP symptoms experienced over a 24 hour period, instead of only a 12 hour period, as a 24 hour period provides more accuracy in quantifying NVP symptoms.

Both the original PUQE scale and the PUQE-24 scale have been validated based on the ability of these scoring systems to predict independent outcomes of NVP. The original PUQE scoring system was tested to predict the following outcomes: 1) pregnant women’s ability to take prenatal multivitamins, 2) rates of emergency room visits and hospitalization for NVP, 3) health cost of NVP, and 4) women’s self scores of well-being. The PUQE-24 was tested to predict the following outcomes: 1) pregnant women’s ability to take prenatal multivitamins, 2) rates of emergency room visits and hospitalization for NVP, and 3) women’s self scores of well-being. Both PUQE scoring
systems were found to possess significant predictive values for each of the outcomes evaluated\textsuperscript{64,65}.

The studies in this dissertation have quantified NVP symptoms using the PUQE-24 scoring system as it is a validated tool specifically designed to allow for convenient and accurate quantification of NVP symptoms over a 24 hour period (Table 2.1).

| How many hours in the past 24 hrs had you felt nauseated/sick to stomach? (hours) | None (1) | ≥ 1 (2) | 2-3 (3) | 4-6 (4) | > 6 (5) |
| How many times in the past 24 hrs did you vomit? | ≥ 7 (5) | 5-6 (4) | 3-4 (3) | 1-2 (2) | None (1) |
| How many times in the past 24 hrs did you experience gagging or retching or dry heaves? | None (1) | 1-2 (2) | 3-4 (3) | 5-6 (4) | ≥ 7 (5) |

To incorporate other factors other than nausea, vomiting and dry heaving, the Well-being scoring system, ranging from 0 (the worst) to 10 (the best), based on how a woman presently feels overall compared to how she felt prior to pregnancy is also used to quantify the severity of NVP symptoms in the research studies conducted in this dissertation. This score incorporates the total impact of NVP on the woman’s quality of life including factors such as sleep, food and fluid intake, energy level, fatigue, and psychosocial effects.

2.2.6 Non-pharmacological Management of NVP

In addition to pharmacological strategies, there are non-pharmacological remedies that have been demonstrated to alleviate NVP symptoms. Dietary changes focused on consuming very small portions every 1 to 1.5 hours minimize hunger pains as
well as bloating and indigestion\textsuperscript{4,66}. Furthermore, consuming liquids 20 to 30 minutes after food intake further reduces bloating and queasiness\textsuperscript{4}. Liquid intake should ideally be equivalent to 2 liters; colder beverages, nutritional supplement beverages or electrolyte-based beverages may help settle the GI tract and provide nourishment\textsuperscript{66}. Additionally, one cup a day of peppermint, chamomile or ginger tea, lukewarm or cool, may also be effective in reducing NVP symptoms.

Numerous studies have demonstrated the effectiveness of ginger root powder capsules in reducing the severity of symptoms of NVP\textsuperscript{67-73}. The maximum amount of ginger root powder that has been studied for fetal safety in pregnancy is 1000 mg per day\textsuperscript{71,72}; however, since ginger can be a stomach irritant, these capsules should be taken with food\textsuperscript{70}. Randomized studies have demonstrated that ginger is comparable in efficacy to dimenhydrinate without the sedative side effect\textsuperscript{70}, and a more effective anti-emetic compared to vitamin B6\textsuperscript{69,71}. Vitamin B6 itself, however, has also been shown to possess anti-emetic properties; in several prospective and randomized trials in early pregnancy, vitamin B6 therapy reduced the severity of NVP\textsuperscript{69,74-79}. The maximum amount of vitamin B6 that is recommended is 200 mg per day as vitamin B6 at higher doses may result in peripheral neuropathy\textsuperscript{4}.

Another form of anti-emetic therapy is acupressure bands, acupressure or acupuncture. A few studies have demonstrated the usefulness of these therapies in the treatment of NVP symptoms; however, results are inconsistent and efficacy may vary among practitioners\textsuperscript{4,76,80,81}. 
In addition to anti-emetic therapy, to improve the severity of NVP, management of secondary symptoms is critical. For instance, heightened olfaction often results in food and beverage aversions, and increases symptoms of NVP; therefore, ventilation or minimizing aversive odours can reduce NVP\textsuperscript{82}. Although excessive saliva needs to be expelled to provide relief, the use of mouthwash may temporarily hinder production\textsuperscript{4}. Furthermore, the bitter, metallic taste in the mouth can be altered using mint or citrus flavoured candies\textsuperscript{4}. Gastrointestinal symptoms such as heartburn, constipation, gas, bloating and indigestion should be managed as well as will be discussed below.

2.2.7 Pharmacological Management of NVP

When examining the safety of using medication during pregnancy, there are several factors to consider. When assessing the teratogenic potential of a drug, emphasis is placed on first trimester exposure as this is when organogenesis occurs, and the majority of exposures to pharmacological therapies to manage NVP do occur in the first trimester when the incidence and severity peak\textsuperscript{2,51}. Randomized controlled trials in pregnant women, for ethical reasons, are not conducted, and the epidemiologic studies that are conducted are observational and are never large enough to establish safety or risk. Consequently, the absence of an increased risk for major malformations does not necessarily establish the safety of a drug. However, most studies do include enough exposures to rule out a major teratogenic risk. To further establish the safety of a drug throughout pregnancy, evaluations from other trimester are also important, especially if the drug affects the nervous system\textsuperscript{51,83}. 
There have been many studies examining the safety of pharmacological treatments during pregnancy; some of these studies will be summarized below to demonstrate that NVP can be effectively and safely managed. Additionally, other pharmacological therapies used to manage NVP that have either not been proven to be effective and/or have not been studied to evaluate fetal safety will be summarized.

2.2.7.1 Antihistamines

Antihistamines are the oldest class of drugs that have been used for the treatment of NVP and work by two separate mechanisms: they directly inhibit the action of histamine at the histamine-1 receptor, and indirectly affect the vestibular system. These mechanisms combine to decrease stimulation of the vomiting centre. Additionally, it has been proposed that muscarinic receptor inhibition could contribute to antihistamine anti-emetic activity.

2.2.7.1a Doxylamine succinate/pyridoxine hydrochloride (Diclectin®)

Diclectin® is a delayed-release combination tablet composed of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, and is the only drug approved for the management of NVP. Doxylamine succinate is an antihistamine that provides anti-nausea and anti-emetic effects; pyridoxine hydrochloride is a vitamin B6 supplement that has been found to alleviate NVP. If Diclectin® is not available, pyridoxine may be used alone to help manage NVP, or doxylamine and pyridoxine may be used together.

Several randomized, controlled trials have been conducted to demonstrate the efficacy of Diclectin®. However, is has also been determined that the efficacy of
Diclectin® depends on optimal dosing: a study conducted in 68 pregnant women experiencing moderate to severe NVP concluded that Diclectin® dosing should be given according to body weight, time and severity of NVP symptoms in order to be most effective. Although the standard recommended dose is up to 4 tablets a day, a study was conducted comparing 123 pregnant women at recommended standard doses and 102 pregnant women higher than recommended doses. This study revealed that higher than standard doses up to 12 tablets a day, when calculated per kg of body weight, do not affect either the incidence of maternal adverse effects or pregnancy outcome, and were found to be more efficacious.

Further studies are required to determine the factors that result in the variability in the therapeutic effect of Diclectin®. Diclectin® is formulated to be delayed-release; therefore, this formation may account for differences observed in the onset of action of Diclectin®. Additionally, pyridoxine hydrochloride requires bioactivation to its active metabolite, pyridoxal-5’-phosphate, through a series of reactions involving kinases, phosphatases and oxidases that have been found to vary among people. Although doxylamine is the other active ingredient, it binds to histamine-1 receptors which may also vary among people as variability in guanine nucleotide-binding protein coupled receptors has been found in some studies. Pharmacokinetic parameters of the active metabolites after Diclectin® administration is required to determine the extent of variability in order to explain the clinical differences observed in both the therapeutic and adverse effects of this doxylamine succinate/pyridoxine hydrochloride combination.
Although temporary side effects such as sleepiness, tiredness, and/or drowsiness are associated with the use of Diclectin® in the mother, no studies to date have demonstrated any teratogenic effects of this medication. Several studies have been performed examining the potential for teratogenicity in animals during organogenesis using 90, 125, 60 and 20 times the maximal human dose in rats, rabbits, mice and monkeys, respectively, and no consistent pattern of fetal malformations were observed. In addition, more than 25 large-scale epidemiological studies have been performed regarding the safety of Diclectin® use during pregnancy, making it the world’s most studied drug in pregnancy.

In the US, Bendectin® was approved for NVP, and contained the same active ingredients as Diclectin®; however, misinformed media publicized alleged teratogenic effects of Bendectin® causing the manufacturers to withdraw it from the market due to financial collapse defending lawsuits, none of which were ever won by a plaintiff against the company. Prior to this withdrawal, it is estimated that approximately 30 million infants were exposed to Bendectin® in early pregnancy. Two meta-analyses were performed on all of the published studies. Neither meta-analyses found an association between Bendectin® exposure and fetal abnormalities. Notably, following the withdrawal of Bendectin® from the market, the National Hospital Discharge Survey noted increased hospitalization rates of women suffering from NVP, but no decreased risk in the rates of birth defects.
2.2.7.1b Dimenhydrinate (Gravol®)

Dimenhydrinate is a first generation antihistamine (H₁ blocker) and it is the chlorotheophylline salt of diphenhydramine (Benadryl®). Dimenhydrinate has been shown to be efficacious for the treatment of NVP in several studies, and currently, it is recommended as second line treatment for breakthrough relief of NVP.

No increased risk for malformations following the use of dimenhydrinate during pregnancy has been documented. In one animal study, rats were administered dimenhydrinate at 75 mg/kg/day throughout pregnancy, and there were no increased risks of congenital malformations. Several prospective and case-control cohort studies have not associated the use of dimenhydrinate and other H₁ blockers in pregnancy with birth defects. One study examined 319 women with first trimester exposures to dimenhydrinate and 697 exposures anytime in pregnancy and found no statistically significant associations with congenital anomalies. Similarly, a cohort study conducted in Germany examined the outcomes of 628 women who took dimenhydrinate or one of three other antiemetic drugs (meclizine, triflupromazine or chlorphenoxamine) during the first trimester, and paired analysis did not reveal any increased incidence of congenital anomalies.

To confirm these findings, a meta-analysis was performed on 24 controlled studies published between 1964 and 1991, and included more than 200 000 first trimester exposures to antihistamines. This meta-analysis revealed that there was no increased risk for congenital malformations in babies whose mothers had used...
antihistamines during the trimester thus verifying the safety of dimenhydrinate use during pregnancy\textsuperscript{97}.

2.2.7.2 Dopamine Antagonists

Several dopamine antagonists have been used for the treatment of NVP. Dopamine (D\textsubscript{2}) receptors in the gastrointestinal tract mediate inhibition of gastric motility and are thought to be a site of action for antiemetic dopamine receptor antagonists\textsuperscript{60}. Dopamine is also implicated in emetic signaling through the chemoreceptor trigger zone\textsuperscript{60}. There are three main classes of D\textsubscript{2} receptor antagonists, and each group has a different mechanism of action\textsuperscript{60}. Phenothiazines exert their antiemetic effects by interfering with dopamine binding to its receptors; butyrophenones also act by blocking dopamine receptors; benzamides are strong central and peripheral D\textsubscript{2}-antagonists that can increase esophageal sphincter tone and decreasing transit time through the gastrointestinal tract\textsuperscript{60}.

2.2.7.2a Promethazine (Phenergan\textsuperscript{®})

Promethazine is a phenothiazine that can be effectively used as an antiemetic, and has been shown to be efficacious in the treatment of HG\textsuperscript{98,99}.

Numerous animal\textsuperscript{100} and human studies\textsuperscript{101} have reported a lack of association between the use of promethazine during pregnancy and an increased risk for congenital malformations. The Collaborative Perinatal Project identified 14 women exposed to promethazine during the first trimester and 746 women exposed throughout pregnancy\textsuperscript{101}. The data obtained from this study indicates that promethazine is not
associated with an increased risk of birth defects\textsuperscript{101}. Another study in 165 women exposed in the first trimester also showed no increased risk for birth defects\textsuperscript{95}.

One follow-up study was conducted in Hungary in children exposed to promethazine \textit{in utero} to assess somatic measurements such as weight and head circumference at birth and at 8 months of age\textsuperscript{5}. There were no differences in the children exposed to promethazine compared to children who were not exposed to teratogens\textsuperscript{5}.

A few studies have suggested that the use of promethazine during labor as an adjunct to narcotic analgesia may induce respiratory distress in the newborn; additionally, platelet aggregation in both the mother and in the newborn may become impaired\textsuperscript{101}. Therefore, although the use of promethazine is not associated with any increased risk for major malformations and can be used in the first trimester for the treatment of NVP, there is some concern for its use near term.

\textit{2.2.7.2b Chlorpromazine (Largactil\textsuperscript{®})}

Chlorpromazine is also in the phenothiazine family, and has been used as an anti-emetic and a major tranquilizer since the 1960s\textsuperscript{95}.

An animal study conducted in 1974 found an association between the use of chlorpromazine in pregnancy and the incidence of oral cleft palate in mice\textsuperscript{102}, and a study conducted in 1982 found decreased vascularization in the cerebellar cortex of rats exposed to high doses of chlorpromazine \textit{in utero}\textsuperscript{103}. These malformations, however, have not been reported after human use of chlorpromazine during pregnancy.
In a cohort study of 264 women treated with a low dose of chlorpromazine for HG in the first trimester of pregnancy, infants did not have any increased incidence of malformations\textsuperscript{104,105}. Additionally, in 142 women exposed to chlorpromazine in the first 4 months of pregnancy and 284 women treated at any time during pregnancy, there were no increased rates of malformations observed\textsuperscript{5,106}. These children were followed up at 4 years of age, and there were no differences in intelligence quotient (IQ) scores\textsuperscript{5,106}.

Some concern has been raised regarding the use of high (150-250 mg/day) doses of chlorpromazine used in the treatment of psychiatric illnesses\textsuperscript{107,108}. Babies exposed to these levels of chlorpromazine have exhibited neonatal withdrawal symptoms\textsuperscript{107}, and extrapyramidal abnormalities which have been observed even weeks after birth\textsuperscript{108}. The doses used for the management of NVP, however, are much lower (10-25 mg every 4-6 hours\textsuperscript{3,4}) than the doses at which these effects were observed.

Based on the available human data, although the use of chronic, high dose in the third trimester may be associated with temporary adverse outcomes on the baby, the use of chlorpromazine for the treatment of NVP during the first trimester is not associated with any increased risks for congenital malformations.

2.2.7.2c Prochlorperazine (Stemetil®)

Prochlorperazine is a phenothiazine antiemetic that is also used as an antipsychotic, and is sometimes used to treat NVP\textsuperscript{95}.

Animal studies regarding the teratogenic potential have found conflicting results. At high doses, prochlorperazine has been found to increase the incidence of cleft palate
in mice and rats\textsuperscript{109}, but this increase has not been observed in rabbits\textsuperscript{110}. Some human case reports have reported congenital malformations in babies born to mothers who had used prochlorperazine; these malformations have not been consistent and include newborns with cleft palate\textsuperscript{111}, a congenital heart defect\textsuperscript{111}, a skeletal malformation\textsuperscript{112}, and a limb malformation\textsuperscript{113}.

In numerous clinical studies, no increased risks for malformations have been associated with the use of prochlorperazine. For example, the Collaborative Perinatal Project conducted a study involving 877 pregnancies with first trimester exposure, and 2023 exposures throughout pregnancy; there was no statistically significant increase in congenital anomalies\textsuperscript{114}. Another study, the Michigan Medicaid surveillance study, reported no increased risk after the first trimester exposure of 704 newborns\textsuperscript{95}. Similarly, numerous other studies have not found an association between the use of prochlorperazine in pregnancy and birth defects\textsuperscript{115-118}.

Although isolated case reports have found congenital malformations after the use of prochlorperazine, the majority of evidence indicates that there is no increased risk.

2.2.7.2d Metoclopramide (Reglan\textsuperscript{®})

Metoclopramide is an anti-emetic medication, which is also used to decrease gastrointestinal emptying time\textsuperscript{95}. Several animal studies have found no increased risk for birth defects after the use of metoclopramide in pregnancy. In fact, when mice, rats, and rabbits were administered 250 times the standard dose for humans, no teratogenesis was observed\textsuperscript{95,119,120}.
Several prospective studies have verified this lack of teratogenicity. In one study involving 309 women exposed to metoclopramide during the first trimester, there was no increased risk for birth defects, and furthermore, there were no significant differences in the mean birthweight and the rate of prematurity in exposed and unexposed infants\textsuperscript{121}. In a prospective cohort study of 126 women who used metoclopramide in the first trimester, no increased risks for congenital malformations, spontaneous abortions and decreased birthweight were noted in the offspring\textsuperscript{122}. An additional surveillance study of 192 women also found no increased risk to the fetus after first trimester exposure to metoclopramide\textsuperscript{95}. A more recent study involving 3478 first trimester exposures to metoclopramide did not find any increased risks for congenital malformations, preterm delivery, low birth weight or perinatal death\textsuperscript{123}.

Based on the available studies, the use of metoclopramide during pregnancy is not associated with increased risks of negative pregnancy outcomes including low birthweight, premature delivery, spontaneous abortions or birth defects.

2.2.7.3 Serotonin Antagonists

Serotonin antagonists are quite effective in treating chemotherapy-induced nausea and vomiting; therefore, some physicians use these medications to treat NVP\textsuperscript{60}. They are thought to work both centrally and peripherally at the 5-hydroxy-tryptamine-3 (5-HT\textsubscript{3})-receptors\textsuperscript{60}. Blocking the serotonin receptors at the small bowel, vagus nerve and the chemoreceptor trigger zone results in decreased stimulation of the medullary vomiting center\textsuperscript{60}. 
2.2.7.3a  **Ondansetron (Zofran®)**

Ondansetron is an antiemetic primarily used for the treatment of chemotherapy-induced nausea and vomiting; however, it is also used in the management of NVP and HG\(^95\).

No evidence of teratogenicity was observed in the offspring of pregnant rats and rabbits treated with ondansetron at physiological concentrations\(^95,124\), and at concentrations 70 times greater than the human dose\(^125\). Furthermore, several case reports involving the birth of healthy babies after first trimester exposure to ondansetron have been published\(^126,127\).

In a study examining the potential risks of birth defects after first trimester use, there were no increased risks\(^128\). Additionally, a randomized, controlled, pilot study was conducted involving 15 women exposed to ondansetron compared to 15 exposed to promethazine for the treatment of HG\(^129\). There were no reported malformations in this study\(^129\).

Two additional studies have been conducted to determine the safety of ondansetron use during pregnancy\(^130,131\). The first study was conducted in Sweden, and consisted of 45 women exposed to ondansetron throughout pregnancy, with 21 exposed in the first trimester\(^130\). No major malformations were reported in this study\(^130\). The second study was conducted at the Motherisk Program in Toronto, Canada, and involved a comparison between women who were exposed to 1) ondansetron, 2) other anti-emetics and 3) other non-teratogens\(^131\). Each group included
176 women, and no differences were found among the 3 groups with respect to live births, spontaneous abortions, major malformations and birthweight\textsuperscript{131}.

Due to these recent studies that have been conducted, there is increased evidence for the safety of the use of ondansetron during pregnancy.

2.2.7.4 Other Pharmacological Therapies to Manage NVP

The pharmacological therapies that have been summarized above have been shown to be safe and effective treatments for NVP\textsuperscript{4,74,132}. A meta-analysis conducted in 2000, found the use of doxylamine-pyridoxine ± dicycloverine, antihistamines, and phenothiazines to be the most effective treatments for NVP\textsuperscript{133}. Based on these efficacy and safety studies, an evidence-based treatment algorithm has been developed to help effectively manage NVP (Figure 2.2)\textsuperscript{4}. 
There are other pharmacological therapies that are available for the management of NVP. Although not generally recommended, these pharmacotherapies
are still used as first-line treatments in various parts of the world due to lower costs, availability, personal preference, and/or word of mouth. In fact, drugs of choice include meclizine, metoclopramide and thiethylperazine in Northern, Southern and Eastern Europe, respectively. It is important to recognize this use; therefore, a brief summary on the safety of other pharmacological therapies for the treatment of NVP is provided below.

2.2.7.4a Antihistamines

Buclizine

Buclizine is a piperazine antihistamine that is associated with an increased risk for jaw and palatal defects in rats; however, in 44 first trimester exposures and 62 exposures throughout pregnancy, no increased risks for major or minor malformations were observed.

Cyclizine

Cyclizine is an antihistamine used for the prevention of motion sickness and postoperative nausea and vomiting. Animal studies have suggested an increased risk for congenital malformations; however, in over 100 human exposures, no increased risk for birth defects has been observed.

Diphenhydramine

Diphenhydramine is also a very well studied antihistamine that is not associated with teratogenicity in animal studies, and in prospective human studies. Between 1974 and 1992, over 2500 babies were exposed in the first trimester and more than 4000 were exposed at any time during pregnancy, and no increased risk was observed in
major or minor malformations. Additionally, several studies have reported the safety of antihistamine use during pregnancy.

**Hydroxyzine**

Hydroxyzine is a piperizine antihistamine, and although it was associated with teratogenicity in an animal study, several human studies involving more than 1000 first trimester exposures and over 1500 total exposures have not found an association with its use during pregnancy and an increased risk of birth defects.

**Meclizine**

Meclizine is a piperizine antihistamine that has been shown to cause birth defects in rodents; however, several large scale human studies have not found an increased risk for major malformations associated with its use in pregnancy. Specifically, almost 2000 first trimester meclizine exposures have been studied and several thousand exposures any time during pregnancy, and there was no evidence of teratogenicity observed.

**2.2.7.4b Dopamine Antagonists**

**Alizapride**

Although alizapride is similar to metoclopramide, we could not locate any studies on the safety of this drug in pregnancy.

**Domperidone**

Domperidone is a dopamine antagonist that has been associated with an increased risk of birth defects in mice, rats and rabbits. Although a few case reports exist, human data on its teratogenic potential is lacking.
**Droperidol**

Droperidol is a tranquilizer, and has not been shown to cause an increased risk for birth defects in rats and in 108 human pregnancies\(^95,106\).

**Perphenize**

Perphenize is a phenothiazine that is not associated with an increased risk for major malformations when it is used during pregnancy based on limited human data\(^95,106\). First trimester exposures have been noted in 203 infants and more than 300 infants have been exposed throughout pregnancy\(^95\).

**Thiethylperazine**

Thiethylperazine a phenothiazine that has been shown to increase the incidence of cleft palate in rodents exposed to high doses but not in rabbits\(^106\). Furthermore, in one human study involving 1374 infants, the incidence of cleft palate was significantly higher in babies exposed to thiethylperazine in the first trimester\(^106\).

**Trifluoperazine**

Trifluoperazine is a piperazine phenothiazine which, at high doses is thought to adversely affect embryo development in animals; however, in 42 human exposures during pregnancy, no negative outcomes were observed\(^95,106\).

**Trimethobenzamide**

Trimethobenzamide is structurally similar to antihistamines. Based on animal studies and 193 first trimester human exposures, trimethobenzamide use in pregnancy is not associated with an increased the risk of congenital anomalies\(^95,106\).
2.2.7.4c Anticholinergics

*Butylhyoscine/Butylscopolamine*

*Butylhyoscine/Butylscopolamine* is an anticholinergic drug; studies on the safety of this medication in pregnancy were not located.

*Dicyclomine/Dicycloverine*

Dicyclomine is an anticholinergic agent that was one of the components of Bendectin®. Dicyclomine is not associated with teratogenicity in both animal and human exposures during pregnancy. As previously mentioned, Bendectin® use during pregnancy was not associated with any increased risk of birth defects, and based on more than 1600 first trimester exposures to dicyclomine, it is not considered teratogenic.

*Scopolamine*

Scopolamine is an anticholinergic medication that is also not associated with an increased risk for major malformations when it is used during pregnancy based on studies in rats and rabbits. In addition, 336 first trimester exposures and almost 400 total exposures did not reveal any increased risk of birth defects.

2.2.7.4d Antidepressants

*Amitriptyline*

Amitriptyline is a tricyclic antidepressant that has been associated with teratogenesis in animal studies; however, an increased risk for birth defects has not been found in several human studies involving 700 first trimester exposures.
Mirtazapine

Mirtazapine is a tetracyclic antidepressant that may be useful in treating severe NVP. Its use is not associated with teratogenicity in rats and rabbits, and in 16 human case reports. A study conducted by Motherisk involving 104 pregnant women exposed to mirtazapine at some point in their pregnancy and 98 exposed during the first trimester did not reveal any increased risk for a child to be born with malformations.

2.2.7.4e Benzodiazepines

Diazepam

Diazepam is a sedative, and a member of the family of benzodiazepines. Based on several cohort and case-control studies, the use of benzodiazepines in pregnancy is associated with a slightly increased risk for oral clefts from 1 in 1000 to 2 in 1000.

2.2.7.4f Corticosteroids (prednisolone, dexamethasone, methylprednisolone)

Treatment with corticosteroids is based on the rationale that severe NVP may be due to a deficiency of corticotrophin, leading to adrenal insufficiency. Although corticosteroids have been evaluated for treatment of severe NVP and hyperemesis gravidarum, no studies have evaluated these agents for treatment of mild symptoms. In addition, orally administered corticosteroids have been associated with a slight increased risk for oral clefts from 1 in 1000 to 2 in 1000 in several studies; therefore, the use of these medications is not recommended in the first trimester.
2.3 GASTROINTESTINAL SYMPTOMS IN PREGNANCY

2.3.1 Heartburn and Acid Reflux in Pregnancy

Heartburn (HB) and/or acid reflux (RF) are common medical disorders occurring due to the accumulation of gastric acid in the stomach or regurgitation up the esophagus, in the case of reflux\textsuperscript{135}. It has been estimated that the incidence of gastroesophageal reflux disorders in pregnancy ranges between 40% to 85\%\textsuperscript{7,18,135-138}. Symptoms associated with gastroesophageal reflux disorders or dyspepsia may include heartburn, acid reflux, regurgitation, eructation, flatulence, stomach bloating, indigestion, and a sensation of a lump in the throat\textsuperscript{139,140}.

The onset of heartburn and acid reflux can occur any time during pregnancy: in one study, 52\% of the symptoms began in the first trimester and almost all by the second trimester with only 8\% of symptoms beginning in the third trimester\textsuperscript{19}. Other studies have reported increased severity and frequency of symptoms as gestational age increases\textsuperscript{20,141}, or similar incidences among the three trimesters with different predictors for each trimester\textsuperscript{142}. A recently published study involving 135 pregnant women in the third trimester found the prevalence of GERD to be 56\% with reflux occurring the most frequently but heartburn rated as the most severe symptom\textsuperscript{143}. In this same study, 23\% of the participants commenced acid-reducing therapy as there was a significant reduction in their quality of life\textsuperscript{143}. Regardless of the time of onset, anecdotal clinical evidence suggests that the presence of pre-existing GI conditions and/or symptoms as well as HB/RF during pregnancy aggravate nausea and vomiting and decrease quality of life\textsuperscript{135,136}. 
Although the symptoms of HB/RF do not differ in the pregnant versus the non-pregnant population, their etiology may differ\textsuperscript{135,136}. The stomach is a highly innervated neuromuscular organ with the interstitial cells of Cajal regulating the rhythmic peristaltic contractions by controlling pacemaker potentials or slow waves at approximately 3 cycles per minute\textsuperscript{7}. A shift in the pacemaker potential to 1.0 to 2.5 cycles per minute results in bradygastria; whereas, a shift to 3.7-10.0 cycles per minute is termed tachygastria\textsuperscript{7}. Changes in motility of the GI tract due to increased levels of circulating female hormones, or by other factors, result in increased GI tract symptoms in pregnancy (Figure 2.3)\textsuperscript{135,136,144-146}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.3.png}
\caption{Neuromuscular abnormalities that occur in patients with dyspepsia symptoms\textsuperscript{7}}
\end{figure}
A decrease in lower esophageal sphincter pressure in pregnancy accompanied by heartburn has been demonstrated\textsuperscript{144}. Furthermore, decrease in sphincter pressure occurs in the presence of estrogen and progesterone among female volunteers using oral contraceptives\textsuperscript{145,146}. Similar changes in gastric motility and dysrhythmias have been observed in NVP\textsuperscript{7,50}. Hence, it is biologically plausible that HB/RF contribute to the severity NVP. If confirmed, this hypothesis can lead to improvement in the management of NVP by treating symptoms of reflux. In pregnancy, treatment of heartburn and acid reflux can involved the use of antacids, H2 blockers or PPIs depending on the severity of symptoms. Several small studies have been conducted to determine the fetal safety of H2 blockers and PPIs in pregnancy; however, due to their limited sample sizes, further research is required to definitively demonstrate the fetal safety of these 2 classes of medication.

2.3.1.1 Treatment of Heartburn and Acid Reflux with Antacids

Antacids are a group of medications that can relieve heartburn and acid reflux symptoms by neutralizing stomach acid\textsuperscript{135}. As a result, they mostly contain forms of calcium carbonate, aluminum or magnesium, or a combination of aluminum and magnesium to counteract side effects of constipation and diarrhea produced by these two ingredients\textsuperscript{147}. Some preparations may also contain simethicone which breaks down gas bubbles in the stomach, or alginic acid which produces foam that floats on top of the stomach contents preventing stomach acid from coming into contact with the esophagus\textsuperscript{148}.
Antacids are effective for the management of mild heartburn and acid reflux\textsuperscript{135,149}. Their onset of action is within one hour; however, the duration of action is typically short\textsuperscript{147,148}. Furthermore, for symptoms of heartburn and acid reflux that are more moderate to severe, antacids are not potent enough to manage symptoms; instead, medications that inhibit acid production, such as H2 blockers or PPIs, are better alternatives\textsuperscript{135,150}.

2.3.1.2 Treatment of Heartburn and Acid Reflux with H2 blockers

Histamine 2 blockers are a class of medication that inhibits acid production by parietal cells\textsuperscript{150}. Parietal cells contain H2 receptor sites and are activated to secrete acid when histamine binds to the receptors; H2 blockers prevent histamine from binding to its receptor site thereby preventing the downstream signals for acid secretion\textsuperscript{151}.

Histamine 2 blockers can be effective for moderate to severe symptoms of heartburn and acid reflux\textsuperscript{149}. The onset of action of H2 blockers is typically less than an hour; however, the maximum duration of action is approximately 12 hours\textsuperscript{147,148}. For prolonged symptoms, or severe symptoms that persist even after treatment with H2 blockers, PPIs would be recommended\textsuperscript{135,150}.

2.3.1.3 Treatment of Heartburn and Acid Reflux with PPIs

Proton pump inhibitors are the most potent form of acid-suppressing therapy available, preventing one of the final steps of acid secretion\textsuperscript{151}. As their name implies, PPIs irreversibly inhibit the proton pump located on parietal cells, and prevent the exchange of a non-acidic potassium ion out of the stomach with an acidic hydrogen ion into the stomach\textsuperscript{152}.
Proton pump inhibitors are used in the treatment of severe forms of heartburn and acid reflux, stomach and duodenal ulcers, erosive esophagitis, Zollinger-Ellison syndrome and *H. pylori*\(^{135,149,150}\). Although they have a delayed onset of action, their duration of action is 24 hours but may even last up to 3 days\(^{152}\).

### 2.3.2 Constipation

Constipation, defined or assessed as incomplete evacuation, substantially decreased bowel movements or bowel movements less than 3 times per week, straining, hard stool, has been reported to occur in approximately 25% of pregnancies\(^{153}\). In a study of 103 pregnant women, 26% experienced constipation in the first trimester and 16% and 24% in the second and third trimesters, respectively\(^{154}\). Hormonal changes in pregnancy are thought to contribute to constipation; specifically, progesterone is thought to decelerate the natural motion of the GI tract resulting in constipation\(^{149,155}\). Additional factors that can contribute to constipation in pregnancy include inadequate fluid and/or dietary fibre intake, decreased physical activity, psychosocial stress or iron-containing prenatal multivitamin supplementation\(^{156,157}\).

As constipation can exacerbate NVP symptoms, management is important. Firstly, increasing dietary or supplementary fibre and fluid intake are recommended\(^{155,158,159}\). First-line pharmacotherapy to treat constipation in pregnancy consists of stool softeners rather than laxatives\(^{155,158,159}\). Another strategy may be to minimize iron intake; however, further research is required to determine the effect of iron-containing prenatal multivitamin supplementation on tolerability and severity of NVP.
2.4.1 Dietary Reference Intakes of Certain Vitamins and Minerals in Pregnancy

Multivitamin supplementation in pregnancy has been shown to be important for the health and well-being of both mother and child\textsuperscript{13}. It has been very well established that nutritional requirements for pregnant women, specifically, those experiencing severe NVP, are often not met through diet alone; therefore, to ensure that sufficient metabolic demands are being met, and that adverse health outcomes are prevented, prenatal multivitamin supplementation is strongly recommend by health authorities\textsuperscript{13,16,160,161}. In addition, prenatal multivitamin supplements contain the Dietary Reference Intakes (DRI), and provide both the mother and fetus with the necessary vitamins and minerals that may not be consumed through the diet\textsuperscript{13,160,161}. To account for physiological changes in pregnancy and the increased nutritional demands, DRI for vitamins and minerals in pregnancy should be followed by the majority of pregnant women (Table 2.2)\textsuperscript{160,161}.
Table 2.2 Daily Dietary Reference Intakes of Vitamins and Minerals in Pregnancy

<table>
<thead>
<tr>
<th>Vitamin or Mineral</th>
<th>RDA per day (upper limit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>770 µg retinol equivalent (3000 µg)</td>
</tr>
<tr>
<td>Vitamin B1 (thiamine)</td>
<td>1.4 mg (n/a)</td>
</tr>
<tr>
<td>Vitamin B2 (riboflavin)</td>
<td>1.4 mg (n/a)</td>
</tr>
<tr>
<td>Vitamin B6 (pyridoxine hydrochloride)</td>
<td>1.9 mg (100 mg)</td>
</tr>
<tr>
<td>Vitamin B12 (cyanocobalamin)</td>
<td>2.6 µg (n/a)</td>
</tr>
<tr>
<td>Vitamin C (ascorbic acid)</td>
<td>85 mg (2000 mg)</td>
</tr>
<tr>
<td>Vitamin D *</td>
<td>5 µg (50 µg)</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>15 mg α-tocopherol equivalent (1000 mg)</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>90 µg (n/a)</td>
</tr>
<tr>
<td>Calcium *</td>
<td>1000 mg (2500 mg)</td>
</tr>
<tr>
<td>Copper</td>
<td>1 mg (10 mg)</td>
</tr>
<tr>
<td>Fluoride *</td>
<td>3 mg (10 mg)</td>
</tr>
<tr>
<td>Folate</td>
<td>600 µg (1000 µg)</td>
</tr>
<tr>
<td>Iodine</td>
<td>220 µg (1100 µg)</td>
</tr>
<tr>
<td>Iron</td>
<td>27 mg (45 mg)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>350 mg (350 mg)</td>
</tr>
<tr>
<td>Niacin</td>
<td>18 mg (35 mg)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>700 mg (3500 mg)</td>
</tr>
<tr>
<td>Selenium</td>
<td>60 µg (400 µg)</td>
</tr>
<tr>
<td>Zinc</td>
<td>11 mg (40 mg)</td>
</tr>
</tbody>
</table>

RDA – Recommended Dietary Allowance
n/a - not available
* - no DRI available; only DRI values of adequate intake

2.4.2 Vitamin and Mineral Deficiencies in Pregnancy

Sufficient intake of vitamins and minerals during pregnancy will prevent adverse maternal and fetal effects associated with vitamin and/or mineral deficiencies; however, many pregnant women and healthcare providers may not be aware of these negative consequences. Negative pregnancy outcomes associated with vitamin and/or mineral deficiencies are less common in developed countries; whereas, in less developed
nations, significant harm may occur to both the mother and fetus especially since multiple nutrient deficiencies are often present. For example, vitamin A deficiency may result in increased risks for congenital ophthalmological malformations\textsuperscript{163}. In a study conducted in 736 pregnant women of high and low socioeconomic status, vitamin A deficiency in the third trimester was associated with higher rates of preterm delivery and anemia\textsuperscript{164}. Similarly, deficiencies of the B vitamins may also result in anemia\textsuperscript{165}. Interestingly, several studies have demonstrated that vitamin B\textsubscript{6} deficiency appears to result in greater severity of NVP symptoms\textsuperscript{71,166}. Recent studies have shown that vitamin B\textsubscript{9}, specifically folic acid, may decrease the risk for congenital anomalies\textsuperscript{15}, prevent neural tube defects\textsuperscript{16}, as well as decrease the risks for certain pediatric cancers\textsuperscript{14}.

Of the other fat-soluble vitamins, vitamin D may be associated with abnormal mineralization of the fetal skeleton as well as long-term neurodevelopmental delays\textsuperscript{167,168}. Vitamin E deficiency has been shown to cause miscarriage, preterm birth, preeclampsia, and intrauterine growth restriction\textsuperscript{169}. Lastly, vitamin K deficiency in pregnancy, although rare, is associated with defective blood clotting and increased bleeding and may increase the risk for craniofacial malformations\textsuperscript{170}.

Of micronutrient deficiencies, the negative effects of iron, zinc, iodine and calcium are the most well known; however, several studies have shown that multiple micronutrient deficiencies, rather than single deficiencies, are common. Although less predominant in developed countries, pregnant women in less developed countries are very likely to have multiple micronutrient deficiencies in pregnancy\textsuperscript{171}. Micronutrient
deficiencies can result in fetal hypothyroidism, neurocognitive delays, altered immune function and other negative central nervous system disorders\textsuperscript{172-177}. Many other negative maternal and fetal consequences may result in addition to the aforementioned effects; therefore, it is evident that adequate intake of vitamins and minerals during pregnancy is necessary.

2.4.3 Adherence to Prenatal Multivitamin Supplementation in Pregnancy

Despite the strong evidence to support the use of folate-containing multivitamin supplements in the periconceptional period, a large proportion of women do not use, or discontinue them in pregnancy\textsuperscript{9,10}. Studies conducted in Canada have demonstrated that adherence to prenatal multivitamin supplements varies substantially. In a recently published study involving 167 pregnant women, adherence throughout pregnancy was approximately 50%, with only 38% of pregnant women adhering to 80% or greater pill intake\textsuperscript{10}. However, in a randomized, cross-over trial involving 135 women, adherence during a two month period was found to be almost 90\%\textsuperscript{17}. Prenatal multivitamin supplements in both studies were similar, and adherence was assessed using both pill counts and self-reports\textsuperscript{10,17}.

Although women may intend to start and even begin prenatal multivitamin supplementation in pregnancy, discontinuation is common\textsuperscript{9,10}. Discontinuation of prenatal multivitamin supplementation is usually associated with factors such as tablet size, and pre-existing gastrointestinal conditions and/or symptoms which are thought to worsen NVP\textsuperscript{10}. In a recent study involving 70 pregnant women, adherence to prenatal multivitamin supplementation was significantly correlated to symptoms of
constipation\textsuperscript{178}. Additionally, the strongest predictors of a woman’s decision to discontinue or not even start prenatal multivitamin supplementation were found to be fear of nausea, fear of vomiting and health-care provider advice\textsuperscript{178}. In order to improve prenatal multivitamin supplementation in pregnancy, further research is necessary to determine tolerability especially in women experiencing NVP and GI symptoms.
∞ 2.5 IRON IN PREGNANCY ∞

2.5.1 Iron Background

Iron exists in oxidation states of -2 to +6; however, in biological systems, iron is primarily found in the ferrous (+2), ferric (+3) and ferryl states (+4)\(^1\). Interconversion among these oxidative states allows for a wide array of physiological roles\(^1\). Iron has several critical physiological roles in the body including the production of hemoglobin, transport and storage of oxygen and electrons, catalyzing reactions in oxidative metabolism, and cellular proliferation\(^1\). The body possesses intricate systems to prevent iron to exist in a free form \textit{in vivo} as this form can catalyze the formation of free radicals; consequently, iron is transported by transferrin among different compartments in the body\(^1\). Iron is supplied to cells in the body by three mechanisms: 1) continuous recycling of iron from catabolized red blood cells; 2) ferritin stores released from the liver; 3) absorbed dietary iron\(^1\). The balance of iron levels in the body is tightly regulated mainly through up- or down- regulation of absorption; hence, exogenous sources of iron play a vital role in preventing deficiency\(^1\).

In order to meet the body’s iron requirements, the DRI of iron in women of child-bearing age is 15 mg daily\(^2\); however, a significant proportion of women, especially adolescents, do not consume sufficient amounts of iron through their diet to replenish iron stores\(^3\). Foods rich in iron include red meat, fish, poultry, lentils, beans, leafy vegetables, tofu, chickpeas, black-eyed peas, fortified bread, and enriched breakfast cereals\(^3\). Depending on the food source, iron can be present in either the heme form, as is found in the hemoglobin and myoglobin in meats, or the non-heme form, found in
other foods and supplements\textsuperscript{184}. Although the absorption of heme iron is higher than that of non-heme, the absorption of non-heme iron can be enhanced\textsuperscript{184}. Consuming vitamin C with iron-containing products increases the absorption of iron; whereas, compounds such as calcium, tea, coffee, and acid-reducing pharmacotherapy will decrease the absorption of iron\textsuperscript{184}.

Iron deficiency anemia (IDA), affecting approximately 3.5 billion people, is the most common medical condition in the world even though diagnosis and treatment are globally available\textsuperscript{185}. Although its prevalence is much higher in less developed countries, it is still a large medical concern in developed countries\textsuperscript{186-188}. High risk groups consist of those with malnutrition, malabsorption, and women of child-bearing age\textsuperscript{185}. Women of child-bearing age are susceptible to IDA due to blood loss during menstruation, accounting for an increased monthly iron requirement of 17.5 mg, and pregnancy, which has an increased monthly iron requirement of 27 mg\textsuperscript{180,183}.

2.5.2 Iron Pharmacology: Bioavailability, Absorption, Metabolism and Excretion

The amount of iron absorbed from the diet ranges from less than 1\% to 80\% depending on the level of body iron stores and gastrointestinal factors; however, it is estimated to be 1 to 2 mg per day from an average Western diet\textsuperscript{189}. Other factors that can influence dietary bioavailability are iron content, and enhancers or inhibitors of iron\textsuperscript{189}. Different salt forms of iron exist as supplements; additionally, newer forms are being developed such as soybean ferritin, caseinophosphopeptide bound iron and double-fortified salt\textsuperscript{190-193}. No consistent information is available on the bioavailability of different salt forms although ferrous fumarate, ferrous sulfate, ferrous
pyrophosphate and ferrous bis-glycinate appear to be more bioavailable than other synthetic salt forms\textsuperscript{194}. However, the absorption of the heme form of iron is much more bioavailable - approximately 25% to 30% - and is minimally affected by dietary factors compared to 0% to 20% bioavailability of the non-heme form\textsuperscript{182}.

There are two pathways for the absorption of iron: one for the heme form and the other for the non-heme form (Figure 2.4)\textsuperscript{182}. Overall, the ferrous form is taken up by the enterocytes across the cellular apical membrane by an energy-dependent, carrier-mediated process, transported intracellularly\textsuperscript{195}. Heme, binds to its receptor and is then internalized and degraded by heme oxygenase to Fe\textsuperscript{2+}, carbon monoxide and biliverdin; whereas, non-heme iron, depending on the solubilization, is reduced to the ferrous form by duodenal cytochrome B (Dcytb) before it is internalized by its transporter, divalent metal transporter 1 (DMT1) (figure 2.4)\textsuperscript{195}. Once internalized, iron in the intracellular labile pool is delivered to the basolateral surface of the enterocyte where it is transported into the circulation by hephaestin (Hp) or iron-regulated transporter (IReg1), or binds to transferrin (Trf) via transferrin receptor 1 (TfR1)\textsuperscript{182,196}. As previously mentioned, iron is transported via transferrin in the plasma to the cells in the body\textsuperscript{196}. 
Figure 2.4 Absorption of heme and non-heme (Fe$^{2+}$) iron into mucosal cells$^{182}$

Transferrin contains two reversible binding sites for iron; therefore, iron can bind and form a complex to a highly specific transferrin receptor located on the plasma membrane surfaces of cells$^{182}$. Iron is released from transferrin, and can be incorporated into functional compounds, stored as ferritin, or used to control future iron metabolism$^{196}$. The synthesis of proteins for iron storage, iron transport and iron metabolism are tightly regulated by the size of the intracellular iron pool$^{196}$. Body iron is highly conserved; in the absence of bleeding or pregnancy, only 0.9 to 1.02 mg of iron are lost each day through the skin, urine and the GI tract$^{182,195}$.

2.5.2 Iron Deficiency in Pregnancy

In the first trimester of pregnancy, iron requirements do not change substantially as the cessation of menstruation counteracts the minimal increased iron requirements of the fetus, placenta and red blood cell mass expansion$^{197,198}$. As pregnancy progresses and the fetus and placenta develop further, iron requirements increase considerably
from 0.8 mg per day to 7.5 mg per day by late pregnancy\textsuperscript{180,199-201}. Consequently, iron supplementation may be required during pregnancy, especially for women with pre-existing low iron stores to prevent iron deficiency anemia\textsuperscript{197-199}.

The prevalence of anemia in pregnancy varies considerably due to differences in socioeconomic conditions, lifestyles and health-seeking behaviours across different cultures\textsuperscript{202}. Anemia affects nearly half of all pregnant women in the world: 52\% in developing countries compared with 23\% in developed countries\textsuperscript{203}. In developed countries, pregnant women more likely to develop anemia include those with a previous history of anemia, closely-spaced pregnancies, multiple gestations, adolescents, vegetarians, women with GI conditions and those of low socioeconomic status\textsuperscript{203}.

Iron deficiency is a serious concern in pregnancy\textsuperscript{202}. Mild maternal anemia results in diminished work capacity, weakness and fatigue; however, as the severity of anemia increases, maternal anemia can result in more serious consequences such as cognitive deficiencies and even maternal death\textsuperscript{204}. Iron deficiency during the first two trimesters of pregnancy doubles the risk of preterm delivery, triples the risk of neonatal low birth weight and may result in iron-deficient neonates\textsuperscript{201}. Studies conducted in iron-deficient neonates have demonstrated delayed motor development, emotional issues, and neurocognitive delays all which may or may not be reversible depending on the extent and severity of deficiency\textsuperscript{205,206}. All of the aforementioned effects result in dramatic costs to the healthcare system; therefore, greater effort and awareness in preventing anemia in pregnancy should be undertaken\textsuperscript{203}. 
To avoid IDA in pregnancy, the recommended daily dose is 27 mg of elemental iron\cite{12,201,203}, and iron content in prenatal multivitamins ranges from 27 to 60 mg. Iron, however, is associated with adverse effects including heartburn, constipation, diarrhea, nausea and vomiting\cite{11}. Additionally, studies have been conducted to determine the tolerability to various salt forms of iron; however, results are not consistent\cite{204}. These adverse effects can either directly or indirectly aggravate NVP symptoms already experienced by pregnant women leading to discontinuation or suboptimal adherence to prenatal multivitamin supplementation\cite{9,10,17}. Further research is required to determine the effects of iron-containing prenatal multivitamins on the severity of NVP and tolerability of prenatal multivitamin supplementation.
2.6 VITAMIN B6 IN PREGNANCY

2.6.1 Vitamin B6 Background

Vitamin B6 comprises a set of three related compounds and their respective 5’-phosphates: pyridoxine (PN) and pyridoxine-5’-phosphate (PNP), pyridoxal (PL) and pyridoxal-5’-phosphate (PLP), and pyridoxamine (PM) and pyridoxamine-5’-phosphate (PMP)\textsuperscript{207}. Food contains three natural forms of vitamin B6: plant-derived foods and supplements mostly contain PN, and animal-derived sources contain PL and PM\textsuperscript{208}. Excellent sources of vitamin B6 include chicken, and the livers of beef, pork and veal; good sources of vitamin B6 are certain fish, nuts, bread, corn, whole grain cereals, lentils and bananas\textsuperscript{208}. As previously mentioned, the DRI of vitamin B6 in pregnancy is 1.9 mg per day (Table 1); however, safety and efficacy studies have determined doses up to 200 mg per day may be useful in managing NVP as vitamin B6 deficiency is associated with more severe NVP symptoms\textsuperscript{4}. Women taking oral contraceptive pills may be more prone to vitamin B6 deficiency as some studies have demonstrated that these pills alter the body’s ability to absorb vitamin B6; therefore, this population may require additional vitamin B6 supplementation\textsuperscript{209}.

Vitamin B6 serves as a coenzyme of almost 100 enzymes that catalyze essential chemical reactions\textsuperscript{210}. Vitamin B6 is involved in the formation of hemoglobin and growth of red blood cells, the absorption of vitamin B12, the downregulation of homocysteine and the production of hydrochloric acid in the GI tract\textsuperscript{211-213}. Vitamin B6 plays a vital role in the metabolism of protein and amino acids, glycogen, sugars, essential fatty acids and certain endogenous chemicals such as serotonin, histamine and
hydroxytryptamine\textsuperscript{207,213}. In addition to the aforementioned metabolic roles, during pregnancy, PN contributes to the embryonic development of the central nervous system influencing brain development and cognitive function; therefore, maternal vitamin B6 deficiency may have negative long-term neurodevelopmental consequences on the fetus\textsuperscript{212-216}. Other symptoms of vitamin B6 deficiency include irritability, confusion, weakness, insomnia, depression, seborrheic dermatitis, microcytic anemia, lowered immunity, neurological disorders, or epileptiform convulsions\textsuperscript{212,214,217,218}.

\subsection*{2.6.2 Vitamin B6 Pharmacology: Bioavailability, Absorption, Metabolism and Excretion}

A few studies have been conducted to determine the bioavailability of vitamin B6. Bioavailability of vitamin B6 in the diet may vary due to the effects of the composition on access of the vitamin to the absorptive surfaces or by delaying diffusion through affects on the brush border membrane\textsuperscript{219}. Through animal studies using labeled PN, and human studies using standard diets, bioavailability of vitamin B6 is approximated to be 75\% to 80\%\textsuperscript{219-223}. The bioavailability of PN from supplements, on the other hand, is assumed to be 100\%; however, further research is required to verify this claim\textsuperscript{222}.

Absorption of vitamin B6 in the GI tract requires phosphatase-mediated hydrolysis followed by nonsaturable passive diffusion of the nonphosphorylated form into mucosal cells\textsuperscript{224}. In the liver, PN is metabolized to its phosphorylated form, PNP, by pyridoxal kinase which, in turn, is converted by pyridoxine phosphate oxidase into PLP (Figure 2.5)\textsuperscript{225}. Pyridoxal-5’-phosphate is the pharmacologically active form of vitamin
B6\textsuperscript{225-227}. Pyridoxal-5'-phosphate is mostly converted into PL which, in turn, leads to urinary excretion of 4-pyridoxic acid (4-PA)\textsuperscript{226}.

![Pyridoxine Metabolism Diagram](image)

**Figure 2.5** Metabolic conversion of pyridoxine by the human liver\textsuperscript{225}

A large proportion of PL compared to PLP is released into the circulation by the liver; the predominant form in the plasma is PLP, however, as PL is rapidly taken up and phosphorylated by other tissues while PLP stays in the plasma as a protein complex\textsuperscript{226-228}. In the plasma, PLP is bound primarily to albumin thereby protecting PLP from catabolism and assisting with transport\textsuperscript{229}. Pyridoxine can also be taken up by red blood cells where it is converted to PLP through PNP and then to PL followed by a gradual release of PL into the plasma\textsuperscript{228,230}. The plasma pool appears to be in rapid equilibrium with an equal sized interstitial fluid pool; therefore, in pregnancy, if there is
a shift in the fluid pool, it could decrease PLP in plasma\textsuperscript{208,231}. The total body pool of B6 in adult humans is approximately 1000 \( \mu \)M with 80\% in the muscle bound to glycogen phosphorylase, and less than 10\% in each of skin and liver\textsuperscript{232,233}. Several studies have determined that urinary excretion is the major route of excretion at approximately 93\%\textsuperscript{234}; whereas, fecal excretion is extremely minimal at less than 3\%\textsuperscript{221}.

2.6.3 Pharmacokinetics of Vitamin B6

As PN is bioactivated to PLP, several studies have examined the pharmacokinetics after oral or intravenous administration of PN, and intravenous administration of PLP. In two separate studies, healthy males received intravenous administration of 50 mg PN hydrochloride\textsuperscript{235,236}. The peak PLP concentration of 70 and 75 ng/mL was found to occur at 6 and 5 hours, respectively\textsuperscript{235,236}; additionally, the clearance of PLP after 5 mg PLP administration intravenously was found to be similar at 31.7 and 32.1 mL/minute. Another study conducted in 10 healthy males given a single oral dose of 600 mg PN hydrochloride, and also daily oral doses of 300 mg per day for 2 weeks found that after single dose, PLP increased moderately, but after 24 hours, PLP had the highest plasma level\textsuperscript{237}. In this same study, steady state concentrations of all metabolites were achieved after 2 days of administration, and PLP, PL and 4-PA elimination curves demonstrated that more than two compartments have to be taken into consideration\textsuperscript{237}.

In a study conducted in 90 patients administered 40 mg of oral PN hydrochloride per day, the following increases were observed after 3 days of treatment: 10-fold increase in plasma PLP, 50-fold increase of 4-PA and 100-fold increase of PL\textsuperscript{229}. This
study determined that steady state is achieved after 3 days of treatment, and further increases of the metabolites are not obtained by prolonged B6 supplementation\(^{229}\). Similarly, a study involving 8 females supplementing with oral doses of 10, 25, 50, 100 mg PN dissolved in 50 mL of water administered biweekly for 8 weeks found that the 100 mg PN dose failed to increase plasma PLP levels significantly above that after 50 mg\(^{238}\).

It is assumed that PLP does not increase in a dose-dependent manner as only a limited amount of PLP can be bound by albumin in plasma, and that excess is metabolized by alkaline phosphatase to PL and then 4-PA\(^{229,238}\). Pyridoxal-5’-phosphate has been found to correlate with albumin\(^{229}\) up to a maximum capacity of human serum proteins to bind PLP at 800 \(\mu g/mL\) which is exceeded in subjects given up to 50 mg PN daily\(^{239,240}\). These findings suggest that, ideally, to maintain optimum circulating PLP levels PN supplementation should either be administered in small, more frequent doses or delayed-release formulations.

Although the pharmacokinetics of PN hydrochloride and its metabolites have previously been studied, more accurate pharmacokinetic data on the active metabolite, pyridoxal-5’-phosphate, is required as the delayed-release preparation of Diclectin\(^\circledR\) may alter pharmacokinetic parameters resulting in variability of the therapeutic effect.
CHAPTER THREE

ADHERENCE AND TOLERABILITY OF IRON-CONTAINING PRENATAL MULTIVITAMINS IN WOMEN WITH PRE-EXISTING GI CONDITIONS
As previously discussed, prenatal multivitamin supplementation is important for the overall health and well-being for both the mother and fetus; unfortunately, adherence is not always optimal. Certain factors, such as GI symptoms, have been associated with reduced adherence to prenatal multivitamin supplementation. Iron supplements in the non-pregnant are associated with similar adverse GI effects; therefore, the role of iron content on the tolerability and adherence to prenatal multivitamin supplementation needs to be identified. Additionally, in pregnant women with pre-existing GI symptoms or conditions, the side effects may be more severe or existing symptoms may be exacerbated. The following study investigates the role of iron content on the tolerability and adherence to prenatal multivitamin supplementation in addition to severity of NVP in pregnant women with pre-existing GI conditions or symptoms.

This study has been published and is referenced as: Gill SK, Nguyen P, Koren G: Adherence and tolerability of iron-containing prenatal multivitamins in pregnant women with preexisting gastrointestinal conditions. J Obstet Gynaecol. 2009; 29(7): 594-8.
3.2 AUTHORS’ CONTRIBUTIONS

Simerpal Kaur Gill recruited and enrolled study subjects, conducted telephone interviews, collected and analyzed the data, and drafted the manuscript. Patricia Nguyen recruited and enrolled subjects, and conducted telephone interviews. Gideon Koren conceived of the study and its design, and edited the manuscript.
Background: Prenatal multivitamin supplementation is strongly recommended during pregnancy to help meet increased nutritional requirements for both mother and fetus. Suboptimal adherence, especially in women experiencing certain medical conditions, has been thought to be attributed to the high elemental iron content in prenatal multivitamins.

Objective: To quantify adherence and tolerability of iron-containing prenatal multivitamins in women with pre-existing gastrointestinal (GI) conditions.

Methods: Women who called either the Motherisk Helpline or the Nausea and Vomiting of Pregnancy Helpline between October 2004 and June 2008 who met the inclusion criteria were recruited. Women with (n=36) and without (n=166) pre-existing GI conditions who consented were randomized to either PregVit® (n=106) or Orifer F® (n=96). Monthly follow-up interviews were conducted to assess pill intake. Gastrointestinal adverse effects associated with prenatal multivitamin supplementation were assessed using the validated gastrointestinal symptom rating scale (GSRS).

Results: There was no observed difference in adherence in women experiencing pre-existing GI conditions randomized to PregVit® (51.0% ± 45.2) compared to Orifer F® (40.7% ± 43.9) (p=0.20). Women with preexisting GI conditions did have a significantly higher initial GSRS score (9.3 ± 5.5) as compared to controls (5.5 ± 4.3) (p<0.0001). However, the mean follow-up GSRS score was slightly higher in the control group randomized to Orifer F® (5.4 ± 4.4) compared to women with preexisting GI conditions randomized to either PregVit® (3.8 ± 3.6) or Orifer F® (3.9 ± 3.8). Women receiving
PregVit® (small tablet size and low iron) appear to have better relief of their NVP symptoms than those receiving Orifer F® (small tablet size and high iron).

**Conclusion:** Our study suggests that with the use of small size and low dose iron prenatal vitamin tablets, women with pre-existing GI conditions do not experience more GI adverse effects or lower adherence than women with no such conditions. Supplementing with small tablets of low dose iron prenatal multivitamins should be considered.
Prenatal multivitamin supplementation is strongly recommended during the periconceptual period. A plethora of evidence exists demonstrating the reduction of congenital malformations and other adverse pregnancy outcomes with folic acid-containing prenatal multivitamin supplementation\textsuperscript{15,16}. More recent evidence also suggests that maternal multivitamin supplementation in pregnancy can reduce the risk of certain pediatric cancers\textsuperscript{14,241}. Supplementation provides both the mother and fetus with the necessary vitamins and minerals that may not be consumed through the diet. Although women may intend to start and even begin prenatal multivitamin supplementation in pregnancy, compliance is often suboptimal\textsuperscript{9}.

Various factors have been proposed to explain low adherence to prenatal multivitamins. The majority of pregnant women experience nausea and vomiting of pregnancy (NVP)\textsuperscript{4}, and hence, swallowing a prenatal multivitamin may induce gagging and vomiting\textsuperscript{9}. Furthermore, adverse effects of prenatal multivitamins such as nausea, heartburn, acid reflux, stomach pain and constipation, may deter pregnant women from continuing supplementation\textsuperscript{7,50,158}. The presence of pre-existing medical conditions, especially those of the gastrointestinal (GI) tract, may also prevent women from continuing supplementation as they may exacerbate GI symptoms and enhance the severity of NVP\textsuperscript{7,8,50,158}.

Several previous studies have determined adherence and tolerability of prenatal multivitamins in pregnancy. In one randomized study, the compliance and tolerability of 2 prenatal multivitamins were compared\textsuperscript{17}. Compliance with Materna\textsuperscript{®} was found to be
lower compared with PregVit®; however, the differences in compliance could have been due to the much smaller size of PregVit® or the lower elemental iron content17. In a more recent randomized study, adherence of similar-sized, small prenatal multivitamins with different amounts of elemental iron, PregVit® and Orifer F®, was found to be similar; however, differences in tolerability and the effects of pre-existing GI medical conditions were not addressed10.

It has been estimated that 40-85 % of pregnant women suffer from pre-existing GI conditions, including gastroesophageal reflux disease, peptic ulcers, constipation, heartburn and infection with Helicobacter pylori18,135. The objective of the present study was to study factors that may affect adherence to prenatal multivitamins, specifically iron content and predisposing medical conditions, in women with pre-existing GI conditions.
3.5 METHODS

The Motherisk Program, located at the Hospital for Sick Children provides evidence-based information and counseling regarding the safety of medications and other exposures during pregnancy and lactation. For the present study, women who called either the general Motherisk Helpline or our Nausea and Vomiting of Pregnancy Helpline were recruited. Women were included if they were pregnant, had not started or had discontinued a prenatal multivitamin due to adverse side effects, had a preexisting GI condition, and consented to participate. Additionally, a control cohort was collected consisting of women who met the aforementioned criteria but who were not experiencing any GI conditions. Women were excluded if they had any hypersensitivity to any of the ingredients in the prenatal multivitamins used in the study, or if they had hemochromatosis, hemosiderosis, or hemolytic anemia.

Once oral consent was obtained, women were randomized using a computer-generated randomization system to one of two prenatal multivitamins already approved by Health Canada. PregVit® is available as two small separate pills (16 mm x 9 mm x 4 mm), one blue and one pink pill. The blue pill contains calcium, vitamin B12, vitamin D and 1.1 mg folic acid, and the pink pill contains the other necessary vitamins and mineral including 35 mg of elemental iron as ferrous fumarate. Orifer F® is available as a single, small, coated tablet (10 mm diameter, 5 mm thickness), and contains 60 mg of elemental iron as ferrous sulfate. Women were not provided with the prenatal multivitamins; they either had to obtain a prescription for PregVit® or purchase Orifer F® over-the-counter.
An initial intake form was completed, and subsequent follow-ups included a weekly follow-up and then monthly follow-ups until delivery. Initial data obtained included medical history, use of medications, severity of NVP as measured by the validated pregnancy-unique quantification of emesis (PUQE) scale\textsuperscript{65,242}, and the presence and severity of GI symptoms as measured by the validated GI symptom rating scale (GSRS)\textsuperscript{243-245}. The PUQE scale quantifies the severity of NVP by the number of hours of nausea, and the number of episodes of retching and vomiting in a 24 hour period; the GSRS rates GI symptoms including heartburn, acid reflux, indigestion, constipation, diarrhea, gas, bloating, belching, abdominal pain, and epigastric pain. Data collection at follow-ups included the aforementioned information as well as prenatal multivitamin pill counts, reasons for not starting or discontinuing the vitamins, including side effects, cost, size of pill, and any adverse effects experienced.

Mean adherence, PUQE and GSRS scores and their standard deviations were calculated. One-way analysis of variance was used to compare the mean scores of different characteristics among the groups with appropriate post hoc analysis if differences were detected, and paired t test was used to compare means within groups.

Statistical significance was determined using the SigmaStat program version 3.1 (Systat Software Inc., 2000, IL, USA).

The study was approved by the Research Ethics Board at the Hospital for Sick Children.
3.6 RESULTS

In total, 202 women were included in this study with 36 women experiencing preexisting GI symptoms, and 166 without any GI symptoms. Of the 36 women in the experimental group, 16 were randomized to receive PregVit®, and 20 were randomized to receive Orifer F®. In the control group, 90 were randomized to receive PregVit®, and 76 were randomized to receive Orifer F® (Figure 3.1).

![Breakdown of subject enrollment](image)

**Figure 3.1** Breakdown of subject enrollment

Mean adherence in women experiencing preexisting GI group randomized to PregVit® was 51.0% ± 45.2; whereas, those randomized to Orifer F® was 40.7% ± 43.9 (p=0.20) (Table 3.1). Mean adherence in the control group randomized to PregVit® was 42.5% ± 42.8, and mean adherence to Orifer F® was 43.6% ± 43.9 (p=0.73) (Table 3.1).
Table 3.1 Comparing the Adherence, Tolerability and Severity of NVP among women with or without pre-existing GI conditions randomized to Orifer F® or PregVit®; * = p<0.01

<table>
<thead>
<tr>
<th>Score</th>
<th>Pre-existing GI Conditions</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PregVit® (n=16)</td>
<td>Orifer F® (n=20)</td>
</tr>
<tr>
<td>Adherence (%)</td>
<td>51.0% ± 45.2</td>
<td>40.7% ± 43.9</td>
</tr>
<tr>
<td>GSRS</td>
<td>3.8 ± 3.6</td>
<td>3.9 ± 3.8</td>
</tr>
<tr>
<td>PUQE</td>
<td>3.6 ± 1.6</td>
<td>3.5 ± 1.9</td>
</tr>
</tbody>
</table>

Women with preexisting GI conditions exhibited a significantly higher initial GSRS score (9.3 ± 5.5) compared to controls (5.5 ± 4.3) (p<0.0001) (not shown). However, the mean follow-up GSRS score was slightly higher in the control group randomized to Orifer F® (5.4 ± 4.4) compared to women with preexisting GI conditions randomized to either PregVit® (3.8 ± 3.6) or Orifer F® (3.9 ± 3.8) (Table 3.1).

The gestational age at the onset of symptoms of NVP did not differ between experimental (5.0 weeks ± 1.4) and control (5.2 weeks ± 1.7) groups (p=0.59). Although initial mean PUQE scores did not differ between the experimental and control groups (6.6 ± 2.9 vs 5.8 ± 2.5, p=0.11), the mean PUQE score at follow-up was slightly higher in the control group randomized to Orifer F® (3.7 ± 1.8) compared to those randomized to PregVit® (3.3 ± 1.6) (Table 3.1).
Although there was no statistically significant difference in adherence, the total pill intake of PregVit® is actually greater than that of Orifer F® since women supplementing with PregVit® are required to take twice the amount of pills in the same time interval (twice a day versus once a day). Both multivitamins are of similar size and composition except for the lower elemental iron content (35 vs 60 mg) of PregVit® suggesting that this is the reason for the increased compliance.

Women randomized to Orifer F® who did not have any pre-existing GI conditions did experience a slightly higher GSRS suggesting that the higher iron content might have resulted in intolerability and adverse GI effects including abdominal pain, heartburn, acid reflux, indigestion, constipation or diarrhea. Furthermore, this group of women with iron-induced GI side effects experienced more severe nausea and vomiting of pregnancy as demonstrated by the slightly higher PUQE score. This finding is consistent with a recently published observational study demonstrating that women with heartburn or acid reflux experience greater severity of NVP, and the management of these symptoms can decrease the severity of NVP. In the current study, only 18.1% of controls were taking acid-reducing pharmacotherapy; whereas, 81.3% of women with pre-existing GI conditions were taking acid-reducing pharmacotherapy explaining why this cohort experienced lower GSRS and PUQE scores. Similarly, of the 81.3% of women with pre-existing GI conditions on these medications, 50% were supplementing with Orifer F® suggesting that this greater proportion of use resulted from GI side effects
women were experiencing. However, due to the management of GI symptoms, increased GSRS and PUQE scores were not observed.

In the present study, the sample size of women with preexisting GI conditions was limited, and therefore, had potentially insufficient statistical power significance for increased adherence of PregVit® although a trend was observed. Furthermore, our results do not allow for a comparison between the tolerability of ferrous fumarate and ferrous sulfate in pregnant women; however, a previous study has demonstrated that adherence to both ferrous fumarate and ferrous sulfate compared to other iron preparations is poor due to adverse GI effects. Our results suggest that there are increased GI effects with the use of ferrous sulfate; however, whether these effects are due to the specific salt form or to higher iron content cannot be presently determined.

The prenatal multivitamin supplements were not provided in this study; women were required to obtain Orifer F® over-the-counter, and PregVit® through a prescription. A small proportion of women did not start supplementation with PregVit® immediately after enrolling as they choose to wait until their next doctor’s appointment. On the other hand, a similar proportion of women did not start Orifer F® immediately as they chose to wait until the next time they were going to the pharmacy. Cost of prenatal multivitamins did not appear to be a factor for the women enrolled in our study albeit during the recruitment phase some women did not consent to participate as either they did not have drug coverage and would prefer to purchase less expensive generic vitamins, or they did have coverage and would prefer to supplement with PregVit®. Results from our study are similar with a previous finding that demonstrates the most
common predictors of prenatal multivitamin adherence are fear of, or experiencing, nausea, vomiting, gagging or constipation, and health-care provider advice. Based on previous findings and ethical considerations, we chose Orifer F® and PregVit® as they are of smaller size and are less likely to induce gagging than larger sized tablets, and because they contain at least the minimum Recommended Dietary Allowance of iron of 27 mg as recommended by various organizations such as the Society of Obstetricians and Gynaecologists of Canada and the American College of Obstetricians and Gynecologists. On the other hand, in other countries such as the United Kingdom, iron supplementation is not routinely administered in the first trimester unless a pregnant women presents with anemia. Based on our findings, this strategy may be more successful in increasing adherence to prenatal multivitamins.

In conclusion, our study suggests that women with pre-existing GI conditions may benefit from low dose iron-containing prenatal multivitamins in a small tablet size. Since iron supplementation is not necessary for every pregnant woman, and intolerability leads to suboptimal adherence of iron-containing prenatal multivitamins, similar to the United Kingdom approach, emphasis should be placed on supplementing with low dose or iron-free prenatal multivitamins especially in non-anemic women with pre-existing GI conditions.
3.8 CONCLUSION

The findings from this study suggest that iron content does have an impact on the tolerability and adherence to prenatal multivitamin supplementation in pregnant women with pre-existing GI conditions. Furthermore, iron-containing prenatal multivitamin supplements appear to exacerbate symptoms of NVP. In women with no previous history or current low iron status, low dose or iron-free prenatal multivitamins may increase tolerability, and hence, adherence, especially in those already experiencing GI symptoms.
CHAPTER FOUR

THE EFFECTIVENESS OF DISCONTINUING IRON-CONTAINING PRENATAL MULTIVITAMIN SUPPLEMENTS ON THE SEVERITY OF NVP
Our previous findings suggest that iron content may play a role in increasing symptoms of NVP. To our knowledge, no studies have examined the role of iron-containing prenatal multivitamins on the severity of NVP. If confirmed, our findings provide strong evidence to decrease or eliminate iron from prenatal multivitamins in the first trimester of pregnancy.

This study has been published and is referenced as: Gill SK, Maltepe C, Koren G: The effectiveness of discontinuing iron-containing prenatal supplements in reducing the severity of nausea and vomiting of pregnancy. J Obstet Gynaecol. 2009; 29(1): 13-16.
∞ 4.2 AUTHORS’ CONTRIBUTIONS ∞

Simerpal Kaur Gill conceived the study design, recruited and enrolled subjects, conducted telephone interviews, collected and analyzed the data, and drafted the manuscript. Caroline Maltepe conceived the notion, recruited and enrolled subjects, conducted telephone interviews, and revised the manuscript. Gideon Koren conceived the notion of the study, and revised the manuscript.
Background: Nausea and vomiting of pregnancy (NVP) is experienced by the majority of pregnant women, and can negatively affect a women’s quality of life. It has been suggested in observational studies that iron-containing prenatal multivitamins may increase the severity of NVP. The objective of this study was to determine whether decreasing iron exposure can mitigate NVP symptoms.

Design: Data were collected from a prospective cohort at the Motherisk Program in Toronto. Women (n=97) seeking advice on managing severe NVP were advised to discontinue prenatal multivitamin administration and switch to folic acid, an adult multivitamin or a children’s chewable multivitamin.

Results: Two-thirds (63 out of 97) (p<0.001) of those women qualitatively reported an improvement in NVP symptoms after discontinuation of iron-containing prenatal multivitamins. These findings were verified quantitatively using both the PUQE (p<0.001) and Well-being (p<0.001) scoring systems.

Conclusions: This is the first interventional study showing that discontinuation of iron results in improvement of NVP symptoms. Our data suggest that avoiding iron-containing prenatal multivitamins in the first trimester is effective in improving NVP symptoms in the majority of pregnant women suffering from morning sickness.
4.3 INTRODUCTION

Nausea and vomiting of pregnancy (NVP) is experienced by 80% of pregnant women. Symptoms commonly occur between the fourth to ninth weeks of pregnancy until the twelfth to sixteenth weeks of pregnancy; however, for 20% of pregnant women, symptoms persist throughout pregnancy of which 1% to 3% experience the most severe form, hyperemesis gravidarum. NVP can drastically impact a woman’s quality of life and her ability to function especially when improperly managed. Causative factors that may trigger or worsen NVP need to be identified to help manage this condition appropriately. Certain factors have been shown to aggravate NVP including certain medical conditions such as acid reflux, migraines and thyroid disorders, maternal age at conception, gravidity and the use of iron containing prenatal multivitamin supplementation.

Multivitamin supplementation in pregnancy has been shown to be important for the health and well-being of both mother and child. It has been very well established that nutritional requirements for pregnant women are often not met through diet alone; therefore, to ensure that sufficient metabolic demands are being met, and that adverse health outcomes are prevented, neonatal multivitamin supplementation is strongly recommend by health authorities. Recent studies have shown that folate-containing prenatal multivitamin supplementation may decrease the risk for congenital anomalies, in addition to prevention of neural tube defects, as well as decreasing the risks for certain pediatric cancers. Despite the strong evidence to support the use of folate in the periconceptional period, a large proportion of women do not use, or
discontinue multivitamins in pregnancy\textsuperscript{9}. Discontinuation of multivitamin supplementation is usually associated with factors such as tablet size, and pre-existing gastrointestinal conditions and/or symptoms which can worsen NVP\textsuperscript{10}.

An important factor in NVP associated with multivitamin supplementation during pregnancy is the iron content\textsuperscript{247}. Iron is an important mineral in pregnancy especially since most women do not consume sufficient amounts through their diet to replenish iron stores. To avoid iron-deficiency anemia in pregnancy, the recommended daily dose is 27 mg\textsuperscript{12}, and iron content in prenatal multivitamins ranges from 27 – 60 mg. Iron, however, is associated with adverse effects including heartburn, constipation, diarrhea, nausea and vomiting\textsuperscript{11}. These symptoms can either directly or indirectly aggravate NVP symptoms already experienced by pregnant women leading to discontinuation of prenatal multivitamin supplementation.

The primary objective of this study was to quantify the effectiveness of discontinuation of iron on the severity of NVP.
4.5 METHODS

The Motherisk Program, located at the Hospital for Sick Children in Toronto, has a specialized helpline for the management of NVP, which, we believe is the only such service worldwide. Women from Canada and the US who are experiencing NVP can call a toll-free information service to receive pharmacological and non-pharmacological advice on the management of NVP. This evidence-based counseling is standardized so that every woman is offered similar strategies to help manage her NVP. The intervention evaluated in the present study is routine in our service; women suffering from NVP are advised to discontinue their iron-containing prenatal vitamins substituting it with a preparation not containing iron.

All data collected by the NVP Helpline from January 2005 to April 2007 were evaluated. Inclusion criteria consisted of women who had previously been using a prenatal multivitamin at the time of initial counseling, and who were advised to discontinue the iron-containing prenatal multivitamin and to switch to folic acid with either an adult multivitamin or a children’s chewable multivitamin. Women who did not meet these requirements or those who were not stabilized on their medication to manage NVP, if they were taking any, were excluded from analysis. A standard follow-up interview was conducted by telephone, where a detailed quantification of symptoms was obtained: 1) a self-report of how the woman perceived her symptoms at follow-up (better, same, or worse); 2) validated quantitative scores were obtained including, a) the Pregnancy-Unique Quantification of Emesis and nausea (PUQE) score was measured at baseline and after the intervention, and b) The Well-Being score ranging
from 0 to 10 was recorded based on how the woman felt overall compared to how she felt before pregnancy. We also recorded the time of the NVP symptoms that appeared, other medical conditions, gravidity, maternal age at conception, gestational age at the initial interview and gestational age at follow-up.

Mean PUQE and Well-being scores were calculated at the initial interview and after the intervention. The paired t test was used to compare the mean scores between the initial and final scores within groups, and Kruskal-Wallis test with post-hoc Dunn’s test was used to compare the mean PUQE and Well-being scores among the groups. Chi-square and Fisher’s Exact test were used to calculated differences in categorical values.
4.6 RESULTS

Out of 97 patients meeting our inclusion criteria, 63 women reported improvement in NVP after discontinuation of the iron-containing prenatal vitamins. Overall, compared to women who reported feeling either the same or worse, there was a favourable effect in 65% of the women ($p<0.001$). There were no significant differences in both the initial PUQE scores ($p=0.18$) (Figure 4.1) or the initial Well-being scores ($p=0.24$) (Figure 4.1) among the three groups (better, same, worse). After the intervention, the women who reported improvement had a significantly lower PUQE score: better vs same ($p<0.001$), better vs worse ($p<0.001$) and same vs worse ($p<0.05$) (Figure 4.1). Similarly, there were significant differences in the final Well-being score between better vs same ($p<0.001$) and better vs worse ($p<0.001$) (Figure 4.1).

**Figure 4.1** The severity of NVP after discontinuation of iron-containing prenatal multivitamins

There were no significant differences in the maternal age, gestational age, gravidity, and the onset of NVP between the responders and the rest (Table 4.1).
Table 4.1 Confounding factors among women reported feeling “better”, “the same” or “worse” after discontinuation of iron-containing prenatal multivitamins

<table>
<thead>
<tr>
<th>Confounding Factor</th>
<th>Mean value ± standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at conception (years)</td>
<td>Better: 31.5 ± 5.0</td>
</tr>
<tr>
<td></td>
<td>Same: 32.7 ± 4.1</td>
</tr>
<tr>
<td></td>
<td>Worse: 34.1 ± 4.8</td>
</tr>
<tr>
<td>Gravidity</td>
<td>Better: 2.0 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>Same: 2.4 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>Worse: 2.0 ± 1.1</td>
</tr>
<tr>
<td>Gestational age at initial interview (weeks)</td>
<td>Better: 9.8 ± 3.9</td>
</tr>
<tr>
<td></td>
<td>Same: 9.5 ± 3.5</td>
</tr>
<tr>
<td></td>
<td>Worse: 9.1 ± 1.9</td>
</tr>
<tr>
<td>Gestational age at follow-up (weeks)</td>
<td>Better: 12.5 ± 3.9</td>
</tr>
<tr>
<td></td>
<td>Same: 11.4 ± 3.7</td>
</tr>
<tr>
<td></td>
<td>Worse: 11.3 ± 2.7</td>
</tr>
<tr>
<td>Gestational age at onset of NVP (weeks)</td>
<td>Better: 5.7 ± 3.4</td>
</tr>
<tr>
<td></td>
<td>Same: 5.8 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>Worse: 6.2 ± 1.9</td>
</tr>
<tr>
<td>Prevalence of Medical Conditions (number of women)</td>
<td>Better: 32 *</td>
</tr>
<tr>
<td></td>
<td>Same: 19 *</td>
</tr>
<tr>
<td></td>
<td>Worse: 0</td>
</tr>
</tbody>
</table>

There were significant differences in the prevalence of medical conditions among the groups, with women reporting improvement having more medical conditions compared to women who felt worse (p=0.04 and p=0.005, respectively) (Table 4.1). There were no significant differences in the prevalence of medical conditions among women who reported feeling better and women who reported feeling the same (p=0.08).
**4.7 DISCUSSION**

Our data document the effectiveness of withholding iron in improving the severity of NVP, and hence, highlights the role of iron in aggravating this condition. The majority of women reported feeling better within several days of discontinuing their iron-containing prenatal multivitamins indicating that it was the removal of the iron and not the natural resolution of NVP symptoms. In addition to subjective reports, the women who reported feeling better had lower PUQE scores and higher Well-being scores.

Certain potential confounding factors were considered in our analysis. It has been shown that as maternal age or the number of pregnancies increase\textsuperscript{55}, women are more likely to experience NVP. We did not detect differences in maternal age or gravidity among those who improved and those who did not. Furthermore, the gestational ages did not differ at the time of the initial interview and at the time of follow-up among the three groups. Similarly, the gestational age at time of initial NVP symptoms did not differ between the three groups as well. These results indicate no differences among the three groups in factors that are associated with increased risk and severity of NVP. It appears, though, that women with preexisting medical conditions were more likely to benefit from the removal of iron.

Previous studies have alluded that the adverse effects of prenatal multivitamin supplementation are due to iron content. In a recent study involving 164 women post-partum, almost half reported at least one adverse effect from iron supplements including constipation (27.4\%) and nausea (10.8\%)\textsuperscript{11}. Other studies have also indicated
that compliance is negatively affected by the adverse effects of iron especially in women who are experiencing NVP and gastrointestinal conditions\textsuperscript{9,247}. In one randomized, crossover, open labeled study in 135 pregnant women, the compliance and tolerability between PregVit\textsuperscript{®}, a prenatal vitamin taken twice a day with iron (35 mg) in one pill and calcium in the other pill, and Materna\textsuperscript{®} (60 mg iron) were determined\textsuperscript{17}. Compliance with the use of PregVit\textsuperscript{®} and Materna\textsuperscript{®} were similar; however, women who were using PregVit\textsuperscript{®} experienced a 30% reduction in constipation rate as compared to Materna\textsuperscript{®}\textsuperscript{17}. Furthermore, compliance of Materna\textsuperscript{®} was negatively associated with the severity of NVP; whereas, no such correlation was found for PregVit\textsuperscript{®}\textsuperscript{17}. While the adverse effects of iron on NVP have been inferred, this is the first interventional study showing that removal of iron from prenatal multivitamins results in symptom improvement.

In the present study, the amount of iron in the prenatal multivitamins varied between 27 and 60 mg. Our sample size was insufficient to study the dose characteristics of the adverse effects of iron; however, this study provides a strong rationale to conduct a randomised controlled trial to determine the effects of iron-containing prenatal multivitamins on the severity of NVP.

Most cases of NVP subside by the end of the first trimester of pregnancy. During the first trimester there are no increased requirements for iron, and hence, decreasing or avoiding iron supplementation in women suffering from NVP should not lead to iron deficiency. If NVP persists in the second and third trimesters, iron should be supplemented either orally or, if NVP is still severe, parenterally. This practice of not
supplementing routinely with iron in the first trimester is already successfully conducted in the United Kingdom.
4.8 CONCLUSION

Our findings demonstrate that discontinuing iron-containing prenatal multivitamins decreases the severity of NVP. These results provide strong evidence to decrease or eliminate iron from prenatal multivitamins in the first trimester of pregnancy to minimize NVP and other GI symptoms. Eliminating the majority of adverse effects associated with the iron content in prenatal supplements would, presumably, lead to increased adherence, and hence, improvements in maternal and fetal nutrition and health.
CHAPTER FIVE

THE EFFECT OF HEARTBURN AND ACID REFLUX ON THE SEVERITY OF NVP
Anecdotal evidence has demonstrated that GI symptoms or conditions such as heartburn and acid reflux may result in nausea and vomiting. Additionally, based on the proposed etiology of NVP, GI conditions would appear to contribute to symptoms of nausea and vomiting. This study focuses on the relationship between heartburn and acid reflux and the severity of NVP.

This study has been published and is referenced as: Gill SK, Maltepe C, Koren G: The effect of heartburn and acid reflux on severity of nausea and vomiting of pregnancy. Can J Gastroenterol. 2009; 23(4): 270-272.
5.2 AUTHORS’ CONTRIBUTIONS

Simerpal Kaur Gill conceived the study design, recruited and enrolled subjects, conducted telephone interviews, collected and analyzed the data, and drafted the manuscript. Caroline Maltepe conceived the notion, recruited and enrolled subjects, conducted telephone interviews, and revised the manuscript. Gideon Koren conceived the notion of the study, and revised the manuscript.
5.3 ABSTRACT

**Background**: Heartburn (HB) and acid reflux (RF) in the non-pregnant population can cause nausea and vomiting; therefore, it is plausible that in women with nausea and vomiting of pregnancy (NVP), HB/RF may increase the severity of symptoms.

**Objective**: To determine whether HB/RF during pregnancy contribute to increased severity of NVP.

**Methods**: A prospectively collected cohort of women who were experiencing NVP and HB, RF or both (n=194) was studied. The Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) scale and the Well-being scale were used to compare the severity of the study cohort’s symptoms. This cohort was compared with a group of women experiencing NVP but no HB/RF (n=188). Multiple linear regression was used to control for the effects of confounding factors.

**Results**: Women with HB/RF reported higher PUQE scores (9.6 ± 2.6) compared with controls (8.9 ± 2.6) (p=0.02). Similarly, Well-being scores for women experiencing HB/RF were lower (4.3 ± 2.1) compared with controls (4.9 ± 2.0) (p=0.01). Multiple linear regression demonstrated that increased PUQE scores (P=0.003) and decreased Well-being scores (P=0.005) were due to the presence of HB/RF as opposed to confounding factors such as pre-existing gastrointestinal conditions/symptoms, *hyperemesis gravidarum* in previous pregnancies and co-morbidities.

**Conclusion**: The present cohort study is the first to demonstrate that HB/RF are associated with increased severity of NVP. Managing HB/RF may improve the severity of NVP.
5.4 INTRODUCTION

Symptoms of nausea and vomiting of pregnancy (NVP), experienced by 80% of pregnant women, typically start between the fourth to ninth weeks of pregnancy until the twelfth to sixteenth weeks of pregnancy. Unfortunately, in 20% of pregnant women, symptoms persist throughout pregnancy of which 1% to 3% of women experience hyperemesis gravidarum (HG). NVP can severely affect a woman’s quality of life and her ability to function, especially when improperly managed. Certain factors have been shown to aggravate NVP including migraines, thyroid disorders, maternal age at conception, gravidity, and the use of iron containing prenatal multivitamin supplementation.

Heartburn (HB) and acid reflux (RF) are common medical disorders; it has been estimated that the incidence of gastroesophageal reflux disorders in pregnancy ranges between 40% to 85%. The onset of HB/RF can occur any time during pregnancy. In one study, 52% of the symptoms began in the first trimester and almost all by the second trimester with only 8% of symptoms beginning in the third trimester. Other studies reported increased severity and frequency of symptoms as gestational age increases. Regardless of the time of onset, anecdotal clinical evidence suggests that the presence of pre-existing gastrointestinal (GI) conditions and/or symptoms as well as HB/RF during pregnancy aggravate nausea and vomiting.

Although the symptoms of HB/RF do not differ in the pregnant versus the non-pregnant population, their etiology may. Changes in motility of the gastrointestinal tract (GIT) due to increased levels of circulating female hormones result
in increased GIT symptoms in pregnancy\textsuperscript{135,136,144-146}. Specifically, a decrease in lower esophageal sphincter pressure in pregnancy accompanied by HB has been demonstrated\textsuperscript{144}. Furthermore, decrease in sphincter pressure occurs in the presence of estrogen and progesterone among female volunteers using oral contraceptives\textsuperscript{145,146}. Similar changes in gastric motility and dysrhythmias have been observed in NVP\textsuperscript{7}. Therefore, it is biologically plausible that HB/RF contribute to the severity NVP. If confirmed, this hypothesis can lead to improvement in the management of NVP by treating symptoms of RF.

The objective of the present study was to determine whether pregnant women suffering from HB, RF or both experience increased severity of NVP.
5.5 METHODS

The Motherisk Program, located at the Hospital for Sick Children in Toronto, Ontario, has a specialized helpline for the management of NVP. Women from Canada and the United States experiencing NVP can call a toll-free service to receive pharmacological and non-pharmacological advice on the management of NVP. This evidence-based counseling is based on research and continuous systematic review of all emerging clinical and experimental evidence.

For the purpose of the present study, a prospective cohort of women counseled by the NVP Helpline from January 1, 2007 to December 31, 2007, was analyzed. The study group consisted of all women who experienced HB/RF while suffering from NVP. A comparison cohort consisting of women who experienced NVP, but not HB/RF was also collected from the same time period. A standard interview was conducted, where detailed quantification of symptoms was obtained using the following tools: 1) the Pregnancy-Unique Quantification of Emesis and nausea (PUQE) score\textsuperscript{63}; 2) The Well-Being score\textsuperscript{15} ranging from 0 (the worse possible) to 10 (the best possible) was recorded based on how the woman felt overall compared to how she felt before pregnancy; and 3) a self-report of how the woman perceived her symptoms (mild, moderate, severe). In addition, the time of onset of the NVP symptoms, gravidity, maternal age at conception, gestational age at the initial interview, other medical conditions, pre-existing GI conditions or symptoms, medication use and the severity of NVP in previous pregnancies were recorded.
Unpaired t test was used to compare the mean scores of different characteristics between the two groups. Characteristics that were found to be statistically different between the two groups were included in a multiple linear regression model to determine factors that contributed to the differences in the PUQE and Well-being scores observed between the two groups.

Statistical significance was set at $P<0.05$ and conducted with the SigmaStat program version 3.1 (Systat Software Inc., 2000, IL, USA).
5.6 RESULTS

Of 194 women in the HB/RF group, 60 experienced only heartburn, 42 experienced only RF, and 92 reported on both HB and RF. Self-reported severity of NVP was statistically different between the groups with 75% of women experiencing both HB and RF classifying their NVP as severe, whereas, only 48% of women in the control group (90 of 188) classified their NVP as severe (p<0.0001) (Table 5.1). Seventy per cent of women with only acid reflux self-reported their NVP as severe which was significantly higher than among controls (p=0.009) (Table 5.1). Additionally, in the HB/RF group, there were statistically fewer women who classified their NVP as moderate (31%) compared to control (47.4%) (p=0.04), and no women experiencing both HB and RF classified their NVP as mild compared to 4.5% of controls (p=0.002) (Table 5.1).

<table>
<thead>
<tr>
<th>Scales to measure NVP severity</th>
<th>Control: NVP only (n=194)</th>
<th>Study Group: NVP + HB/RF (n=188)</th>
<th>Subset of Study Group: NVP + HB + RF (n=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% self-reported as:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe</td>
<td>48.0</td>
<td>67.8 *</td>
<td>75.3 *</td>
</tr>
<tr>
<td>moderate</td>
<td>47.4</td>
<td>30.6 *</td>
<td>24.7 *</td>
</tr>
<tr>
<td>mild</td>
<td>4.5</td>
<td>1.6 *</td>
<td>0 *</td>
</tr>
<tr>
<td>PUQE score</td>
<td>8.9 ± 2.6</td>
<td>9.6 ± 2.6 *</td>
<td>10.0 ± 2.4 *</td>
</tr>
<tr>
<td>Well-being score</td>
<td>4.9 ± 2.0</td>
<td>4.3 ± 2.1 *</td>
<td>3.9 ± 2.1 *</td>
</tr>
</tbody>
</table>

The PUQE scores corroborated the self-reports: the mean PUQE score of women experiencing both HB and RF was higher (9.6 ± 2.6) compared with controls (8.9 ± 2.6); this difference in score was statistically significant (p=0.02) (Table 5.1). Women
experiencing both HB and RF had the highest mean PUQE score (10.0 ± 2.4) which was found to be significantly higher than in controls (p<0.0004) (Table 5.1).

The Well-being scores reflected a similar pattern. The mean score of controls (4.9 ± 2.0) was higher than in the HB/RF group (4.3 ± 2.1) (p<0.01), and significantly higher than the mean Well-being score of women experiencing both HB and RF (3.9 ± 2.1) (p<0.0004) (Table 5.1).

Potential confounding factors were compared; no differences between control and HB/RF in maternal age at conception, gravidity, gestational age at onset of symptoms, gestational age at interview, multiple gestation, and vitamin use were found. In contrast, there were higher rates of anti-emetic use (p=0.0001) and the use of antacids (p<0.0001) in the HB/RF group. Similarly, there was significantly higher prevalence of pre-existing gastrointestinal conditions/symptoms (p=0.004), co-morbidities (p<0.0001), and history of severe NVP or hyperemesis gravidarum in previous pregnancies (p=0.03) in the HB/RF group when compared with the controls.

These aforementioned characteristics that were found to be statistically different between the two groups were incorporated into a multiple linear regression analysis. The multiple linear regression analysis revealed that the presence of HB/RF could predict PUQE scores (p=0.03) as did pre-existing gastrointestinal conditions/symptoms (p=0.045). Similarly, the presence of HB/RF solely accounted for the ability to predict Well-being scores (p=0.02). When only the subset of women experiencing both HB and RF was analyzed, again, the presence of HB/RF solely predicted PUQE scores (p=0.002), and Well-being scores (p=0.006).
5.7 DISCUSSION

Our data demonstrate that women experiencing heartburn and/or acid reflux in pregnancy experience increased severity of NVP as indicated by validated tools for NVP. Furthermore, assuming women experiencing both HB and RF have increased severity of disease compared with women who have heartburn alone, trends were observed where more women experiencing both HB and RF classified their NVP as severe compared to control, and compared to women only experiencing either HB or RF. These same trends were observed in both the PUQE scores and the Well-being scores, indicating that more severe symptoms result in increased severity of nausea and vomiting.

Despite dearth of studies examining the relationship between HB and RF and severity of NVP, several references recommend treatment of HB/RF during pregnancy to reduce pregnancy complications.\textsuperscript{18,135-138}

Certain potential confounding factors were considered in our multiple linear regression analysis and demonstrated that the only factor that could consistently account for the increased PUQE scores and the decreased Well-being scores observed in the study group was the presence of HB/RF. Furthermore, the increased use of antiemetics and antacids observed in the HB/RF group confirms the increased severity of NVP, and the presence of heartburn and/or acid reflux, respectively.

Our study documents for the first time, a correlation between HB/RF and increased severity of NVP. Future controlled studies should determine whether treatment of HB/RF in pregnancy can reduce the severity of NVP.
5.8 CONCLUSION

The current study demonstrates that heartburn and/or acid reflux in pregnancy are associated with more severe symptoms of NVP suggesting that management of these GI symptoms can improve the severity of NVP. This hypothesis, however, remains to be tested.
CHAPTER SIX

THE EFFECT OF ACID-REDUCING PHARMACOTHERAPY ON THE SEVERITY OF NVP
Our previous findings have demonstrated that heartburn and acid reflux symptoms increase the severity of NVP. Seemingly, treatment with either H2 blockers or PPIs to manage HB/RF should, in turn, reduce the severity of NVP. This study focuses on the relationship between acid-reducing pharmacotherapy and the severity of NVP.

This study has been accepted for publication and is referenced as: Gill SK, Maltepe C, Mastali K, Koren G: The effect of acid-reducing pharmacotherapy on severity of nausea and vomiting of pregnancy. Obstet Gynecol Int 2009; doi:10.1155/2009/585269.
6.2 AUTHORS’ CONTRIBUTIONS

Simerpal Kaur Gill conceived the study design, recruited and enrolled subjects, conducted telephone interviews, collected and analyzed the data, and drafted the manuscript. Caroline Maltepe conceived the notion, recruited and enrolled subjects, conducted telephone interviews, and revised the manuscript. Katayoon Mastali recruited and enrolled subjects, and conducted telephone interviews. Gideon Koren conceived the notion of the study, and revised the manuscript.
Background: Heartburn and acid reflux (HB/RF) are associated with increased severity of nausea and vomiting. The ability of acid-reducing drugs to reduce symptoms of nausea and vomiting of pregnancy has not been previously tested.

Objective: To determine whether acid-reducing pharmacotherapy decreases the severity of NVP symptoms.

Methods: We studied a cohort of women experiencing NVP, who were also experiencing HB/RF. Women were counseled to commence acid-reducing pharmacotherapy. The effectiveness of the acid-reducing medication in decreasing symptoms of both HB/RF, and NVP was measured.

Results: Acid-reducing drugs resulted in significant decreases in PUQE (9.6 ± 3.0 to 6.5 ± 2.5) (p<0.0001), and Well-being scores from the initial (4.0 ± 2.0) to the follow-up interview (6.8 ± 1.6) (p<0.0001). After intervention with acid-reducing pharmacotherapy, a reduction in acid symptoms was found to predicted reduction in NVP symptoms (R=0.85, p<0.001).

Conclusion: This is the first study to demonstrate that management of HB/RF can reduce the severity of NVP.
Nausea and vomiting of pregnancy (NVP) is the most common medical condition in pregnancy, experienced by up to 80% of women. NVP has been shown to severely affect a woman’s quality of life and her ability to function, especially when improperly managed. Anti-emetics are usually successful in managing NVP; however, certain medical conditions or symptoms, such as heartburn (HB) and/or acid reflux (RF), can exacerbate the severity of NVP.

Heartburn and/or acid reflux are common medical disorders; it has been estimated that the incidence of gastroesophageal reflux disorders in pregnancy ranges between 40% to 85%. Symptoms associated with gastroesophageal reflux disorders or dyspepsia may include heartburn, acid reflux, regurgitation, eructation, flatulence, stomach bloating, indigestion, and a sensation of a lump in the throat, and may even affect quality of sleep. These aforementioned symptoms can occur any time during pregnancy, and the severity of symptoms ranges possibly as a result of gastrointestinal tract motility changes due to increased levels of circulating sex hormones. Similar changes in gastric motility and dysrhythmias have been observed in women suffering from NVP.

In a recent prospective, cohort study, we demonstrated that women experiencing both NVP and HB/RF (n=194) experienced greater severity of NVP compared to women who did not have any HB/RF (N=188) after controlling for certain confounders. Trends were observed with more women experiencing both heartburn and acid reflux classifying their NVP as severe compared to controls, and compared to
women only experiencing either heartburn or acid reflux. However, presently no study has examined the effectiveness of pharmacotherapy on NVP symptoms.

The objective of this study was to quantify whether acid-reducing pharmacotherapy is effective in decreasing the severity of NVP in women experiencing HB/RF.
6.5 METHODS

The Motherisk Program, located at the Hospital for Sick Children in Toronto, has a specialized helpline for the management of NVP. Women from Canada and the US experiencing NVP can call a toll-free service (1-800-436-8477) to receive pharmacological and non-pharmacological advice on the management of NVP. This evidence-based counseling is based on research and continuous systematic review of emerging clinical and experimental evidence.

For the purpose of the present study, we enrolled women counseled by the NVP Helpline from November, 2007 to June, 2008. The study group consisted of all women who experienced HB/RF while suffering from NVP. As per our standard, evidence-based counseling, these women were advised by us to commence on acid-reducing pharmacotherapy, and based on the severity of their HB/RF symptoms and on previous pregnancy use, if any, antacids, histamine 2 (H2) blockers or proton pump inhibitors (PPIs) were recommended. Additionally, as H2 blockers are available over-the-counter in Canada, usually they are recommended initially. All women agreed to continue their antiemetic at the dose taken prior to adding the acid-reducing medication. Women who changed their antiemetic dose were excluded from analysis.

A standard interview was conducted, where detailed quantification of symptoms was obtained using the following validated tools: 1) the Pregnancy-Unique Quantification of Emesis and nausea (PUQE) score; 2) The Well-Being score ranging from 0 to 10 was recorded based on how the woman felt overall compared to how she felt before pregnancy; 3) a self-report of how the woman perceived her symptoms
(mild, moderate, severe). In addition, we recorded the time of onset of the NVP symptoms, gravidity, maternal age at conception, gestational age at the initial interview and at follow-up, medical conditions that are associated with increased severity of NVP, medication use and the severity of NVP in previous pregnancies.

A standard follow-up interview was subsequently conducted to determine PUQE and Well-being scores, and to inquire as to the acid-reducing pharmacotherapy used. To determine the role of acid-reducing pharmacotherapy in decreasing the severity of NVP, women were asked to rate on a scale of 0 to 10, the effectiveness of their medication in reducing their acid symptoms, and the effectiveness of this medication in reducing their NVP.

Paired t test was used to compare the mean PUQE and Well-being scores between the initial and follow-up interviews. Linear regression was used to determine the relationship between the reduction in heartburn and acid reflux and NVP. Similarly, linear regression was also performed on the initial PUQE scores and the change in PUQE scores, and on the onset of NVP and the onset of symptoms of HB/RF.

Statistical analyses were conducted with the SigmaStat program version 3.1 (Systat Software Inc., 2000, IL, USA).
**6.6 RESULTS**

Of 140 women, there were 80 women who experienced HB/RF but were not stabilized on antiemetics, and therefore, were excluded from our analysis. The final cohort consisted of 60 women with NVP: 14 experienced only heartburn, 35 experienced only acid reflux, and 11 reported on both heartburn and acid reflux. Of the women included in our analysis, the self-reported severity of NVP was as follows: 72% of women classified their NVP as severe, 19% as moderate, and 9% as mild.

Mean gestational ages at initial counseling and at follow-up were 9.6 ± 3.8 weeks and 12.4 ± 2.1 weeks, respectively. Mean gestational age at onset of NVP was at 5.5 ± 3.0 weeks, and mean gestational age at which symptoms of HB/RF occurred was 6.8 ± 2.4 weeks. Additionally, linear regression demonstrated that the onsets of NVP and HB/RF were significantly correlated (R=0.5, p=0.004).

There were no significant differences in PUQE scores of women excluded from the study and initial PUQE scores of women included in the study (9.5 ± 2.5 and 9.6 ± 3.0) (p=0.2376). Use of acid-reducing medication resulted in a significant decrease in PUQE scores at follow-up (from 9.6 ± 3.0 to 6.5 ± 2.5) (p<0.0001) (Table 6.1). Similarly, there was a significant improvement in the Well-being scores from the initial (4.0 ± 2.0) to the follow-up interview (6.8 ± 1.6) (p<0.0001) (Table 6.1).
Table 6.1 Severity of NVP before and after intervention with acid-reducing pharmacotherapy; *\(=p<0.05\) compared to initial interview, \((n=60)\)

<table>
<thead>
<tr>
<th>Measures</th>
<th>Initial Interview</th>
<th>Follow-up Interview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PUQE score ± SD</td>
<td>9.5 ± 2.7</td>
<td>6.5 ± 2.5 *</td>
</tr>
<tr>
<td>Mean Well-being score ± SD</td>
<td>4.0 ± 2.0</td>
<td>6.8 ± 1.6 *</td>
</tr>
<tr>
<td>Mean effectiveness of acid therapy in reducing HB/RF</td>
<td>n/a</td>
<td>8.2/10</td>
</tr>
<tr>
<td>Mean effectiveness of acid therapy in reducing NVP</td>
<td>n/a</td>
<td>7.7/10</td>
</tr>
</tbody>
</table>

The most commonly used acid-reducing pharmacotherapy were H2 blockers, used by two-thirds of women \((40/60)\). Proton pump inhibitors were used by 13 out of 60 women, and other over-the-counter antacids were used by 7 out of 60 women. The mean effectiveness of acid-reducing pharmacotherapy rated by the women was 8.2 out of 10, and the mean effectiveness of the acid-reducing pharmacotherapy in reducing NVP was 7.7 out of 10. Women noticed improvement, on average, 3 to 4 days after commencing acid-reducing pharmacotherapy. Linear regression demonstrated that a reduction in acid symptoms significantly predicted the reduction in NVP with the use of acid-reducing pharmacotherapy \((R=0.85, p<0.001)\) (Figure 6.1).

Figure 6.1 Linear regression comparing the effectiveness of acid-reducing pharmacotherapy in reducing HB/RF, and in reducing NVP; \(R=0.85, p<0.001, (n=60)\)
As the severity of PUQE increased, there was a greater reduction in PUQE scores after the use of acid-reducing pharmacotherapy as demonstrated by linear regression (R=0.39, p=0.003).
6.7 DISCUSSION

Our data demonstrate for the first time that acid-reducing pharmacotherapy reduces the severity of NVP. There was a strong correlation between the reduction in acid symptoms and the reduction in the severity of NVP suggesting that treatment of HB/RF will cause improvement in NVP. Women reported an improvement in both HB/RF and NVP symptoms within 3 to 4 days after starting acid-reducing pharmacotherapy. Furthermore, women experiencing the most severe NVP had the greatest change in their NVP after using acid-reducing pharmacotherapy. These results support our initial observational study in suggesting that HB/RF is a significant contributor to NVP\textsuperscript{246}. Additionally, the onset of symptoms of NVP significantly correlated with the onset of symptoms of HB/RF providing further evidence that HB/RF exacerbates NVP.

Since withholding treatment was not considered ethical in the context of our clinical practice in the NVP help-line, our study could not recruit a cohort of women experiencing symptoms of HB/RF who did not use acid-reducing pharmacotherapy. The lack of a comparison group is a limitation; however, the results from this pilot study provide valuable data for a future controlled study. To ensure, however, that the potential effect of acid-reducing drugs on NVP severity can be attributed to these medications, we excluded women who increased their antiemetics during the study. This exclusion was done prior to evaluating the potential effects of acid suppressing drugs on the severity of NVP.
Nausea and vomiting of pregnancy and HB/RF result in adverse maternal outcomes including decreasing a woman’s quality of life and her ability to function\textsuperscript{58,59}, and more serious gastrointestinal morbidities such as gastroesophageal reflux disorder or peptic ulcers\textsuperscript{142}. Treatment of HB/RF by H\textsubscript{2} blockers or PPIs should be considered to alleviate symptoms, especially since these classes of drugs have been quite well studied in pregnancy, and have not been associated with increased fetal risks\textsuperscript{21-31}.
Although this study is not controlled, it demonstrates that management of heartburn and acid reflux in pregnancy can result in a reduction in the severity of NVP. An additional controlled study can strengthen our findings. Furthermore, although studies are published regarding the fetal safety of H2 blockers and PPIs in pregnancy, a larger sample size would provide more reassuring data.
CHAPTER SEVEN

THE SAFETY OF HISTAMINE 2 BLOCKERS IN PREGNANCY: A META-ANALYSIS
Previous studies have demonstrated that H2 blockers are not associated with increased fetal risks in pregnancy; however, the sample size in these studies was fairly small. As our previous results suggest that management of heartburn and acid reflux with H2 blockers can decrease the severity of NVP, more reassuring data is required to advocate the use of H2 blockers in the first trimester of pregnancy.

This study has been published and is referenced as: Gill SK, O’Brien L, Koren G. The safety of histamine 2 (H2) blockers in pregnancy: a meta-analysis. Dig Dis Sci. 2008; Dec.3 [epub ahead of print]
7.2 AUTHORS’ CONTRIBUTIONS

Simerpal Kaur Gill conceived the notion and the study design, conducted the literature search, collected and analyzed the data, and drafted the manuscript. Lisa O’Brien confirmed the data collection and analysis, and revised the manuscript. Gideon Koren conceived the notion of the study, and revised the manuscript.
7.3 ABSTRACT

**Background**: Heartburn and acid reflux increase the severity of nausea and vomiting of pregnancy, and may lead to more serious medical conditions. The fetal safety of histamine 2 (H2) blockers, the most common anti-reflux medication, during pregnancy needs to be determined.

**Objectives**: To determine the fetal safety of H2 blockers during pregnancy through systematic review.

**Methods**: All original research assessing the safety of H2 blockers in pregnancy was sought. Data included congenital malformations, spontaneous abortions, preterm delivery, and small for gestational age. A random-effects model combined results.

**Results**: With data from 2398 exposed and 119,892 non-exposed to H2 blockers, the overall odds ratio and 95% CI was 1.14 [0.89, 1.45]. Further analysis revealed no increased risks for spontaneous abortions, preterm delivery and small for gestational age with odds ratios and 95% CI of 0.62 [0.36-1.05], 1.17 [0.94, 1.147] and 0.28 [0.06, 1.22].

**Conclusion**: Histamine 2 blockers are not associated with increased risks for congenital malformations, spontaneous abortions, preterm delivery, and small for gestational age.
Heartburn (HB) and/or acid reflux (RF) are common medical disorders; various studies have estimated that the incidence of gastroesophageal reflux disorders (GERD) in pregnancy ranges between 40% to 85%. The onset of HB/RF can occur any time during pregnancy: in one study of 88 pregnant women, more than half (52%) of the symptoms began in the first trimester and almost all (40%) by the second trimester with only 8% of symptoms beginning in the third trimester. Other studies, however, report increased severity and frequency of symptoms as gestational age increases.

Regardless of the time of onset, anecdotal and clinical evidence suggest that the presence of pre-existing gastrointestinal (GI) conditions and/or symptoms as well as HB/RF during pregnancy result in increased stomach upset including symptoms ranging from acidity, constipation, diarrhea, indigestion, flatulence, bloating, epigastric pain, nausea and vomiting. Heartburn in pregnancy is also associated with an increased risk for GERD during pregnancy. Furthermore, a more recent study has demonstrated that heartburn during pregnancy may also result in increased prevalence of GERD postpartum as well even after adjustment for confounders including weight change and body mass index.

Treatment of HB/RF in pregnancy is important for management of symptoms, as well to reduce nausea and vomiting of pregnancy (NVP). In a recent study, we have demonstrated that pregnant women suffering from HB/RF (n=194) experience increased severity of NVP compared to pregnant women who do not experience HB/RF (n=188) as measured by the validated Pregnancy Unique Quantification of Emesis (PUQE) scale and
the Well-being (WB) scale\textsuperscript{246}. Therefore, by managing HB/RF, there can be a significant improvement in the quality of life of a pregnant woman. Treatment of HB/RF initially entails minor lifestyle and diet modifications such as sleeping elevated and avoiding acid-containing foods. Pharmacological therapy consists of calcium and magnesium antacids; however, as symptoms worsen, more medications may be required including histamine 2 (H2) blockers or proton pump inhibitors (PPIs). Importantly, though, pharmacotherapy during fetal development must be based on medications that will not adversely affect fetal well-being.

Several small studies have been conducted to determine the safety of H2 blockers in pregnancy; however, their limited sample sizes preclude definitive demonstration on the fetal safety of this class of medication. The aim of the present study was to systematically review studies evaluating the safety of H2 blockers to determine the overall fetal safety of H2 blockers in pregnancy.
7.5 METHODS

A literature search was conducted to identify all published articles examining the safety of H2 blockers in pregnancy. The inclusion criteria consisted of all original research articles written in any language involving at least the first trimester of pregnancy exposure of an H2 blocker with the presence of a comparison group unexposed to H2 blockers, and description of outcome in terms of congenital malformations.

Searches were conducted using the following electronic databases: MEDLINE, Embase, International Pharmaceutical Abstracts, all EBM Reviews, and Cumulative Index to Nursing & Allied Health Literature. Each of the aforementioned databases was searched from inception to January 2008 using the following search terms: H2 blockers, H2 antagonists, histamine 2, birth defect, fetal abnormality, teratogenicity, malformation, Zantac (ranitidine), Pepcid (famotidine), Tagamet (cimetidine), Axid (nizatidine). In addition, references from retrieved studies and reviews were searched for further papers not captured by our search strategy.

Two independent reviewers performed article selection, and disagreements were resolved through consensus. Based on the inclusion and exclusion criteria, studies were selected that specifically examined the rate of congenital malformations after maternal exposure to H2 blockers.

Data extracted from selected articles included the rate of congenital malformations, spontaneous abortions, premature delivery and birth-weight.
Individual quality scores of accepted articles were determined by the validated Downs-Black scale\textsuperscript{249}. This scale allows for quality scoring of randomized control trials and observational studies by assessing study quality of reporting, external and internal validities, bias, confounders and power with a possible total score of 32.

Outcomes from included articles were pooled and weighted, and combined using a random effects model. The data were analyzed using Cochrane’s Review Manager version 4.1.1. Odds ratios and 95% confidence intervals were calculated. Publication bias was assessed with the use of a funnel plot. Heterogeneity of effects was assessed using the Q statistic.
7.6 RESULTS

We retrieved 906 articles for potential analysis. After reviewing the titles and abstracts and excluding studies that did not include information regarding the safety of H2 blockers in pregnancy, 13 were selected for closer assessment. Four were excluded because they did contain usable, extractable or relevant data, and an additional four were excluded because the study did not contain control groups. One article was excluded also because a portion of exposed women and controls were obtained from a site that had published a study already included in our analysis. Therefore, 4 articles were included in our analysis [21-23,30].

Of the studies selected, 2 were prospective cohorts and 2 were retrospective cohorts (Table 7.1).

Table 7.1 Characteristics of Included Studies; BW=birthweight, SGA=small for gestational age (<3rd centile), SA=spontaneous abortions, Pre=premature delivery (<36 weeks gestation)

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study Type</th>
<th>Number Exposed</th>
<th>Number Unexposed</th>
<th>Included Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garbis (2005)</td>
<td>Prospective cohort</td>
<td>553</td>
<td>1390</td>
<td>BW, SA, Pre</td>
</tr>
<tr>
<td>Magee (1996)</td>
<td>Prospective cohort</td>
<td>142</td>
<td>143</td>
<td>BW, SGA, SA, Pre</td>
</tr>
<tr>
<td>Matok (2008)</td>
<td>Retrospective cohort</td>
<td>1148</td>
<td>116 812</td>
<td>Pre</td>
</tr>
<tr>
<td>Ruigomez (1999)</td>
<td>Retrospective cohort</td>
<td>555</td>
<td>1547</td>
<td>SGA, SA, Pre</td>
</tr>
</tbody>
</table>

The average quality score was 70 ± 0.04 %, which is considered to be on the border of “fair” and “good” quality. The funnel plot (data not shown) was symmetrical, indicating the absence of publication bias. The Q-statistic for heterogeneity of effects was nonsignificant ($\chi^2=3.44$, p=0.33) rendering the data combinable.
Data from a total of 2398 exposed and 119,892 unexposed controls were included in the meta-analysis. Using a random effects model, the odds ratio and 95% CI for the incidence of congenital malformations after *in utero* exposure to H2 blockers was 1.14 [0.89, 1.45] (Figure 7.1).

Based on 738 exposures and 1575 unexposed controls from 2 studies, the odds ratio for the incidence of spontaneous abortions after *in utero* exposure to H2 blockers was 0.62 [0.36, 1.05]. Odds ratio for the incidence of preterm delivery from 2321 exposures and 119,072 unexposed controls from 4 studies was 1.17 [0.94, 1.47], and for the incidence of small for gestational age from 611 exposures and 794 unexposed controls from 2 studies was 0.28 [0.06, 1.22].
7.7 DISCUSSION

This meta-analysis based on 2398 H2 blocker-exposed and 119,892 unexposed controls demonstrated that the use of H2 blockers is not associated with an increased risk for congenital malformations. The 95% confidence intervals were very tight, suggesting that it is unlikely that a beta error may contribute to the lack of significant effect. Furthermore, secondary analysis revealed no apparent increased risks for spontaneous abortions, preterm delivery and small for gestational age. In fact, based on our findings, H2 blockers appear to have a trend towards a protective effect with respect to spontaneous abortions and small for gestational age.

Although only 4 studies are included in this meta-analysis, including one large study, the funnel plot did not reveal concerns related to a publication bias, and the included studies were homogeneous, making the data from the four studies combinable. Furthermore, based on the overall acceptable quality of the studies included in this meta-analysis as assessed by using the validated Downs-Black scale, the results obtained are reassuring with respect to the safety of the use of H2 blockers in pregnancy especially considering the large sample size. Additionally, our results are consistent with previous findings that suggest that H2 blockers are not associated with an increased risk for malformations\textsuperscript{21-24}.

Our data suggest that H2 blockers can be considered safe in managing heartburn and acid reflux in pregnancy, especially to prevent increased severity of NVP and the potential for GERD.
7.8 CONCLUSION

This meta-analysis provides strong evidence that H2 blockers can be used in pregnancy as they are not associated with increased risks for major malformations, preterm delivery, spontaneous abortions and small for gestational age. This data should provide pregnant women and healthcare providers with the confidence to safely manage heartburn and acid reflux, thereby improving management of NVP.
CHAPTER EIGHT

THE SAFETY OF PROTON PUMP INHIBITORS IN PREGNANCY: A META-ANALYSIS
Previous studies have demonstrated that PPIs are not associated with increased fetal risks in pregnancy; however, the sample size in these studies is fairly small. As our previous results suggest that management of heartburn and acid reflux with PPIs can improve the severity of NVP, more reassuring data is required to advocate the use of PPIs in the first trimester of pregnancy.

This study has been published and is referenced as: Gill SK, O’Brien L, Einarson TR, Koren G. The safety of proton pump inhibitors (PPIs) in pregnancy: a meta-analysis. American Journal of Gastroenterology (28 April 2009) doi:10.1038/ajg.2009.122.
∞ 8.2 AUTHORS’ CONTRIBUTIONS ∞

Simerpal Kaur Gill devised the notion, conducted the systematic review and analysis and wrote the manuscript. Lisa O’Brien conducted the systematic review and revised the manuscript. Thomas R Einarson assisted in conducting the analysis and revised the manuscript. Gideon Koren devised the notion and revised the manuscript.
8.3 ABSTRACT

Background: Heartburn and acid reflux are common medical disorders in pregnancy, and can result in serious discomfort and complications. Furthermore, some pregnant women also experience more severe gastrointestinal conditions such as *Helicobacter pylori*, peptic ulcers, and Zollinger-Ellison syndrome. To allow use of proton pump inhibitors (PPIs) in pregnancy, the fetal safety of this drug class must be established.

Outcome Measures: To determine the fetal safety of PPIs during early pregnancy through systematic literature review.

Methods: All original research assessing the safety of PPIs in pregnancy was sought from inception to July 2008. Two independent reviewers identified articles, compared results, and settled differences through consensus. The Downs-Black scale was used to assess quality. Data assessed included congenital malformations, spontaneous abortions, and preterm delivery. A random-effects meta-analysis combined results from included studies.

Results: Of 60 articles identified, 7 met our inclusion criteria. With data from 134,940 patients, including 1530 exposed and 133,410 non-exposed to PPIs, the overall odds ratio (OR) for major malformations was 1.12 (95% confidence interval (CI) of 0.86-1.45). Further analysis revealed no increased risk for spontaneous abortions (OR=1.29, CI95%=0.84-1.97); similarly, there was no increased risk for preterm delivery (OR=1.13, CI95%=0.96-1.33). In secondary analysis of 1341 exposed and 120,137 unexposed to omeprazole alone, the OR and CI95% for major malformations were 1.17 and 0.90-1.53, respectively.
Conclusion: Based on the current results, PPIs are not associated with an increased risk for major congenital birth defects, spontaneous abortions or preterm delivery. The arrow range of 95% CIs is further reassuring suggesting that PPIs can be safely used in pregnancy.
Gastrointestinal (GI) complications in pregnancy are common: the incidence of gastroesophageal reflux disorders (GERD) in pregnancy ranges between 40% to 85%\textsuperscript{18,135-138}. Serious GI conditions that are fairly common in pregnancy and that require pharmacological treatment include *Helicobacter pylori* (*H. pylori*) infections, peptic and duodenal ulcers, and Zollinger-Ellison syndrome\textsuperscript{7}. The onset of these medical conditions can occur any time during pregnancy, and may be related to gastric arrhythmias and reduced gastrointestinal motility\textsuperscript{19,20,141}. Furthermore, these aforementioned medical conditions are associated with increased nausea and vomiting of pregnancy, which, in turn, results in decreased quality of life\textsuperscript{58}. Although initial treatment in pregnancy usually involves lifestyle and diet modifications for less severe GERD symptoms, pharmacotherapy is required when symptoms are not controlled, specifically in the case of *H. pylori* and ulcers\textsuperscript{136,137}.

Proton pump inhibitors (PPIs) were introduced to the market in 1989, and are considered a key advancement in the treatment of acid-peptic diseases\textsuperscript{250}. Their mechanism of action in reducing acid involves irreversible inhibition of the H\textsuperscript{+}/K\textsuperscript{+} ATPase enzyme in parietal cells resulting in decreased acid secretion by the proton pump\textsuperscript{250,251}. Proton pump inhibitors are more potent and have a more rapid onset in eliminating GERD symptoms compared to H2 blockers; furthermore, this class of medications is essential to effectively treat *H. pylori*, peptic ulcers, GERD and Zollinger-Ellison\textsuperscript{251}. Proton pump inhibitors are commonly used and may be necessary in pregnancy for effectively managing symptoms. Only one previous meta-analysis has been published
demonstrating no increased risks for congenital malformations after *in utero* exposure to PPIs; however, the sample size was limited\textsuperscript{252}. Several smaller studies have since been conducted; combining the results from all of these studies can provide more conclusive information regarding the fetal safety of PPIs. Although their safety in the non-pregnant population has been well established\textsuperscript{250,251}, determining the fetal safety of PPIs is critical.
8.5 METHODS

A search was conducted to locate all published articles examining the safety of proton pump inhibitors in pregnancy. We accepted all original research articles and abstracts written in any language. Studies must have included 1) human exposure to a proton pump inhibitor during at least the first trimester of pregnancy, 2) a comparison group not exposed to PPIs, and 3) description of fetal outcomes. The outcomes of interest included congenital malformations, spontaneous abortions, and premature delivery.

Searches were conducted using the following electronic databases: MEDLINE, Embase, International Pharmaceutical Abstracts, all EBM Reviews, and Cumulative Index to Nursing & Allied Health Literature. Each of the aforementioned databases was searched from inception to July 2008 using the following search terms: proton pump inhibitor, birth defect, fetal abnormality, teratogenicity, malformation, omeprazole, pantoprazole, rabeprazole, lansoprazole, and esomeprazole. In addition, references from retrieved studies and reviews were searched for further papers not captured by our search strategy.

Two independent reviewers (S.G., L.O’B.) performed article selection, and disagreements were resolved through consensus. On the basis of the inclusion and exclusion criteria, studies were selected that specifically examined the rate of congenital malformations after maternal exposure to PPIs, were selected.

Individual quality scores of accepted articles were determined using the validated Downs-Black scale. This scale scores the for quality of randomized control
trials and observational studies by assessing reporting, external and internal validities, bias, confounders and power with a possible total score of 32.

Outcomes from included articles were pooled and weighted, and combined using a random effects model. The data were analyzed using Cochrane’s Review Manager version 4.1.1. Odds ratios (OR) and confidence intervals (CI_{95%}) were calculated by taking the natural logarithms of the odds ratio. Publication bias was assessed with the use of a funnel plot. Heterogeneity of effects was assessed using the Q and I² statistics.
We retrieved 60 articles for potential analysis. After reviewing the titles and abstracts and excluding studies that did not include information regarding the safety of PPIs in pregnancy, 7 were selected for closer assessment. Additional data from one, yet unpublished study was also provided (Moretti, February 2008). Of the 8 articles selected, one was excluded because it did not contain a non-exposed control group. Therefore, six articles and one abstract were included in our final analysis \(^{23,24,28,29,253-255}\).

Of the studies selected, four were prospective cohorts and three were retrospective cohorts (Table 8.1).

**Table 8.1** Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study Type</th>
<th>Number Exposed</th>
<th>Number Unexposed</th>
<th>Included Data</th>
<th>Quality Score (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diav-Citran (2005)</td>
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<td>279</td>
<td>778</td>
<td>OMPZ, SA, Pre</td>
<td>69</td>
</tr>
<tr>
<td>Lalkin (1998)</td>
<td>Prospective cohort</td>
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<td>98</td>
<td>OMPZ, SA, Pre</td>
<td>72</td>
</tr>
<tr>
<td>Källen (1998)</td>
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<td>255</td>
<td>OMPZ</td>
<td>69</td>
</tr>
<tr>
<td>Matok (2008)</td>
<td>Retrospective cohort</td>
<td>658</td>
<td>117 302</td>
<td>OMPZ, Pre</td>
<td>69</td>
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<tr>
<td>Morretti (personal communication)</td>
<td>Prospective cohort</td>
<td>63</td>
<td>75</td>
<td>OMPZ</td>
<td>69</td>
</tr>
<tr>
<td>Neilson (1999)</td>
<td>Retrospective cohort</td>
<td>38</td>
<td>13 327</td>
<td>Pre</td>
<td>72</td>
</tr>
<tr>
<td>Ruigomez (1999)</td>
<td>Retrospective cohort</td>
<td>139</td>
<td>1575</td>
<td>OMPZ, Pre</td>
<td>66</td>
</tr>
</tbody>
</table>

Only 1 study contained information regarding the duration of treatment: the median duration of treatment was 22 days (4-47 days) for omeprazole, 14 days (7-32 days) for lansoprazole and 14 days (7-23 days) for pantoprazole\(^{253}\). Further information was
obtained from the authors of the published abstract\textsuperscript{254}. This study was a retrospective, computerized, data linkage study conducted in Israel\textsuperscript{254}. Data were collected from 1998 to 2007 and included filled prescriptions for any PPI, the daily dose, and fetal outcomes\textsuperscript{254}. A multiple regression statistical model was used to account for certain confounders such as smoking, maternal diabetes, parity, ethnicity, and maternal age; therefore, the results obtained are appropriate and relevant to include in this current study\textsuperscript{254}.

The average quality score for all of the included studies was 69 ± 2.1% (range: 66-72%) (Table 8.1), which was considered “fair” quality. The funnel plot (data not shown) was symmetrical, indicating no obvious publication bias. The Q-statistic for heterogeneity of effects was non-significant ($\chi^2=1.03$, $p=0.98$) and $I^2$-statistic was 0, suggesting that it was reasonable to combine these data.

Data from a total of 1530 exposed and 133,410 non-exposed controls were included in the meta-analysis. Using a random effects model, the OR for the incidence of congenital malformations after \textit{in utero} exposure to PPIs was 1.12 (Cl\textsubscript{95%}:0.86-1.45) (Figure 8.1).

\textbf{Figure 8.1} Overall effect of the incidence of major malformations after \textit{in utero} exposure to PPIs
On the basis of 524 exposed and 981 non-exposed controls from two studies, the OR for the incidence of spontaneous abortions after *in utero* exposure to PPIs was 1.29 (CI 95%: 0.84-1.97). The OR for the incidence of preterm delivery from 1253 exposures and 132,190 non-exposed controls from 5 studies was 1.13 (CI 95%: 0.96-1.33).

Data were also analyzed using a total of 1341 exposed to omeprazole alone and 120,137 non-exposed controls from 6 studies. The OR and 95% CI for the incidence of major malformations after *in utero* exposure to omeprazole was 1.17 (CI 95%: 0.90-1.53) (Figure 8.2).

**Figure 8.2** Overall effect of the incidence of major malformations after *in utero* exposure to omeprazole
8.7 DISCUSSION

This meta-analysis, based on 1530 PPI-exposed and 133,410 non-exposed controls, demonstrated that first trimester use of PPIs does not appear to be associated with an increased risk for major congenital malformations. The confidence intervals are tight, suggesting that it is unlikely that a beta error may contribute to the lack of significant effect. Furthermore, secondary analysis revealed no apparent increased risk for spontaneous abortions or preterm delivery. Based on 1341 omeprazole-exposed and 120,137 non-exposed controls, the use of omeprazole does not appear to be associated with an increased risk for congenital malformations.

The funnel plot did not reveal a potential publication bias, and the included studies were not heterogeneous. Based on the overall acceptable quality of the studies included in this meta-analysis, the results obtained offer reassurance with respect to the safety of the use of PPIs in pregnancy; similarly, the same can be said about the use of omeprazole in pregnancy. Our results should be interpreted with some caution as these results may not be generalizable to all populations; however, it is encouraging that our results are consistent with previous studies.

Several animal studies have been conducted to determine the potential teratogenicity of PPIs, including omeprazole; however, no increased risks have been observed. Furthermore, a human study involving 955 omeprazole-exposed infants – 863 in early pregnancy, and 92 in later pregnancy – concluded that in utero exposure of omeprazole does not pose a risk to the baby. Results from a much smaller, previous meta-analysis examining the fetal safety of PPIs, and specifically, omeprazole, have not
identified an increased risk for congenital malformations either, with odds ratios of 1.18 (CI<sub>95%</sub>:0.72-1.94) and 1.05 (CI<sub>95%</sub>:0.59-1.85) respectively<sup>252</sup>. Therefore, it is reassuring that our updated results corroborate these previous findings with respect to the fetal safety of PPIs during pregnancy, especially since PPIs have dramatically improved management of GI disorders and are usually considered gold-standard treatment<sup>258-260</sup>.

Our data suggest that PPIs may be safe in pregnancy in managing GERD, <i>H. pylori</i>, gastric and duodenal ulcers, and Zollinger-Ellison syndrome, and as a result, in preventing increased severity of nausea and vomiting during pregnancy.
8.8 CONCLUSION

This meta-analysis provides strong evidence that PPIs, particularly omeprazole, can be used in pregnancy as they are not associated with increased risks for major malformations, preterm delivery, and spontaneous abortions. This data should provide pregnant women and healthcare providers with the confidence to safely manage heartburn and acid reflux, thereby improving management of NVP.
CHAPTER NINE

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PHARMACOKINETICS OF DOXYLAMINE AND PYRIDOXAL-5’-PHOSPHATE AFTER DICLECTIN® ADMINISTRATION
In Canada, Diclectin®, a delayed-release drug composed of 10 mg of doxylamine succinate and 10 mg of pyridoxine hydrochloride, is the first line pharmacotherapy for the treatment of NVP as it is the only drug approved for this indication by Health Canada. There appears to be large variability in the onset and effectiveness of this drug combination often resulting in suboptimal therapy for NVP. In order to improve management of NVP using doxylamine succinate/pyridoxine hydrochloride, more information is required regarding the pharmacokinetic variability of its two active ingredients, doxylamine and pyridoxal-5'-phosphate.
∞ 9.2 AUTHORS’ CONTRIBUTIONS ∞

This study was conducted by Duchesnay® at the Anapharm Clinical Research Facility. Simerpal Kaur Gill conducted the pharmacokinetic data analysis. Facundo Garcia-Bournissen mentored her in the pharmacokinetic data analysis. Gideon Koren conceived of the study concept.
$\approx 9.3$ ABSTRACT $\approx$

**Background:** Diclectin®, composed of 10 mg of doxylamine succinate and 10 mg of pyridoxine hydrochloride, is the drug of choice for the management of NVP; however, there is large variability in its onset and duration of action among women. In order to understand and improve its effectiveness, the variability of the two active ingredients in this doxylamine succinate/pyridoxine hydrochloride combination, doxylamine (DOX) and pyridoxal-5'-phosphate (PLP), must be studied.

**Objectives:** To determine the pharmacokinetic variability in doxylamine succinate and PLP after Diclectin® administration.

**Methods:** 18 non-pregnant, non-lactating, healthy females between 18 and 45 years of age were administered 2 tablets of Diclectin® with 240 mL of water on an empty stomach. Blood samples were analyzed for doxylamine and PLP concentrations using tandem mass spectrometry. Pharmacokinetic values were adjusted for bodyweight, and their variability were calculated.

**Results:** The calculated mean DOX-AUC$_{0\rightarrow\infty}$ was $3137 \pm 634$ ng·hr/mL with 2.1-fold variability from 2057 to 4376 ng·hr/mL. The mean PLP-AUC$_{0\rightarrow\infty}$ was $5513 \pm 2362$ ng·hr/mL with 6.5-fold variability between 1573 to 10 154 ng·hr/mL.

**Conclusion:** There is a 2.1-fold difference in the DOX-AUC$_{0\rightarrow\infty}$ and a 6.5-fold difference in the PLP-AUC$_{0\rightarrow\infty}$ after oral administration of 20 mg of Diclectin®. These differences may be important sources of variability in the effectiveness of the doxylamine succinate/pyridoxine hydrochloride combination for the management for NVP, and may need to be addressed in dosing guidelines.
For the treatment of NVP, there are many pharmacological and non-pharmacological treatments that are not associated with increased fetal risks. In terms of pharmacological management, in Canada, Diclectin® is approved by Health Canada for the treatment of NVP. Diclectin® is composed of 10 mg of an antihistamine, doxylamine succinate, and 10 mg of vitamin B6 in the form of pyridoxine hydrochloride (PN-HCl). Doxylamine (DOX) is the pharmacologically active form; however, PN-HCl requires bioactivation to pyridoxal-5’phosphate (PLP) for its anti-emetic effects.

This doxylamine succinate/pyridoxine hydrochloride combination is formulated to be delayed-release in order to manage symptoms of NVP for longer duration; as a result, the dosing schedule of this drug is very important to ensure onset of action occurs when NVP symptoms are peaking. The standard recommended dose of Diclectin® is typically 4 tablets a day: 2 at bedtime, 1 in the morning, and 1 in the afternoon assuming that NVP symptoms are worst in the morning; however, it is important to adjust the schedule according to the pattern of NVP in a particular individual. Higher than standard doses of doxylamine succinate/pyridoxine hydrochloride have been studied in pregnancy with some women taking up to 12 tablets a day with no increased fetal risks. Clearly, there is variability in the effectiveness of doxylamine succinate/pyridoxine hydrochloride; however, the factors underlying this variability are poorly understood.

In order to understand and improve the effectiveness of the doxylamine succinate/pyridoxine hydrochloride combination, the variability of the two active
ingredients, DOX and PLP, must be studied. The primary objective of the current study is to determine the variability in the area under the curve for both DOX and PLP after Diclectin® administration.
9.5 METHODS

This was a single-centre, single dose, open-label study to determine the variability in pharmacokinetic parameters of doxylamine succinate and PN-HCl after single dose Diclectin® administration. Subjects were recruited from the general population. Subjects were asked to abstain from consuming food and beverages with a high vitamin B6 content, including brewer’s yeast, carrots, chicken, eggs, fish, meats, peas, spinach, sunflower seeds, walnuts and wheat germ, from 7 days prior to admission. Subjects were required to abstain from prescription medication from 14 days prior to drug administration, from natural food supplements and vitamins from 7 days prior to drug administration, and from multivitamins containing B6 or B6 supplements from 28 days prior to drug administration.

Eighteen non-pregnant, non-lactating, pre-menopausal, healthy females between 18 and 45 years of age with a body mass index between 19 and 30 kg/m² were recruited. After women provided informed consent, they were confined at the Anapharm Clinical Research Facility 28 hours prior to dosing where they were provided with standard meals and snacks at set times. Subjects were administered 2 tablets of Diclectin® with 240 mL of room temperature water under empty-stomach conditions, defined as 2 hours before and after eating.

Blood samples were taken at 24 and 12 hours prior to dosing and at time of dosing. After dosing, blood samples were taken at the following times: 0.5, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.33, 4.67, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 11.0, 12.0, 14.0, 16.0, 20.0, 24.0, 36.0, 48.0, 72.0, and 120.0 hours.
For DOX analysis, 3 mL of blood was drawn into EDTA K<sub>2</sub> collection tubes. Whole blood was centrifuged at 3000 rotations per minute for 10 minutes at 4°C. Two aliquots of 0.5 mL of plasma were transferred into polypropylene tubes. Samples were placed into a -20°C freezer until analysis. Samples were analyzed using tandem mass spectrometry.

For PLP analysis, 3 mL of blood was drawn into EDTA K<sub>2</sub> collection tubes. Whole blood was centrifuged at 3000 rotations per minute for 10 minutes at 4°C. Two aliquots of 0.250 mL of plasma were transferred into polypropylene tubes. Samples were placed into a -80°C freezer until analysis. Pyridoxine, its metabolites and doxylamine were extracted using protein precipitation. Samples were injected into a liquid chromatograph equipped with a tandem mass spectrometry detector, and were quantitated using the peak area ratio method with a lower limit of quantitation of 1 ng per mL.

All subjects were baseline-corrected for PLP by dividing the baseline concentration by the elimination rate constant (k<sub>el</sub>) and subtracting this value from the area under the curve (AUC); baseline-correction was not required for DOX. The k<sub>el</sub> was derived from the slope of the least squares regression line for the samples from 24 to 120 hours. The AUC for DOX was calculated for from 0 to infinity (DOX-AUC<sub>0→∞</sub>), and for PLP the AUC was calculated from 0 to infinity (PLP-AUC<sub>0→∞</sub>), and from 0 to 48 hours (AUC<sub>0→48</sub>) using the trapezoid rule. As all women were administered the same dose of doxylamine succinate/pyridoxine hydrochloride, to account for variability associated with bodyweight, the AUC values for corrected for dose per kilogram.
9.6 RESULTS

The mean DOX-AUC$_{0\rightarrow\infty}$ was calculated to be $3137 \pm 634$ ng·hr/mL with a range of 2057 to 4376 ng·hr/mL (Table 9.1). The mean time to appearance of DOX in the plasma was $4.4 \pm 2.1$ hours with a range of 0.5 to 8.2 hrs, and the mean half-life was $1.4 \pm 0.5$ hours with a range of 0.6 to 2.4 hrs (Table 9.1).

**Table 9.1** Pharmacokinetic parameters for doxylamine

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Mean ± SD</th>
<th>Lower &amp; Upper Values</th>
<th>Fold Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0\rightarrow\infty}$ (ng·hr/mL)</td>
<td>$3137 \pm 634$</td>
<td>2057 - 4376</td>
<td>2.1</td>
</tr>
<tr>
<td>Time to onset (hours)</td>
<td>$4.4 \pm 2.1$</td>
<td>0.5 – 8.2</td>
<td>16.3</td>
</tr>
<tr>
<td>T$_{1/2}$ (hours)</td>
<td>$1.4 \pm 0.5$</td>
<td>0.6 - 2.4</td>
<td>4.4</td>
</tr>
</tbody>
</table>

The mean PLP-AUC$_{0\rightarrow\infty}$ was calculated to be $5513 \pm 2362$ ng·hr/mL with a range of 1573 to 10 154 ng·hr/mL (Table 9.2). The mean half-life was $65.8 \pm 19.8$ hours with a range of 31.5 to 117.2 hrs (Table 9.2).

**Table 9.2** Pharmacokinetic parameters for pyridoxal-5’-phosphate

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Mean ± SD</th>
<th>Lower - Upper Value</th>
<th>Fold Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0\rightarrow\infty}$ (ng·hr/mL)</td>
<td>$5513 \pm 2362$</td>
<td>1573 - 10 154</td>
<td>6.5</td>
</tr>
<tr>
<td>AUC$_{0\rightarrow48}$ (ng·hr/mL)</td>
<td>$930 \pm 333$</td>
<td>522 – 1597</td>
<td>3.1</td>
</tr>
<tr>
<td>T$_{1/2}$ (hours)</td>
<td>$65.8 \pm 19.8$</td>
<td>31.5 - 117.2</td>
<td>3.7</td>
</tr>
</tbody>
</table>
Our data demonstrates that after 20 mg of doxylamine succinate/pyridoxine hydrochloride administration, there is a 2.1-fold difference in the DOX-AUC$_{0 \to \infty}$. This moderate difference in the DOX-AUC$_{0 \to \infty}$ indicates that there is not large variation in the bioavailability and absorption of doxylamine. The bioavailability of doxylamine succinate was not calculated in the current study; however, the bioavailability is estimated to be 24.7% after oral administration$^{261}$. More importantly, in the current study, the time to onset of the appearance of DOX in the blood varied enormously from 30 minutes up to 8 hours after dosing demonstrating that after Diclectin® administration some woman may not experience any anti-emetic effect until 8 hours after dosing. The mean half-life calculated in the current study was 1.4 hours, and although the time to peak concentration was not determined in the current study, two separate studies involving 10 and 22 healthy woman found the time to peak to be 2.4 hours after 50 mg and 25 mg of doxylamine succinate administration, respectively$^{262,263}$. These data suggest that individual dosing regimens are important to determine to ensure optimal management of NVP symptoms.

Contrary to the moderate variability in the DOX-AUC$_{0 \to \infty}$, the variability in the PLP-AUC$_{0 \to \infty}$ was found to be 6.5-fold. This large variation could be due to a variety of factors including the bioavailability or biotransformation of PN-HCl to PLP. Using the PLP-AUC$_{0 \to 48}$ calculated in the current study, crude estimates on the bioavailability and biotransformation can be calculated using the PLP-AUC$_{0 \to 48}$ after 50 mg PN-HCl intravenous administration, and the PLP-AUC$_{0 \to \infty}$ after 5 mg of PLP intravenous
administration in healthy males calculated in a previously published study\textsuperscript{236}. The mean PLP-AUC\textsubscript{0→48} in the current study was calculated to be 930 ± 333 ng·hr/mL after oral administration of 20 mg PN-HCl. Based on the PLP-AUC\textsubscript{0→48} of 2282 ± 220 ng·hr/mL determined in a study of healthy males after 50 mg PN-HCl intravenous administration\textsuperscript{236}, we can approximate the bioavailability of PN-HCl to be 1.0 or 100%.

Furthermore, results from the same study found the PLP-AUC\textsubscript{0→∞} after 5 mg of PLP intravenous administration in healthy males to be 2.1268 μM·hr/L\textsuperscript{236}; this data combined with the PLP-AUC\textsubscript{0→∞} of 0.5043 μM·hr/L after 20 mg oral PN-HCl determined in the current study would estimate that the biotransformation of PN-HCl to PLP is approximately 23.7%.

The bioavailability is estimated to be approximately 100%, which is what has been assumed, but, to our knowledge, not yet shown, for vitamin B6 supplements\textsuperscript{222}. Combining data from the current study and a previously published study in healthy males, the biotransformation of PN-HCl to PLP is estimated to be approximately 23.7%. Although these values are obtained through data from two different studies and two different populations, they do provide estimates that can be confirmed with future studies. Interestingly, in the current study, there was a smaller, yet significant extent, of variability of 3.7-fold in the half-life of PLP suggesting that other physiological factors, such as variability in the amount of phosphatases or protein binding, may also contribute to the large variability in the PLP-AUC\textsubscript{0→∞}.

The results from the current study suggest that the effectiveness of the doxylamine succinate/pyridoxine hydrochloride combination does depend on optimal
dosing. Similarly, a study conducted in 68 pregnant women experiencing moderate to severe NVP concluded that Diclectin® dosing should be given according to body weight, time and severity of NVP symptoms in order to be most effective. Furthermore, although the standard recommended dose is up to 4 tablets a day, a study was conducted comparing 123 pregnant women at recommended standard doses and 102 pregnant women at higher than recommended doses of up to 12 tablets a day. This study revealed that higher than standard doses up to 12 tablets a day were found to be more efficacious suggesting that there is variability among women, and standard doses may not be adequate for all women to effectively manage NVP symptoms.

Although our data demonstrates that there is large variability in the pharmacokinetic parameters of both DOX and PLP, further research is required to determine which differences result in suboptimal therapy of the doxylamine succinate/pyridoxine hydrochloride combination in order to optimize the management of symptoms of NVP with this pharmacotherapy.
9.8 CONCLUSION

Our findings demonstrate that there is very large variability in the pharmacokinetics of DOX and PLP after Diclectin® administration. In women with smaller area under the curves for the active metabolites, this drug combination may not be as effective at standard doses. Further research is required to determine the effects of the variability observed in the current study on the effectiveness of the doxylamine succinate/pyridoxine hydrochloride combination in order to translate this variability into dosing guidelines to provide effective management of NVP symptoms.
CHAPTER TEN

GENERAL DISCUSSION, CONCLUSIONS AND FUTURE DIRECTIONS
10.1 SUMMARY AND GENERAL DISCUSSION

The seven studies presented in this dissertation provide further insight into several sources of variability which result in clinical pharmacology challenges associated with the management of NVP. Nausea and vomiting of pregnancy is the most common medical condition in pregnancy, and can result in adverse physical, financial and psychosocial issues, yet limited research has been conducted in this area to improve management. Although a variety of pharmacological and non-pharmacological strategies to manage NVP symptoms have been studied, there is a great degree of variability in pharmacological response to NVP among pregnant women that can render these strategies ineffective. The focus of this dissertation was to study major sources of variability in an attempt to optimize clinical pharmacology strategies in managing NVP symptoms.

The first source of variability in clinical pharmacology is adherence and tolerability of iron-containing prenatal multivitamins in pregnant women with pre-existing GI conditions. Although it was hypothesized that women with pre-existing GI conditions would have reduced adherence to Orifer F®, a prenatal multivitamin with high iron content, there was no statistically significant difference in adherence although the actual pill intake of PregVit® was greater as it is taken twice a day. Women with pre-existing GI conditions did not differ significantly in tolerability to higher or lower iron content prenatal multivitamins. Interestingly, pregnant women with no pre-existing GI conditions did have reduced tolerability to prenatal multivitamins to Orifer F® as well greater severity of NVP symptoms. These findings led us to the assumptions that GI
symptoms and/or iron content may exacerbate NVP symptoms. Additionally, of women with pre-existing GI symptoms, over 80% were using acid-reducing pharmacotherapy, the majority of whom were randomized to Orifer F®; therefore, an actual difference in tolerability and adherence may not have been apparent as women may have treated their GI symptoms by adjusting their acid-reducing pharmacotherapy doses accordingly.

Our sample size was insufficient to allow for a comparison between the tolerability of the two iron preparations used in this study, ferrous fumarate in PregVit® and ferrous sulfate in Orifer F®. A previous study has demonstrated that adherence to both ferrous fumarate and ferrous sulfate compared to other iron preparations is poor due to adverse GI effects11. Our results suggest that there are increased adverse GI effects with the use of ferrous sulfate; however, whether these effects are due to the specific salt form or to higher iron content cannot be presently determined. Results from two separate studies, however, have demonstrated that regardless of the salt form, supplementation with low-dose iron improves tolerability and adherence while still being effective in preventing anemia in pregnancy264,265. Alternatively, other strategies to improve adherence and minimize adverse GI effects are weekly dosages rather than daily doses of iron supplements. Since iron supplementation is not necessary for every pregnant woman, and intolerability leads to suboptimal adherence of iron-containing prenatal multivitamins, emphasis should be placed on supplementing with low dose or iron-free prenatal multivitamins especially in non-anemic women with pre-existing GI conditions.
As results from the first study suggested that iron content may increase the severity of NVP symptoms, the objective of the second study was to determine the effects of discontinuing iron-containing prenatal multivitamins on the severity of NVP. Two-thirds of pregnant women who were advised to switch to folic acid plus either an adult multivitamin or a children’s chewable multivitamin that contain less iron than a prenatal multivitamin noticed improvement in their NVP symptoms within 1 to 3 days. These self-reports were verified using a validated scale to quantify the initial and follow-up NVP symptoms. This is the first interventional study showing that discontinuation of iron results in improvement of NVP symptoms providing a strong rationale to conduct a randomized controlled trial to verify our results. Similar to these findings and our previous results, a recent study involving 164 women, almost half reported at least one adverse effect from iron supplements including constipation (27.4%) and nausea (10.8%) suggesting that NVP severity may be also exacerbated by GI symptoms11. Our data suggest that avoiding iron-containing prenatal multivitamins in the first trimester is effective in improving NVP symptoms in the majority of pregnant women suffering from NVP.

The second main source of variability in clinical pharmacology strategies to manage NVP that we focused on was based on data from our first two studies. We were prompted to examine the effects of heartburn and acid reflux on the severity of NVP as our previous results had suggested an association between these two symptoms. Gastrointestinal symptoms are experienced by 40% to 85% of pregnant women7,18,138 possibly due to changes in motility of the GI tract associated with increased levels of
circulating female hormones\textsuperscript{135,136,144-146}. Similar GI changes have been observed in women experiencing NVP\textsuperscript{7}; therefore, it is biologically plausible that GI symptoms such as heartburn and acid reflux contribute to the severity of NVP. To test this hypothesis, we collected two cohorts of pregnant women experiencing NVP, one including women also experiencing heartburn or acid reflux, and the other excluding women with any GI symptoms. Women with heartburn or acid reflux did experience greater severity of NVP as measured by validated qualitative and quantitative scores. Certain potential confounding factors were considered in our analysis; however, our multiple linear regression results demonstrate that the only factor that could consistently account for the increased PUQE scores and the decreased Well-being scores observed in the study group was the presence of heartburn or acid reflux. Furthermore, the increased use of anti-emetics and antacids observed in the study group confirms the increased severity of NVP, and the presence of heartburn and/or acid reflux, respectively.

To expand on the aforementioned findings, for our fourth study, we aimed at determining whether treatment of heartburn or acid reflux in pregnancy reduces the severity of NVP. We collected a cohort of 60 pregnant women who were experiencing NVP symptoms in addition to heartburn or acid reflux. At the initial interview, NVP severity was assessed using quantitative measures, and women were counseled to commence acid-reducing therapy. At the follow-up interview, women reported a reduction in both their NVP symptoms as well as their GI symptoms 3 to 4 days after starting acid-reducing pharmacotherapy with no other changes in medications. There was a strong correlation between the reduction in acid symptoms and the reduction in
the severity of NVP suggesting that treatment of GI symptoms results in improvement of NVP. Additionally, the onset of symptoms of NVP significantly correlated with the onset of symptoms of heartburn or acid reflux providing further evidence that these GI symptoms exacerbate NVP. The lack of a comparison group is a limitation; however, the results from this pilot study provide valuable data for a future controlled study, and do provide evidence that to improve NVP symptoms in women experiencing heartburn or acid reflux, acid-reducing pharmacotherapy should be recommended.

Acid-reducing pharmacotherapy typically consists of antacids, H2 blockers or PPIs. To strengthen our recommendations that GI symptoms should be treated in pregnancy, we sought to provide reassuring evidence that both H2 blockers and PPIs are not associated with increased fetal risks. Therefore, our next two studies involved systematic reviews of all original research assessing the safety of H2 blockers and PPIs in pregnancy. For both studies, electronic databases were searched from inception to locate all articles meeting our inclusion criteria. To ensure accuracy, two independent reviewers performed article selection, and disagreements were resolved through consensus.

Based on the inclusion and exclusion criteria, studies were selected that specifically examined the rate of congenital malformations after maternal exposure to either H2 blockers or PPIs. Additionally, individual quality scores of accepted articles were determined by the validated Downs-Black scale\textsuperscript{249}. With data from 2398 exposed and 119,892 non-exposed to H2 blockers, the overall odds ratio for congenital malformations was 1.14 [0.89, 1.45]. Further analysis revealed no increased risks for
spontaneous abortions, preterm delivery and small for gestational age with odds ratios and 95% CI of 0.62 [0.36-1.05], 1.17 [0.94, 1.147] and 0.28 [0.06, 1.22]. Similarly, with data from 134,940 patients, including 1530 exposed and 133,410 non-exposed to PPIs, the overall odds ratio for major malformations was 1.12 (CI_{95%} of 0.86-1.45). Further analysis revealed no increased risk for spontaneous abortions (OR=1.29, CI_{95%}:0.84-1.97) and preterm delivery (OR=1.13, CI_{95%}:0.96-1.33). In secondary analysis of 1341 exposed and 120,137 unexposed to omeprazole alone, the odds ratio and CI_{95%} for major malformations was 1.17 [0.90-1.53]. Based on the results from these two studies, H2 blockers and PPIs are not associated with increased risks for major congenital birth defects, spontaneous abortions or preterm delivery. The narrow range of 95% confidence intervals is further reassuring suggesting that H2 blockers or PPIs can be safely used in pregnancy to manage GERD symptoms, and hence, reduce the severity of NVP.

The focus of my first two clinical pharmacology strategies was based on the variability of tolerability to iron-containing prenatal multivitamins and GI symptoms that commonly occur in pregnancy; therefore, based on these sources of variability, specific strategies can be recommended to prevent or limit the severity of NVP symptoms. The third clinical pharmacology focus of this dissertation was the variability associated with the anti-emetic effects of Diclectin® (doxylamine succinate/pyridoxine hydrochloride). Although Diclectin® is approved and used by millions of women for the management of NVP symptoms, its therapeutic effect can be suboptimal. There appears to be large
variability in the onset and efficacy of this doxylamine succinate/pyridoxine hydrochloride combination resulting in incomplete management of NVP.

In order to improve management of NVP using doxylamine succinate/pyridoxine hydrochloride, we sought to determine the variability in the pharmacokinetics of the two active ingredients, doxylamine and PLP in healthy females of childbearing age. These women were confined in a research facility from 28 hours prior to doxylamine succinate/pyridoxine hydrochloride administration, and were fed standard meals and snacks at set times, and were administered 2 tablets of Diclectin® with 240 mL of room temperature water under empty-stomach conditions. Blood samples were obtained prior to and after dosing. Samples were analyzed for doxylamine and PLP concentrations using tandem mass spectrometry. Pharmacokinetic parameters and their variability were calculated. We found a 2.1-fold difference in the area under the curve of doxylamine, and a 6.5-fold difference in the area under the curve of PLP after oral administration of 20 mg of doxylamine succinate/pyridoxine hydrochloride. Large variability also exists in the time to appearance of doxylamine in the plasma with a range of 0.5 to 8.15 hrs, and in the half-life of PLP with a range of 31.50 to 117.18 hrs. These aforementioned differences may account for the variability in effectiveness of doxylamine succinate/pyridoxine hydrochloride for the management for NVP; however further research would be required to determine the roles on the onset, duration and extent of anti-emetic action.

This dissertation examined three predominant areas of variability in an attempt to optimize clinical pharmacology strategies in managing NVP symptoms. Although we
designed and conducted the studies as ideally as possible, there are limitations in our studies. Firstly, the majority of the subjects included in both the cohort studies and the adherence study were recruited from the Motherisk Nausea and Vomiting of Pregnancy Helpline. These women tend to be of higher socioeconomic status and more motivated to comply with study protocols; therefore, the adherence to prenatal multivitamins calculated in our study may be higher than that of the general population. The primary outcome, however, was to determine the tolerability to prenatal multivitamins with different iron content; therefore, socioeconomic status and motivation are less likely to affect our results. Secondly, our second and fourth studies, the effects of discontinuing iron and of acid-reducing pharmacotherapy on NVP severity, did not contain comparison groups; however, ethical considerations were required, and as they were designed to be pilot studies, they still provide valuable information and a strong rationale to conduct randomized controlled trials. Thirdly, the pharmacokinetic analysis of the active metabolites of doxylamine succinate/pyridoxine hydrochloride provide variables that can affect the effectiveness of doxylamine succinate/pyridoxine hydrochloride; however, a more complex study involving efficacy parameters concurrently with pharmacokinetic analysis would be required to demonstrate a causal relationship.

Notwithstanding the limitations discussed above, this dissertation provides research that can result in improved management of NVP symptoms through the clinical pharmacology strategies recommended based on the sources of variability identified.
10.2 CONCLUSIONS

The interindividual variability with respect to treatment of NVP symptoms creates clinical pharmacology challenges in effective management of this common medical condition. Three key areas of variability have been identified, and our results suggest methods in which to improve management of NVP. Firstly, to minimize exacerbation of NVP and GI symptoms, prenatal multivitamins with low iron content should be used in the first trimester of pregnancy in non-anemic women. This strategy will also improve adherence resulting in better nutrition for the mother and fetus. Secondly, GI conditions and symptoms are very prevalent in pregnant women, and contribute to increased severity of NVP symptoms. Treatment of these GI symptoms is necessary in preventing aggravation of NVP symptoms and improving the quality of life of pregnant women. Furthermore, since treatment with acid-reducing pharmacotherapy is not associated with increased fetal risks, the maternal benefits of treating GI symptoms with either H2 blockers or PPIs outweigh the potential fetal risks. Lastly, although doxylamine succinate/pyridoxine hydrochloride does provide some degree of anti-emetic relief in most women, there is variability in the onset, duration and extent of its pharmacological activity. Large variability was observed in the pharmacokinetics of the active metabolites; however, further research is required to determine if these differences result in a causal relationship with the anti-emetic properties.
Although this dissertation has addressed several areas of variability for the clinical pharmacological management of NVP, further research is required in this field to ensure optimization of maternal and fetal health.
Based on the findings of this research project, there are several additional studies that are required to verify and strengthen our findings. As previously mentioned, a randomized controlled trial would be necessary to confirm the association between iron content and increased severity of NVP, tolerability and adherence. If confirmed, these results will provide strong evidence to remove iron from prenatal multivitamins or minimize the dose especially since iron requirements do not change substantially in the first trimester of pregnancy when NVP symptoms are the most severe. Similarly, an additional randomized controlled trial is necessary to verify our results that suggest acid-reducing therapy and management of GI symptoms reduce the severity of NVP. Since treatment is not associated with increased fetal risks and may improve NVP severity, further evidence to support the association between GI symptoms and severity of NVP would provide health-care providers and pregnant women with the reassurance to manage GI symptoms effectively.

In order to effectively manage NVP symptoms with doxylamine succinate/pyridoxine hydrochloride, we sought to identify variability in the pharmacokinetics of the two active metabolites that compose this drug combination. Although we did detect large differences in the pharmacokinetic parameters, our study was not designed to determine the effects of this variability on the effectiveness of doxylamine succinate/pyridoxine hydrochloride. However, our research provides a starting point in which to focus subsequent studies, for instance, the large variability in the onset of appearance of doxylamine in the plasma may explain the differences in the
onset of anti-emetic relief, or the significant variation in the half-life of PLP may explain the differences in the duration of anti-emetic effects. Determining cause-and-effect relationships is critical to create optimal dosing guidelines of the doxylamine succinate/pyridoxine hydrochloride combination in order to improve management of NVP symptoms.

Furthermore, determining the variability of pharmacokinetic parameters after multiple dose doxylamine succinate/pyridoxine hydrochloride administration is also critical as, clinically, this combination is administered daily for prolonged periods of time. Variability in steady-state concentrations will also affect dosing schedules and therapeutic effect of Diclectin®; therefore, once any differences are detected, again, it is important to associate these differences with the effectiveness of Diclectin®.

This dissertation focused on only three of the main areas of variability in the clinical pharmacological management of NVP. Other medical conditions are also thought to increase the severity of NVP symptoms, as well as factors such as dietary strategies and sleep. It is important to identify other aggravating factors in order to design studies that will provide evidence of these relationships. Once these associations are identified, studies can be conducted to determine whether treatment results in decreased severity of NVP. More research is required in this area as NVP is the most common medical condition, and it can drastically affect a woman’s life physically, emotionally and financially. By providing evidence that sources of variability can exacerbate NVP symptoms, and that management of these factors is vital to effectively
manage NVP, pregnant woman and health-care providers can be more reassured with respect to clinical pharmacology strategies to manage NVP.
REFERENCES


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∞ LIST OF PUBLICATIONS
AND ABSTRACTS ∞
∞ PUBLICATIONS ∞


Gill SK, Maltepe C, Koren G. Improving iron supplementation in pregnancy. Presented at the IXth International Conference on Clinical Pharmacology and Therapeutics, Quebec City, Canada, July 2008.


∞ APPENDICES ∞
Appendix A.1 Initial Recruitment Intake Form

Adherence and Tolerability of Iron-containing Multivitamins in Women with Pre-existing GI conditions

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Pregnant woman</td>
<td>□ Pregnant women who discontinued either PregVit® or Orifer F®.</td>
</tr>
<tr>
<td>□ Did not start or discontinued multivitamins</td>
<td></td>
</tr>
</tbody>
</table>

Did not start/discontinued because of:

- □ Nausea and vomiting of pregnancy
- □ Gastrointestinal symptoms
- □ Gastrointestinal/medical conditions:
  - □ Hypothyroidism
  - □ Crohn’s disease
  - □ Ulcerative colitis
  - □ Peptic/duodenal ulcer
  - □ Irritable colon
  - □ Celiac disease
  - □ Other

<table>
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<tr>
<th>Exclusion Criteria</th>
<th></th>
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</thead>
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<tr>
<td>□ Pregnant women with hypersensitivities to ingredients in either PregVit® or Orifer F®.</td>
<td></td>
</tr>
<tr>
<td>□ Pregnant women with hemochromatosis, hemosiderosis, and hemolytic anemia (Orifer F formulation is contraindicated).</td>
<td></td>
</tr>
<tr>
<td>□ Women who do not agree to participate in the study.</td>
<td></td>
</tr>
<tr>
<td>□ Women who do not have nausea or vomiting, gastrointestinal symptoms and/or conditions</td>
<td></td>
</tr>
</tbody>
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DATE (d/m/y): ________________  Study coordinator: ________________
Signature: ____________________

Most convenient contact time(s):
### PATIENT CONTACT INFO.

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<th>PHYSICIAN CONTACT INFO.</th>
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<td>(W) _____________________________</td>
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### CURRENT PREGNANCY

| LMP: ___________________________ |
| Cycle: _______days |
| EDC: ___________________________ |

| GA:__________wks | PPW: ___________lbs/kg | WT: ___________lbs/kg |

Method of conception: natural_____ fertility drugs_____ in vitro fert. _____

Previous multivitamin: ______________________ Dose (no. tablets per day): _______

Frequency: ☐ Everyday ☐ Every other day ☐ ____ days per week

Start: _______________ Stop: _______________

Why: _____________________________________
### Past Pregnancy History

<table>
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<tr>
<th>No.</th>
<th>Gender</th>
<th>Year of birth</th>
<th>GA (wks)</th>
<th>Prenatal vitamins/ multivitamins/dose/freq.</th>
<th>Side Effects</th>
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<td></td>
</tr>
</tbody>
</table>

### Nausea and Vomiting of Previous Pregnancies

<table>
<thead>
<tr>
<th>No.</th>
<th>Year</th>
<th>NVP</th>
<th>Duration</th>
<th>Severity</th>
<th>Treatments/Effective Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>From:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td>To:</td>
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<td></td>
<td>To:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### SUBSTANCE USE

<table>
<thead>
<tr>
<th>Substance</th>
<th>Start</th>
<th>Stop</th>
<th>Dose/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>✔ Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>✗ No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>✔ Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>✗ No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marijuana</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>✔ Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>✗ No</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>✔ Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### DRUG EXPOSURE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Start</th>
<th>Stop</th>
<th>Dose/ Frequency/ Route</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>
## CURRENT MEDICAL HISTORY

<table>
<thead>
<tr>
<th>Medical Category</th>
<th>Medical Condition</th>
<th>Medical Notes</th>
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</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other _________</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(NVBP = nausea and vomiting before pregnancy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Crohn's disease</td>
<td>NVBP Yes No</td>
</tr>
<tr>
<td></td>
<td>Ulcerative colitis</td>
<td>NVBP Yes No</td>
</tr>
<tr>
<td></td>
<td>Peptic/duodenal ulcer</td>
<td>NVBP Yes No</td>
</tr>
<tr>
<td></td>
<td>Irritable colon</td>
<td>NVBP Yes No</td>
</tr>
<tr>
<td></td>
<td>Irritable bowel syndrome</td>
<td>NVBP Yes No</td>
</tr>
<tr>
<td></td>
<td>Celiac disease</td>
<td>NVBP Yes No</td>
</tr>
<tr>
<td>Organ disease</td>
<td>Heart disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kidney disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other _________</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Migraines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Iron deficiency anemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bacterial/viral infection</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bipolar</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>
NAUSEA AND VOMITING OF CURRENT PREGNANCY

Are you experiencing nausea and vomiting?  □ Yes  □ No

When did NVP begin? ___________________________wks/date

Have you spoken to healthcare provider about NVP?  □ No  □ Yes

Treatment/Advice
__________________________________________________________________________

Start____________  Stop ____________

Dose/Freq.__________________

Effective? □ Yes  □ No

SE______________________________

BEFORE TAKING ASSIGNED VITAMIN

In 1 week, how often nauseous?

<table>
<thead>
<tr>
<th></th>
<th>□ Always</th>
<th>□ Most/time</th>
<th>□ Sometimes</th>
<th>□ Rarely/never</th>
</tr>
</thead>
</table>

In 1 week, # of retching/gagging episodes?

<table>
<thead>
<tr>
<th></th>
<th>&gt;5/day</th>
<th>2-5/day</th>
<th>1/day</th>
<th>&lt;1/day</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

In 1 week, # of vomiting episodes?

<table>
<thead>
<tr>
<th></th>
<th>&gt;5/day</th>
<th>2-5/day</th>
<th>1/day</th>
<th>&lt;1/day</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
PUQUE SCORING PRIOR TO TAKING ASSIGNED VITAMIN

How many hours in the past 24 hrs did you sleep?

<table>
<thead>
<tr>
<th>How many hours in past 24 hrs had you felt nauseated/sick to stomach?</th>
<th>None (1)</th>
<th>1 hr or less (2)</th>
<th>2-3 hrs (3)</th>
<th>4-6 hrs (4)</th>
<th>&gt; 6 hrs (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many times in the past 24 hrs did you vomit?</td>
<td>≥ 7 times (5)</td>
<td>5-6 times (4)</td>
<td>3-4 times (3)</td>
<td>1-2 times (2)</td>
<td>None (1)</td>
</tr>
<tr>
<td>How many times in the past 24 hrs did you experience gagging or retching or dry heaves?</td>
<td>None (1)</td>
<td>1-2 times (2)</td>
<td>3-4 times (3)</td>
<td>5-6 times (4)</td>
<td>≥ 7 times (5)</td>
</tr>
</tbody>
</table>

PUQUE Score: _____  (Mild: ≤6  Moderate: 7-12  Severe: ≥13)
### GASTROINTESTINAL SYMPTOMS: GSRS RATING BEFORE TAKING ASSIGNED VITAMIN

**Abdominal Pain**
- **Symptom:** Abdominal pain/discomfort
  - **GSRS Rating:**
    - 0: No/brief pain
    - 1: Some aches/pains
    - 2: Prolonged and troublesome pains
    - 3: Severe/crippling pains
  - **Treatment:**

- **Symptom:** Sucking sensation in epigastrium (upper and middle abdomen)
  - **GSRS Rating:**
    - 0: No/brief sucking sensation
    - 1: Sometimes, short discomfort
    - 2: Frequent, prolonged episodes
    - 3: Continuous discomfort
  - **Treatment:**

- **Symptom:** Nausea and vomiting of specific medical condition(s)
  - **GSRS Rating:**
    - 0: No nausea
    - 1: Sometimes, brief nausea
    - 2: Frequent, prolonged nausea
    - 3: Continuous nausea, frequent vomiting
  - **Treatment:**

- **Symptom:** Heartburn
  - **GSRS Rating:**
    - 0: No/brief heartburn
    - 1: Sometimes, short discomfort
    - 2: Frequent, prolonged discomfort
    - 3: Continuous discomfort
  - **Treatment:**

- **Symptom:** Acid reflux
  - **GSRS Rating:**
    - 0: No/brief acid reflux
    - 1: Sometimes, troublesome
    - 2: Once or twice a day
    - 3: Several times a day
  - **Treatment:**

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>SYMPTOM</th>
<th>GSRS RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal</td>
<td>Abdominal pain/discomfort</td>
<td>0  No/brief pain 1  Some aches/pains 2  Prolonged and troublesome pains 3  Severe/crippling pains</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td>Treatment</td>
</tr>
<tr>
<td>Abdominal</td>
<td>Sucking sensation in epigastrium (upper and middle</td>
<td>0  No/brief sucking sensation 1  Sometimes, short discomfort 2  Frequent,</td>
</tr>
<tr>
<td>Pain</td>
<td>abdomen)</td>
<td>prolonged episodes 3  Continuous discomfort</td>
</tr>
<tr>
<td>Abdominal</td>
<td>Nausea and vomiting of specific medical condition(</td>
<td>0  No nausea 1  Sometimes, brief nausea 2  Frequent, prolonged nausea 3  Continuous nausea, frequent vomiting</td>
</tr>
<tr>
<td>Pain</td>
<td>s)</td>
<td>Treatment</td>
</tr>
</tbody>
</table>
## GSRS RATING (cont’d)

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>SYMPTOM</th>
<th>GSRS RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigestion</td>
<td>Abdominal rumbling</td>
<td>0 No/brief rumbling 1 Sometimes, short,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>troublesome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Frequent, prolonged 3 Continuous, crippling</td>
</tr>
<tr>
<td>Indigestion</td>
<td>Bloating</td>
<td>0 No/brief bloating 1 Sometimes, short discomfort</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Frequent, prolonged bloating 3 Continuous, crippling</td>
</tr>
<tr>
<td>Indigestion</td>
<td>Belching</td>
<td>0 No/brief belching 1 Sometimes, troublesome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Frequent, prolonged 3 Continuous, crippling</td>
</tr>
<tr>
<td>Indigestion</td>
<td>Excessive passing gas</td>
<td>0 No increased passing gas 1 Sometimes, short passing gas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Frequent, prolonged 3 Continuous, crippling</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Increased passage of stool</td>
<td>0 Once a day 1 3x a day 2 5x a day 3 7x or more a day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 Normal consistency 1 Somewhat loose 2 Runny 3 Watery</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Loose stool</td>
<td>0 Normal control 1 Sometimes feeling urgent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Frequently feeling urgent 3 Inability to control</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Urgent need to pass stool</td>
<td>0 Normal control 1 Sometimes feeling urgent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Frequently feeling urgent 3 Inability to control</td>
</tr>
</tbody>
</table>
## GSRS RATING (cont’d)

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>SYMPTOM</th>
<th>GSRS RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Decreased passage of stool</td>
<td>[ ] Yes [ ] No</td>
</tr>
<tr>
<td>Constipation</td>
<td>Hard stool</td>
<td>[ ] Yes [ ] No</td>
</tr>
<tr>
<td>Constipation</td>
<td>Feelings of incomplete evacuation</td>
<td>[ ] Yes [ ] No</td>
</tr>
</tbody>
</table>

## GSRS RATINGS

<table>
<thead>
<tr>
<th>Total score of each syndrome:</th>
<th>*Mean score of each syndrome:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Abdominal Pain</td>
<td>1. Abdominal Pain</td>
</tr>
<tr>
<td>2. Reflux</td>
<td>2. Reflux</td>
</tr>
<tr>
<td>3. Indigestion</td>
<td>3. Indigestion</td>
</tr>
<tr>
<td>4. Diarrhea</td>
<td>4. Diarrhea</td>
</tr>
<tr>
<td>5. Constipation</td>
<td>5. Constipation</td>
</tr>
</tbody>
</table>
Appendix A.2 Weekly Intake Form: Adherence and Tolerability of Iron-containing Multivitamins in Women with Pre-existing GI conditions

<table>
<thead>
<tr>
<th>DATE:</th>
<th>Study coordinator:</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENT NAME:</td>
<td></td>
</tr>
<tr>
<td>DATE OF BIRTH:</td>
<td>Received pamphlets: ☐ Yes ☐ No</td>
</tr>
<tr>
<td>PHONE NUMBER: (H)</td>
<td>(W)</td>
</tr>
<tr>
<td>HEALTH CARE PROVIDER:</td>
<td></td>
</tr>
</tbody>
</table>

Have you started to take the vitamins? Complete only one panel.

☐ YES

1. When did you start? (d/m/y)

______________________________

2. Dose:

☐ 1 tablet per day
☐ *Only 1 morning tablet per day
☐ *Only 1 evening tablet per day
☐ *One morning tablet and one evening tablet per day
☐ Other __________________________

3. Frequency (# of days of vitamin intake):
Initial recruitment (d/m/y): _____________

☐ 7 days ☐ 6 days ☐ 5 days
☐ 4 days ☐ 3 days ☐ 2 days
☐ 1 day ☐ Other: _______ days

4. Number of tablets taken:
Total ______ *AM______ *PM______

5. Side effects: ______________________
_________________________________
_________________________________

☐ NO

Why?
☐ Nausea
☐ Vomiting
☐ Abdominal pains
☐ Constipation
☐ Diarrhea
☐ Indigestion
☐ Reflux
☐ Tablet size/can't swallow
☐ Cost
☐ No insurance
☐ *Tedious to take 2 tablets a day
☐ *Tedious to get doctor’s prescription
☐ Do not have the vitamins yet
☐ Other

_________________________________

Do you think you might start the vitamins later on?
☐ Yes: Follow-up.
    Contact date_______________________
☐ No: Mention other vitamin
Appendix A.3 Monthly Intake Form

Adherence and Tolerability of Iron-containing Multivitamins in Women with Pre-existing GI conditions

<table>
<thead>
<tr>
<th>DATE:</th>
<th>Study coordinator:</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENT NAME:</td>
<td></td>
</tr>
<tr>
<td>DATE OF BIRTH:</td>
<td></td>
</tr>
<tr>
<td>PHONE NUMBER: (H)</td>
<td>(W)</td>
</tr>
<tr>
<td>HEALTH CARE PROVIDER:</td>
<td></td>
</tr>
</tbody>
</table>

CURRENT PREGNANCY
GA: __________________ Current weight: __________________ lbs/kg

DRUG EXPOSURE - any new exposures since last contact

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Start</th>
<th>Stop</th>
<th>Dose/ Frequency/ Route</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>
### MEDICAL/OBSTETRICAL CONDITIONS OR SYMPTOMS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment (previous contact)</th>
<th>Any changes to treatment?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

### SUBSTANCE USE - document any changes since last contact

<table>
<thead>
<tr>
<th>Substance</th>
<th>Start</th>
<th>Stop</th>
<th>Dose/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Tobacco</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Marijuana</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Other</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Have you continued to use the multivitamin during the past month (since we last spoke to you)? Complete only one panel.

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dose:</td>
<td>1. When did you stop?</td>
</tr>
<tr>
<td>□ 1 tablet per day</td>
<td>__________________________ wks/date</td>
</tr>
<tr>
<td>□ *Only 1 morning tablet per day</td>
<td>2. Prior to stopping ..........</td>
</tr>
<tr>
<td>□ *Only 1 evening tablet per day</td>
<td>a) Dose:</td>
</tr>
<tr>
<td>□ *One morning tablet and one evening tablet per day</td>
<td>□ 1 tablet per day</td>
</tr>
<tr>
<td>□ Other _____________________</td>
<td>□ *Only 1 morning tablet per day</td>
</tr>
<tr>
<td></td>
<td>□ *Only 1 evening tablet per day</td>
</tr>
<tr>
<td></td>
<td>□ *One morning tablet and one evening tablet per day</td>
</tr>
<tr>
<td></td>
<td>□ Other _____________________</td>
</tr>
<tr>
<td>2. Frequency:</td>
<td>b) Frequency:</td>
</tr>
<tr>
<td>From (d/m/y): ________________</td>
<td>From (d/m/y): ______________________</td>
</tr>
<tr>
<td>To (d/m/y): ________________</td>
<td>To (d/m/y of stop date): ______________</td>
</tr>
<tr>
<td>Total days of vitamin intake: ______</td>
<td>Total days of vitamin intake: ______</td>
</tr>
<tr>
<td>Missed days:</td>
<td>3. Number of vitamin tablets taken:</td>
</tr>
<tr>
<td>□ No □ Yes _______ days</td>
<td>Total______ *AM______ *PM______</td>
</tr>
<tr>
<td></td>
<td>4. Why?</td>
</tr>
<tr>
<td>3. Number of vitamin tablets taken:</td>
<td>□ Cost □ No insurance</td>
</tr>
<tr>
<td>Total______ *AM______ *PM______</td>
<td>□ Nausea</td>
</tr>
<tr>
<td></td>
<td>□ Vomiting</td>
</tr>
<tr>
<td></td>
<td>□ Abdominal pains</td>
</tr>
<tr>
<td></td>
<td>□ Constipation</td>
</tr>
<tr>
<td></td>
<td>□ Diarrhea</td>
</tr>
<tr>
<td></td>
<td>□ Indigestion</td>
</tr>
<tr>
<td></td>
<td>□ Reflux</td>
</tr>
<tr>
<td></td>
<td>□ Tablet size</td>
</tr>
<tr>
<td></td>
<td>□ *Tedious to take 2 pills a day</td>
</tr>
<tr>
<td></td>
<td>□ *Tedious to get doctor's prescription</td>
</tr>
<tr>
<td></td>
<td>□ Other ____________________</td>
</tr>
</tbody>
</table>

*PregVit only
## Nausea and Vomiting of Current Pregnancy

**Are you experiencing nausea and vomiting?**
- [ ] Yes
- [ ] No

**How are you treating it?**

<table>
<thead>
<tr>
<th>Medication/treatment (0-10 best)</th>
<th>Dose</th>
<th>Frequency</th>
<th>Effective</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**AFTER TAKING ASSIGNED VITAMIN**

<table>
<thead>
<tr>
<th>In 1 week, how often nauseous?</th>
<th>□ Always □ Most/time □ Sometimes □ Rarely/never</th>
</tr>
</thead>
<tbody>
<tr>
<td>In 1 week, # of retching/gagging episodes?</td>
<td>□ &gt;5/day □ 2-5/day □ 1/day □ &lt;1/day □ Never</td>
</tr>
<tr>
<td>In 1 week, # of vomiting episodes?</td>
<td>□ &gt;5/day □ 2-5/day □ 1/day □ &lt;1/day □ Never</td>
</tr>
</tbody>
</table>
### PUQUE SCORING AFTER TAKING ASSIGNED VITAMIN

How many hours in the past 24 hrs did you sleep?
_______________________

<table>
<thead>
<tr>
<th>How many hours in past 24 hrs had you felt nauseated/sick to stomach?</th>
<th>None (1)</th>
<th>1 hr or less (2)</th>
<th>2-3 hrs (3)</th>
<th>4-6 hrs (4)</th>
<th>&gt; 6 hrs (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many times in the past 24 hrs did you vomit?</td>
<td>≥ 7 times (5)</td>
<td>5-6 times (4)</td>
<td>3-4 times (3)</td>
<td>1-2 times (2)</td>
<td>None (1)</td>
</tr>
<tr>
<td>How many times in the past 24 hrs did you experience gagging or retching or dry heaves?</td>
<td>None (1)</td>
<td>1-2 times (2)</td>
<td>3-4 times (3)</td>
<td>5-6 times (4)</td>
<td>≥ 7 times (5)</td>
</tr>
</tbody>
</table>

**PUQUE Score:** _____  **Mild:** ≤ 6  **Moderate:** 7-12  **Severe:** ≥ 13
**GASTROINTESTINAL SYMPTOMS:**
**GSRS RATING AFTER TAKING ASSIGNED VITAMIN**

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>SYMPTOM</th>
<th>GSRS RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal</td>
<td>Abdominal pain/discomfort</td>
<td>0  No/brief pain</td>
</tr>
<tr>
<td>Pain</td>
<td>□ Yes □ No</td>
<td>1  Some aches/pains</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>2  Prolonged and troublesome pains</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3  Severe/crippling pains</td>
</tr>
<tr>
<td>Abdominal</td>
<td>Sucking sensation in epigastrium (upper and middle abdomen)</td>
<td>0  No/brief sucking sensation</td>
</tr>
<tr>
<td>Pain</td>
<td>□ Yes □ No</td>
<td>2  Frequent, prolonged episodes</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>3  Continuous discomfort</td>
</tr>
<tr>
<td>Abdominal</td>
<td>Nausea and vomiting of specific medical conditions</td>
<td>0  No nausea</td>
</tr>
<tr>
<td>Pain</td>
<td>□ Yes □ No</td>
<td>1  Sometimes, brief nausea</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>2  Frequent, prolonged nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3  Continuous nausea, frequent vomiting</td>
</tr>
<tr>
<td>Reflux</td>
<td>Heartburn</td>
<td>0  No/brief heartburn</td>
</tr>
<tr>
<td></td>
<td>□ Yes □ No</td>
<td>1  Sometimes, short discomfort</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>2  Frequent, prolonged discomfort</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3  Continuous discomfort</td>
</tr>
<tr>
<td>Reflux</td>
<td>Acid reflux</td>
<td>0  No/brief acid reflux</td>
</tr>
<tr>
<td></td>
<td>□ Yes □ No</td>
<td>1  Sometimes, troublesome</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>2  Once or twice a day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3  Several times a day</td>
</tr>
</tbody>
</table>
### GSRS RATING (cont’d)

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>SYMPTOM</th>
<th>GSRS RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigestion</td>
<td>Abdominal rumbling</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Yes □ No</td>
<td>□ 0 No/brief rumbling</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 1 Sometimes, short, troublesome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 2 Frequent, prolonged</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 3 Continuous, crippling</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Indigestion</td>
<td>Bloating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Yes □ No</td>
<td>□ 0 No/brief bloating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 1 Sometimes, short discomfort</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 2 Frequent, prolonged</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 3 Continuous, crippling</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Indigestion</td>
<td>Belching</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Yes □ No</td>
<td>□ 0 No/brief belching</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 1 Sometimes, troublesome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 2 Frequent, prolonged</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 3 Continuous, crippling</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Indigestion</td>
<td>Excessive passing gas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Yes □ No</td>
<td>□ 0 No increased passing gas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 1 Sometimes, short discomfort</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 2 Frequent, prolonged</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 3 Continuous, crippling</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Increased passage of stool</td>
<td>□ 0 Once a day</td>
</tr>
<tr>
<td></td>
<td>□ Yes □ No</td>
<td>□ 1 3x a day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 2 5x a day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 3 7x or more a day</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Loose stool</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Yes □ No</td>
<td>□ 0 Normal consistency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 1 Somewhat loose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 2 Runny</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 3 Watery</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Urgent need to pass stool</td>
<td>□ 0 Normal control</td>
</tr>
<tr>
<td></td>
<td>□ Yes □ No</td>
<td>□ 1 Sometimes feeling urgent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 2 Frequently feeling urgent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ 3 Inability to control</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td></td>
</tr>
</tbody>
</table>
**GSRS RATING (cont’d)**

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>SYMPTOM</th>
<th>GSRS RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Decreased passage of stool</td>
<td>0  Once a day</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Yes No</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>Hard stool</td>
<td>0  Normal consistency</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>Feelings of incomplete evacuation</td>
<td>0  Complete evacuation, no strain</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GSRS RATINGS**

Total score of each syndrome:  
1. Abdominal Pain________  
2. Reflux ___________  
3. Indigestion _________  
4. Diarrhea _________  
5. Constipation _________  

*Mean score of each syndrome:
1. Abdominal Pain________  
2. Reflux ___________  
3. Indigestion _________  
4. Diarrhea _________  
5. Constipation _________  

*Higher mean scores indicate greater severity of symptoms.
**MULTIVITAMIN SUPPLEMENTATION (cont’d)**

Please complete only one panel.

<table>
<thead>
<tr>
<th>Continued taking vitamin</th>
<th>Discontinued vitamin</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. What is it about the multivitamin that allows you to take it?</td>
<td>4. Do you think you will resume the vitamins later on?</td>
</tr>
</tbody>
</table>
| □ Feel no or less nausea | □ Yes  
Next monthly contact  
______________ |
| □ Feel no or less vomiting | □ No  
Mention other vitamin  
______________ |
| □ Feel no or less gagging/retching |  
| □ Feel no or less abdominal pains |  
| □ Feel no or less constipation |  
| □ Feel no or less diarrhea |  
| □ Feel no or less reflux |  
| □ Small tablet size/ easy to swallow |  
| □ Cost |  
| □ *Insurance |  
| □ *2 pills that separate the ingredients |  
| □ Other __________________________ |  
| |  
| * PregVit only |
Appendix C: Nausea and Vomiting of Pregnancy Helpline Form

**THE MOTHERISK PROGRAM - NFP FORM**
THE DIVISION OF CLINICAL PHARMACOLOGY AND TOXICOLOGY, THE HOSPITAL FOR SICK CHILDREN, TORONTO, ONTARIO

<table>
<thead>
<tr>
<th>NFP no.</th>
<th>internet</th>
<th>health professional</th>
<th>media</th>
<th>MR</th>
<th>family/friend</th>
<th>other</th>
<th>Can</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Contact**

- Contact:
- Contact time:
- Counselor:
- Date:

**MATERNAL DATA**

<table>
<thead>
<tr>
<th>Name:</th>
<th>Date of birth:</th>
<th>Phone: (E)</th>
<th>Telephone: ( )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stable contact #: ( )</th>
<th>Fax: ( )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Address: | |
|----------||
|          | |

**DOCTOR'S INFORMATION**

<table>
<thead>
<tr>
<th>Name:</th>
<th>GP</th>
<th>OR</th>
<th>midwife/nurse practitioner</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BASELINE DATA**

- **Severity of NVP?**
  - □ mild
  - □ moderate
  - □ severe

- **When did your NVP start?**
  - □ weeks
  - □ date

- **Did you ever expect to have NVP in this pregnancy?**
  - □ No
  - □ Yes

- **Have you spoken to your healthcare provider about NVP?**
  - □ No
  - □ Yes

**OVER THE LAST WEEK, HOW OFTEN HAD YOU HAD NAUSEA?**

- □ always
- □ most of the time
- □ some of the time
- □ rarely/never

**OVER THE LAST WEEK, RETCHING EPISODES?**

- □ > 5/day
- □ 3-5/day
- □ 1-2/day
- □ 1/day
- □ never

**OVER THE LAST WEEK - VOMITING EPISODES?**

- □ > 5/day
- □ 3-5/day
- □ 1-2/day
- □ 1/day
- □ never

**WHEN IS YOUR NVP WORSE?**

- □ morning
- □ afternoon
- □ evening

**MATERNAL DEMOGRAPHICS (Please check only ONE box)**

<table>
<thead>
<tr>
<th>ETHNICITY</th>
<th>LIVING ARRANGEMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>Single</td>
</tr>
<tr>
<td>Black</td>
<td>Married</td>
</tr>
<tr>
<td>Native American</td>
<td>Living with partner</td>
</tr>
<tr>
<td>South Asian</td>
<td>Divorced</td>
</tr>
<tr>
<td>Hispanic</td>
<td>Widowed</td>
</tr>
<tr>
<td>Oriental</td>
<td>Other</td>
</tr>
</tbody>
</table>

**EDUCATION**

- Public school
- High school
- College
- University
- Post-graduate training

**OCCUPATION**

- Employed
- Self-employed
- Unemployed
- Homemaker
- Student
- PT

**JOB:**

**Time lost from work:**

**PREGNANCY HISTORY:**

- G P S A T A defects in previous pregnancies? □ No □ Yes

- Have you used fertility drugs in this pregnancy? □ No □ Yes

- **MP:**

<table>
<thead>
<tr>
<th>CYCLE:</th>
<th>EDC:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **FPW:**

- **lb/kg**

- **wt**

- **lb/kg**

- **wt**

**IF Wgt > 5% body wt, may be dehydrated**

- **GA:**

- **wks**

**How many times did you pass urine in the last 24 hrs:**

- (If < 3 times, may be dehydrated)

**Last ultrasound scan:** □ No □ Yes □ wks

**Result:**

**Reason:**

**220**
### PREVIOUS PREGNANCY HISTORY
Please complete table. Efficiency: 1 = no effect, 10 = best.

<table>
<thead>
<tr>
<th>No.</th>
<th>Same Partner</th>
<th>Yr. Till</th>
<th>NVP</th>
<th>SEV</th>
<th>MED/TM/ET/TV (1-M)</th>
<th>EFF'N (0-10)</th>
<th>SW &amp; GA or REJ</th>
<th>SEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Same</td>
<td>From:</td>
<td></td>
<td></td>
<td>mild</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>to:</td>
<td></td>
<td></td>
<td>mod</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Same</td>
<td>From:</td>
<td></td>
<td></td>
<td>mild</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>to:</td>
<td></td>
<td></td>
<td>mod</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Same</td>
<td>From:</td>
<td></td>
<td></td>
<td>mild</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>to:</td>
<td></td>
<td></td>
<td>mod</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>severe</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>4</td>
<td>Same</td>
<td>From:</td>
<td></td>
<td></td>
<td>mild</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>to:</td>
<td></td>
<td></td>
<td>mod</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Same</td>
<td>From:</td>
<td></td>
<td></td>
<td>mild</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>to:</td>
<td></td>
<td></td>
<td>mod</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td>severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Same</td>
<td>From:</td>
<td></td>
<td></td>
<td>mild</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>to:</td>
<td></td>
<td></td>
<td>mod</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>severe</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### CURRENT NVP
Please fill out the Mother's PEQ Scoring System for the last 24 hours.

<table>
<thead>
<tr>
<th>1. In the last 24 hours, for how long have you felt nauseated or sick in your stomach.</th>
<th>Not at all (1)</th>
<th>1 hour or less (2)</th>
<th>2-3 hours (3)</th>
<th>4-6 hours (4)</th>
<th>More than 6 hours (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. In the last 24 hours, have you vomited or thrown up.</td>
<td>7 or more times (1)</td>
<td>5-6 (4)</td>
<td>3-4 (3)</td>
<td>1-2 (2)</td>
<td>1 did not throw up (1)</td>
</tr>
<tr>
<td>3. In the last 24 hours, how many times have you had retching or dry heaves without bringing anything up.</td>
<td>No time (1)</td>
<td>1-2 (2)</td>
<td>3-4 (3)</td>
<td>5-6 (4)</td>
<td>5 or more (5)</td>
</tr>
</tbody>
</table>

How many hours have you slept out of 24 hours?

Why?

On a scale of 0-10, how would you rate your Well Being?

0 (Worst possible) __________ 10 (The best you felt before pregnancy)

Can you tell me what causes you to feel that way?

### SUBSTANCE USE

<table>
<thead>
<tr>
<th>SUBSTANCE</th>
<th>START</th>
<th>STOP</th>
<th>DISCONT</th>
<th>VITAMIN</th>
<th>START</th>
<th>STOP</th>
<th>DISCONT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tobacco</td>
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<tr>
<td>Marijuana</td>
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</tr>
</tbody>
</table>

Please report substance use.

### VITAMIN USE

Please report vitamin use.
### Medical History and Exposures

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Dx:</th>
<th>Symptoms</th>
<th>Dx:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Disease</td>
<td></td>
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<tr>
<td>Respiratory Disease</td>
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<tr>
<td>Diabetes</td>
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<td></td>
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<tr>
<td>Thyroid</td>
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<td></td>
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<tr>
<td>Kidney Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please complete table. Rx = prescription. OTC = over the counter meds. IND = medical indication. SE = side effect.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE/FREQ</th>
<th>IND</th>
<th>START</th>
<th>STOP</th>
<th>EFFICACY (0 to 10)</th>
<th>X</th>
<th>SF</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>

**Bacterial/Viral Infections or GI Conditions**

(please record above all treatments and Dx)

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Presently</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral Infection</td>
<td>□ No □ Yes</td>
<td></td>
</tr>
<tr>
<td>Bacterial Infection</td>
<td>□ No □ Yes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Presently</th>
<th>Treatment</th>
<th>In the past</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heartburn</td>
<td>□ No □ Yes</td>
<td>□ No □ Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acid Reflux</td>
<td>□ No □ Yes</td>
<td>□ No □ Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach pain</td>
<td>□ No □ Yes</td>
<td>□ No □ Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indigestion</td>
<td>□ No □ Yes</td>
<td>□ No □ Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. Pylori</td>
<td>□ No □ Yes</td>
<td>□ No □ Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gas/Bloating</td>
<td>□ No □ Yes</td>
<td>□ No □ Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>□ No □ Yes</td>
<td>□ No □ Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive Saliva</td>
<td>□ No □ Yes</td>
<td>Not relevant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
NVP FOLLOW-UP FORM

<table>
<thead>
<tr>
<th>NVP no.:</th>
<th>Contact date:</th>
<th>Contact time:</th>
<th>Counselor:</th>
</tr>
</thead>
</table>

CURRENT PREGNANCY

How far along are you in the pregnancy? ____________________________
Since we last spoke, is your NVP: ☐ worse ☐ same ☐ better
WT: ____________________ lb/kg
How many times did you pass urine in the last 24 hrs: ______
(if < 3 times, may be dehydrated)
Last ultrasound scan: __________ wks
Reason: ____________________________
Result: ____________________________

Have you gone to ER for NVP, since we last spoke? ☐ Yes ☐ No
Comments:
Since we last spoke to you, have you tried any of our recommendations?
Comments:

CURRENT NVP

Please fill out the Motherisk PUQE Scoring System for the last 24 hours (please tick box and write total score)

<table>
<thead>
<tr>
<th>1. In the last 24 hours, for how long have you felt nauseated or sick in your stomach?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all (1)</td>
</tr>
<tr>
<td>2. In the last 24 hours, have you vomited or thrown up?</td>
</tr>
<tr>
<td>7 or more times (5)</td>
</tr>
<tr>
<td>3. In the last 24 hours, how many times have you had retching or dry heaves without bringing anything up?</td>
</tr>
<tr>
<td>No time (1)</td>
</tr>
</tbody>
</table>

How many hours have you slept out of 24 hours? ____________________________
Why? ____________________________

On a scale of 0-10, how would you rate your Well Being? __________
0 (Worst possible) __________ 10 (The best you felt before pregnancy)

Can you tell me what causes you to feel that way? ____________________________________________

How would you rate the effectiveness of your acid-reducing medication in:

1) Rating acid symptoms from 0 (no effect) to 10 (best):

2) Rating acid symptoms from 0 (no effect) to 10 (best):

How long after starting this medication did you notice improvement?

MAILING INFORMATION

Have you received the written information we’ve mailed out to you? ☐ No ☐ Yes
Did you find the information useful? ☐ No ☐ Yes
Did your partner find the information useful? ☐ No ☐ Yes

COMMENTS: ____________________________