DRUG-TREATED HYPEREMESIS GRAVIDARUM

Efficacy and safety

Frida Harlin
Abstract

**Introduction:** Hyperemesis Gravidarum (HG) which is a severe and serious condition of pregnancy-related nausea and vomiting and occurs in about 0.5-2% of pregnant women compared to less severe and common nausea and vomiting of pregnancy (NVP) which occurs in about 75% of all pregnant women. NVP and HG treatment regimens coincides with the embryonic developmental phases most sensitive to any possible risk for malformations. First-line treatments such as lifestyle changes, diet changes, ginger, vitamin supplementations, acupressure and acupuncture, should be considered before pharmacological interventions. Studies suggest that promethazine, metoclopramide and ondansetron can all be used for symptomatic relief. Out of these drugs ondansetron is the only off-label prescription substance. There is little good-quality evidence to support any available interventions to be superior to another. The research questions of this study are therefore: Are promethazine, metoclopramide and ondansetron safe and effective treatment options for NVP and HG? Is one therapy regime superior to another? Could NVP/HG be considered indication for ondansetron instead of an off-label option?

**Method:** The study is a literature-based study. Words used and combined to search material were: hyperemesis, gravidarum, infant, nausea, vomiting, pregnancy, treatment, safety, effect, optimal treatment, risk, adverse effect, malformation, antiemetic, ondansetron, promethazine, metoclopramide, compare, randomized.

**Results:** Three studies regarding efficacy were included; ondansetron and metoclopramide showed similar effects although ondansetron showed a slightly better adverse effect-profile. Metoclopramide and promethazine showed similar therapeutic effects but adverse effects were better with metoclopramide. When comparing ondansetron to first-line standard treatment with vitamin supplementation and doxylamine ondansetron was superior. Four studies regarding possible malformations after ondansetron exposure were included and no associations between any increased risks for spontaneous abortions, still birth, unhealthy babies according to size and weight nor any higher risks for birth defects or malformations in the infant were seen. Possibly a higher risk of cardiac septum defects could exist. To conclude the results there is no support for teratogenic risks for ondansetron use for HG and the women treated with ondansetron were actually more likely to report a live birth.

**Discussion:** The fetal development is at its most sensitive period during the same weeks as the NVP/HG peaks, anyhow ondansetron treatment is not associated with any significant increase in malformations above baseline. The reasons for NVP/HG are also discussed and theories of an overall healthy pregnancy due to higher hormonal levels and a well-functioning placenta could be associated with NVP/HG symptoms. Non-pharmacological options and pyridoxine/doxylamine alongside to metoclopramide and promethazine regimes have been used more frequently and for longer time than ondansetron and should therefore be considered first, even though all studies failed to show any statistically increased risks with any pharmacological medication and some studies suggest that ondansetron could be superior to other substances due to better profile regarding vomiting frequency and adverse effects.

**Conclusion:** The safety and effect of promethazine, metoclopramide and ondansetron are validated for treating HG. Non-pharmacological interventions shall remain the first-line treatment. One regime cannot be said to be superior to another. HG after 10th week of pregnancy could possibly be considered an indication for ondansetron while NVP should remain off-label and an option only after other methods have failed. More and larger studies should be undertaken and larger randomized controlled trials are needed to make final conclusions.

**Keywords:**
Hyperemesis Gravidarum, Antiemetic, Ondansetron, Embryotoxicity, Pregnancy.
# Table of contents

1. Introduction  
   1.1 Fetal development  
   1.2 Reasons for NVP/HG  
   1.3 Differential diagnosis  
   1.4 Mechanisms of nausea and vomiting  
   1.5 Pharmacokinetics and dynamics of promethazine  
   1.6 Pharmacokinetics and dynamics of metoclopramide  
   1.7 Pharmacokinetics and dynamics of ondansetron  
   1.8 Treatments for NVP/HG  
   1.9 Measurement of nausea  

2. Objectives  

3. Method  

4. Results  
   4.1 Results from original studies on treatment efficacy:  
      4.1.1 Study 1.  
      4.1.2 Study 2.  
      4.1.3 Study 3.  
   4.2 Results from original studies on ondansetron and safety:  
      4.2.1 Study 4.  
      4.2.2 Study 5.  
      4.2.3 Study 6.  
      4.2.4 Study 7.  

5. Discussion  
   5.1 Method  
   5.2 Result  
   5.3 Limitations  
   5.4 Final summary  

6. Conclusion  

7. Acknowledgements  

8. References  

9. Appendix 1
List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC</td>
<td>Anatomic Therapeutic Chemical classification system</td>
</tr>
<tr>
<td>BBB</td>
<td>Blood Bain Barrier</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BPM</td>
<td>Beats Per Minute</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CRTZ</td>
<td>Chemoreceptor Trigger Zone</td>
</tr>
<tr>
<td>hCG</td>
<td>Human Chorionic Gonadotropin hormone</td>
</tr>
<tr>
<td>hERG</td>
<td>Human Ether-à-go-go-Related Gene</td>
</tr>
<tr>
<td>HG</td>
<td>Hyperemesis Gravidarum</td>
</tr>
<tr>
<td>NNT</td>
<td>Number Needed to Treat</td>
</tr>
<tr>
<td>NNTb</td>
<td>Number Needed to Treat to benefit</td>
</tr>
<tr>
<td>NVP</td>
<td>Nausea and Vomiting in Pregnancy</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PUQE</td>
<td>Pregnancy-unique Quantification of Emesis and Nausea</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
</tbody>
</table>
1. Introduction

Hyperemesis Gravidarum, further referred to as HG is a severe and serious condition of pregnancy-related nausea and vomiting and occurs in about 0.5-2% of pregnant women compared to less severe and common nausea and vomiting of pregnancy further referred to as NVP which occurs in about 75% of all pregnant women. These conditions are most often peaking at week 7-12 [1,2,3]. To differentiate between NVP and HG criteria of electrolyte imbalances, ketonuria, nutrition deficiencies, and weight-loss of more than 5% of the pre-pregnancy weight are accessed. The women often require hospitalization and in-patient treatments for HG [4]. The affected women are accessed according to a pregnancy-unique quantification of emesis and nausea-scale (PUQE) where a score of 6 or less indicates mild symptoms, 7-12 indicating moderate HG and a score of 13 or more indicates severe HG [Appendix 1]. Because NVP and HG occurs and peaks during the first trimester of pregnancy, medication strategies need to be evaluated regarding teratogenicity since this is the most critical period of the embryos development in the uterus. An example of failed evaluation is the Thalidomide catastrophe where pregnant women were prescribed Thalidomide for morning sickness. This prescription caused the offspring to be born with birth defects caused by the immunosuppressive properties of the substance which causes a 30% increased risk of life-threatening malformations [5]. After this tragedy of a teratogen prescription for NVP studies must be correctly obtained for all substances prescribed for NVP/HG and awareness of the problem with possible teratogenic risks during pregnancy is highly recognized in the population.

1.1 Fetal development

The fetus develops life-important structures early in pregnancy and by four weeks gestation the embryo starts to develop three layers of cells in which the brain, spinal cord, nerves, skeleton, muscles, cardiac system and lungs will develop from. By five weeks gestation the embryo, the size of a sesame seed, has a heartbeat with a one chamber heart, the neural tube has also formed by now. These weeks are essential and important phases of the embryonic development and the sensitivity of the fetus is high [6].

At six weeks gestation, the heart is forming four chambers and beats about 150 beats per minute (bpm), facial features and the tongue are forming as well as the extremities. The neural tube continues to develop. By week seven the brain increases by a third and the teeth and palate are forming. Heart and brain cells start to specialize and grows fast. This week throughout the twelfth week are said to be the peak of NVP/HG [1]. Eight weeks of gestation marks the last week of the embryonic stage, and by the ninth week the fetal stage begins and will continue until birth. The fetal stage is a period of growth and maturation for a life outside the womb, but the major tissues were developed in the embryonic stage and are now ready to grow and optimize their function. By week 10 the heart is fully developed and beating, and the yolk sac slowly decreases leaving the nutrient provision to the placenta. By the twelfth week of gestation the palate fuse together and the most critical stages of development is now over. The upcoming months is all about growing bigger and getting ready for the outside world [6]. Malformations in human fetuses are most common between week 5-10, after that the major organs are already formed and a well-functioning placenta nourishes the fetus. When the child is delivered the APGAR-score is set by the doctor or mid-wife. Apgar score is a point-system evaluating the health of the new born baby regarding appearance, pulse, grimace, activity, respiration (APGAR) established by Dr. Virginia Apgar. A point between 0 and 2 are set for each category, the test is made first at one minute after birth and a second time five minutes after birth [7]. There has been no association between low APGAR-scores for babies exposed to substances for treating NVP/HG [8].
1.2 Reasons for NVP/HG

The reason for NVP and HG are discussed in various articles and linked to this very sensitive period in the embryonic development. Only in severe cases the HG does not subside by mid-pregnancy. Studies suggest that there could be a correlation between the body mass index (BMI) of the mother, as well as female sex of the fetus. HG also occurs more frequently in first parity and twin pregnancies [4, 9]. A possible correlation between earlier eating disorders and non-smokers are at higher risk for developing HG. If the parents have had many years of unwanted childlessness this could also correlate to the development of NVP and HG in the mother [4, 9, 10]. Also, hormonal levels and a well-functioning placenta are closely related to the experience of NVP and HG suggesting that the pregnancy outcome could be better if the mother experiences NVP [8].

1.3 Differential diagnosis

NVP/HG should be considered as serious matters and should be treated [11]. If the healthcare personnel have no doubt the nausea and vomiting is due to pregnancy, symptomatic treatment should be considered. Women who experience nausea and vomiting later on after the first trimester needs further evaluation to whereas the trigger for nausea is evolving from [4, 8]. Other reasons are rarely encountered but failure to determinate the condition could cause serious complications for woman and baby [4, 8]. Possible differential diagnosis for NVP/HG is summarized in Table 1 [4, 8].

Table 1: Summary of differential diagnosis to NVP/HG by type and alphabetical order

<table>
<thead>
<tr>
<th>Conditions related to pregnancy</th>
<th>Gastrointestinal</th>
<th>Genitourinary tract</th>
<th>Metabolic/Endocrine</th>
<th>Neurological</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute fatty liver of pregnancy, Preeclampsia</td>
<td>Achalasia, Appendicitis, Biliary tract disease, Bowel obstruction, Cholecystitis Gastroenteritis, Gastroparesis, GERD’s, Helicobacter pylori, Hepatitis Pancreatitis, Peptic-Ulcer disease</td>
<td>Degenerating uterine leiomyoma, Kidney stones, Nephrolithiasis Ovarian torsion, Pyelonephritis, Uremia</td>
<td>Addison’s Disease, Diabetic ketoacidosis, Hypercalcemia Hyper/hypothyroidism, Porphyria</td>
<td>Migraine Pseudomotor cerebri, Tumors of CNS Vestibular lesions,</td>
<td>Cyclic vomiting syndrome, Drug intolerance, Drug toxicity, Infections, Psychological or psychiatric disorders</td>
</tr>
</tbody>
</table>
1.4 Mechanisms of nausea and vomiting

The vomiting center can be activated by irritants or directly by input from the GI-canal, cerebral cortex and thalamus, vestibular region and the chemoreceptor trigger zone (CRTZ) [12]. The CRTZ is not protected by the blood-brain barrier (BBB) and is thus more sensitive to irritants either corporal or chemically induced [12]. The CRTZ is triggered by the blood concentration of substances and the dominant receptors in the area are of dopamine and serotonin (5-HT) type, but also histamine (H1) and acetylcholine are neurotransmitters involved in nausea. [13]. To reduce nausea in women suffering from NVP/HG substances such as promethazine (H1-blocker) metoclopramide (dopamin3-antagonist) and ondansetron (5-HT-antagonist) are used to chemically block these sites and reduce the nausea and vomiting activation.

Table 2: Summary of substances [14, 15, 16].

<table>
<thead>
<tr>
<th>Substance</th>
<th>ATC ¹</th>
<th>Drug type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promethazine</td>
<td>R06AD02</td>
<td>Antihistamine H1-antagonist</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>A03FA01</td>
<td>Dopamine-receptor antagonist</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>A04AA01</td>
<td>5HT-receptor antagonist</td>
</tr>
</tbody>
</table>

1.5 Pharmacokinetics and dynamics of promethazine

Promethazine is a potent long-acting antihistamine of H1-receptors in the central nervous system. Disturbance of sleep patterns are reported as adverse effect in both healthy and patients suffering from sleep-disorders. Promethazine absorbs from the gastrointestinal tract and reaches maximum plasma concentration within 2-3 hours. Distribution volume for promethazine is approximately 13L per kilogram body weight, and 80-90% bound to plasma proteins. First passage metabolism is high and the bioavailability is low after oral administrations. The half-life of promethazine is about 13 hours and eliminated mostly as metabolites through urine [14].

1.6 Pharmacokinetics and dynamics of metoclopramide

Metoclopramide is a dopamine antagonist with a centrally acting antiemetic effect and promotes motility within the ventricular-duodenal-small intestine tract. Metoclopramide synchronizes antral and duodenal contractions and activates the peristaltic of the bowel. Distribution volume for metoclopramide is about 3,5 L per kilogram body-weight and the bioavailability is individual and approximately between 32-97%. Metoclopramide eliminates through urine, 20-30% as unchanged metoclopramide the rest as metabolites. Animal testing does not suggest any risks in particular for human use [15].

¹ ATC = Anatomic Therapeutic Chemical classification system used in FASS to categorize substances.
1.7 Pharmacokinetics and dynamics of ondansetron

Ondansetron is a potent and strongly selective 5-HT3-antagonist, the antiemetic mechanism of action is not yet known. Ondansetron is selectively blocking serotonin receptors which could initiate nausea and vomiting though vagal afferent nerves. Ondansetron is absorbed in the GI-tract and reaches maximum plasma concentration within 1.5 hours after administration. Distribution volume for ondansetron is about 140L per kilo body weight. Ondansetron has a bioavailability after first passage metabolism of about 60% and 70-75% bound to plasma proteins. Ondansetron is eliminated from the systemic circulation mostly by liver enzymes, less than 5% is eliminated in urine as unchanged form. The half-life is approximately 3 hours. Studies on toxicity and carcinogenicity showed no specific risks for humans but one study on human heart cells showed a possible effect on QT-prolongation [16].

1.8 Treatments for NVP/HG

Because of the sensitivity and teratogenicity of substances used for antiemetic properties in pregnancy, first -line treatments such as lifestyle changes, diet changes, ginger, vitamin supplementations, acupressure and acupuncture, [4] should be considered before prescribing any of the pharmacological interventions mentioned above. Standard treatment today is vitamin supplementation with pyridoxine and in addition doxylamine if monotherapy with pyridoxine is not enough [2].

Studies suggest that H1-blockers, dopamine antagonists and serotonin antagonists can all be used as second-line treatments [17]. Out of these drugs ondansetron is the only off-label prescription substance [14, 15, 16]. The effect and safety must be considered before choosing one alternative over another. The safety profiles of the substances are studied continually and there is little good-quality evidence to support any available interventions to be superior to another. Further, study results are somewhat confliction on the matter but the pharmacological interventions are better to undertake than not treating the HG patients at all due to fatal risks for the women and a possible source for choosing to terminate a wanted pregnancy [17].

1.9 Measurement of nausea

To be able to address these conditions in clinical trials there has to be a way to measure the subjective feeling of nausea and well-being. To do this a Visual Analog Scale (VAS) can be used [2, 17, 23]. VAS scores are used to measure a certain characteristic or attitude that has a subjective range over a continuum of imagined values. This instrument is used for example in clinical research to give an estimate of intensity or frequency of symptoms like nausea in this case [2]. Studies on this matter tend to address the nausea from a personal diary filled by the participating women where they can rate their well-being on an imaginary scale alongside with the emesis frequency [2, 3,19]. Further has a Pregnancy-Unique Quantification of Emesis (PUQE) been developed to classify the severity of the NVP/HG. This can be found in appendix 1 [28].

For the statistical analysis, it is common to use odds ratios (OR) and estimated hazard ratios. These analysis tools will give an idea of the association between for example treatment options and the outcome of these. The OR are then representing the odds that a certain outcome will occur given the treatment; compared to the odds that the outcome will occur in absence of the treatment. For the adjusted hazard ratio, the values are describing at what rate the study endpoint e.g. a malformation occurs compared to that the same outcome occurs in the controls. 95% confidence interval (CI) are used in the studies to give an estimate of in what range the true value lies within [1, 2].
2. Objectives

NVP and HG treatment regimens coincides with the most sensitive embryonic developmental phases, therefore there is a particular risk with pharmacological treatments for the women suffering from these conditions. Because of this the effect and safety between different medication regimes need to be compared and taken in to consideration before choosing an alternative over another. Off-label prescription of antiemetics for the indications are used due to the lack of adequate treatment regimes. The research questions of this project are therefore:

- Are promethazine, metoclopramide and ondansetron safe treatment options during pregnancy?
- Are promethazine, metoclopramide and ondansetron effective for treating NVP/HG?
- Is one therapy regime superior to another?
- Could NVP/HG be considered indication for ondansetron instead of an off-label option?

3. Method

The study was conducted as a literature-based study. Selection of articles was made by searches in the following databases: PubMed, Cochrane Library and the search engine Google. FASS were used as complementary source for basic information as well as the Green-top Guideline no.69 of the management of nausea and vomiting of pregnancy and hyperemesis gravidarum from the Royal College of Obstetricians & Gynecologists. The searches for articles were conducted during the period from 5th of January to 17th of January, FASS was used throughout the writing process from 5th of January to 24th of February. The Websites of Läkemedelsboken and Socialstyrelsen were used to verify background information for writing the introduction during the same period.

Words used for the article search were: hyperemesis, gravidarum, infant, nausea, vomiting, pregnancy, treatment, safety, effect, optimal treatment, risk, adverse effect, malformation, antiemetic, ondansetron, promethazine, metoclopramide, compare, randomized. These were combined in numerous ways. When the searched words generated >50 hits only the first 20 articles sorted by best matching according to NCBI were looked upon. Headings were read and the articles of possible interest were opened and abstracts were read before choosing to include or exclude.

Criteria for the original studies were that they should be original articles of randomized controlled human trials, prospective comparative studies or retrospective cohort studies. Full texts available and published within the last 15 years. The articles had to be written in English or Swedish. Other hits were excluded. The following table shows what articles were found under what terms searched. The searching process started out with looking upon articles siting general treatment regimens and optimal management and continued with adding ondansetron and safety of the substance to the search and then promethazine and metoclopramide where added to fulfil the complete objects of this study.
<table>
<thead>
<tr>
<th>Date of search</th>
<th>Search words</th>
<th>Number of hits</th>
<th>Top hits</th>
<th>Chosen study</th>
</tr>
</thead>
<tbody>
<tr>
<td>218-01-07</td>
<td>(((hyperemesis) AND pregnancy) AND ondansetron) AND promethazine</td>
<td>9</td>
<td></td>
<td>McParlin [17]</td>
</tr>
<tr>
<td>2018-01-07</td>
<td>(((hyperemesis) AND gravidarum) AND ondansetron) AND compare</td>
<td>2</td>
<td></td>
<td>*Abas [3]</td>
</tr>
</tbody>
</table>
In total over 30 articles were partly read and finally three randomized double-blind controlled studies [2, 3, 19] were selected, one prospective comparative observational study [20], three retrospective cohort studies [1, 21, 22] were chosen.
<table>
<thead>
<tr>
<th><strong>Randomized Double-blind Controlled Studies:</strong></th>
<th>Author:</th>
<th>Publishing information:</th>
<th><strong>Prospective Comparative Studies:</strong></th>
<th>Author:</th>
<th>Publishing information:</th>
<th><strong>Retrospective Cohort Studies:</strong></th>
<th>Author:</th>
<th>Publishing information:</th>
</tr>
</thead>
</table>
4. Results

4.1 Results from original studies on treatment efficacy:

4.1.1 Study 1. Ondansetron Compared with Metoclopramide for Hyperemesis Gravidarum by Abas et al. 2014 [3]

This study was conducted as a randomized controlled trial where ondansetron was compared to metoclopramide for treating women suffering from HG during the first 16 weeks of pregnancy. The recruiting period started 5th of November 2011 and continued until 4th of August 2012. The criteria for the diagnosis were presence of nausea and vomiting enough to cause dehydration and metabolic disturbances, ketonuria +2 or more, and the need of supervised medical care and hospitalization. 160 women met the inclusions criteria and were enrolled to participate in the study after all ethical considerations were met and written informed consents were submitted. Characteristics were stratified as well as physiological parameters e.g. renal function/liver function/blood tests which were all similar in both groups. The women were given either ondansetron 4mg intravenously or 10mg metoclopramide intravenously every eight hours. All participating women had a diary to fill in scores for well-being at set times as well as an emesis count. The trial was double blind and controlled, the study drugs were masked in saline solution to hide the volumes, all samples were colorless and packed and prepared in advance and the providers were all blind to what study drug were given to the participants.

The intensity of the felt nausea was recorded in the participants diary on a numerous scale of 0-10 points. 10 being maximum nausea. The participants were recording their nausea at start of the study and then every eight hours for a 24-hour period. Alongside the experienced nausea, vomiting episodes were also recorded. After 24-hours a questionnaire was filled regarding experienced symptoms. There were six women who failed to receive the full dosage of the study drugs. Four women in the ondansetron group withdrew, three felt fully recovered before four doses and one withdrew due to safety concerns. Two women in the metoclopramide group withdrew, one felt fully recovered before the four doses and one experienced excessive skin rashes due to drug allergy.

Table 5: Recorded numerical values for well-being and vomiting frequency in 24h. Data are median (interquartile range)

<table>
<thead>
<tr>
<th></th>
<th>Ondansetron</th>
<th>Metoclopramide</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-being</td>
<td>9 (8-10)</td>
<td>9 (7-10)</td>
<td>P=0.330</td>
</tr>
<tr>
<td>Vomiting frequency in 24 hours</td>
<td>1 (0-2)</td>
<td>2 (0-2.75)</td>
<td>P=0.380</td>
</tr>
</tbody>
</table>

Well-being after treatment were similar for median values of 9, the ondansetron group had a slimmer interquartile range indicating a slightly better well-being reported in general. The vomiting frequency in 24 hours were less for the ondansetron group where the median value was 1 compared to 2 in the metoclopramide group and the interquartile range were also wider by 0.75 units in the metoclopramide group suggesting overall higher frequency of vomiting in the group treated with metoclopramide.

2 Ketonuria = excretion of abnormal amounts of ketones in urine due to starvation measured on a scale of 0 (negative) to +4 (severe ketonuria).
From the questionnaire, results of adverse effects could be analyzed. The following symptoms were mentioned and recorded:

Table 6: Results on perceived adverse effects in women treated with ondansetron and metoclopramide respectively.

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Ondansetron</th>
<th>Metoclopramide</th>
<th>P-values</th>
<th>NNT(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>12.5%</td>
<td>30.0%</td>
<td>P&lt;0.01</td>
<td>6</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10.0%</td>
<td>24.0%</td>
<td>P&lt;0.01</td>
<td>8</td>
</tr>
<tr>
<td>Ketonuria</td>
<td>12.5%</td>
<td>30.0%</td>
<td>P=0.01</td>
<td>6</td>
</tr>
</tbody>
</table>

The table shows that a higher percentage of participants reported adverse effects when administered metoclopramide compared to ondansetron. Other symptoms such as sleeping-problems, experience of dizziness and headaches, diarrhea, and skin rashes were reported in similar proportions in both groups.

After the 24h trial the study drugs were not given anymore and an open label treatment with metoclopramide orally was given to the women still in need of antiemetics. Intravenous antiemetics were in some cases continued.

The results were analyzed by intention to treat, the normal distribution was checked with one-sample Kolmogorov-Smirnov test for continuous variables and the student t-test were used for normally distributed variables and Mann-Whitney U-test for the not normal continuous variables. Numbers needed to treat were generated by graphic software when the results were significant with a value of P <0.05.

The study has both strengths and limitations. Bias is reduced when double-blind designs are practiced, and the authors claims that the power of the trial to detect a one-unit difference was 99.6%with the sample size and analyzing methods used. Limitations to the study according to the authors were the time frame, the 24-hour window of treatment might need adjustment in further studies however, 84% of the participants needed only the four doses intravenous study drug before they could change to oral antiemetics and be discharged from hospitalization the following day.

Conclusions drawn in this study were that ondansetron and metoclopramide showed similar effects regarding nausea and vomiting, but ondansetron had a slightly better overall effect when including the following adverse effects: drowsiness, dry mouth and ketonuria. On these three secondary outcomes of the study the difference was statistically significant between the two groups, ondansetron allocated women in favor [3].

4.1.2 Study 2. **Ondansetron Compared with Doxylamine and Pyridoxine for Treatment of Nausea in Pregnancy by Oliviera et al. 2014 [2]**

This study was conducted as a randomized controlled trial where ondansetron was compared to Doxylamine-Pyridoxine for treating women suffering from HG. The primary outcome was improvements in nausea reported on a 100-mm visual analog scale. Secondary outcomes were reduction in vomiting frequency, and adverse effects such as

---

\(^3\) NNT= number needed to treat, the number of patients who need treatment to prevent one bad outcome.
sedation and constipation due to the drugs studied. 40 women were enrolled to the study both from the ER and the obstetrics and gynecology department between October 2012 and April 2013 where four women declined participation in the study. 36 women were finally enrolled and 30 completed the study (ondansetron 13, doxylamine-pyridoxine 17).

Inclusion criteria for participating were >18 years of age and >16 weeks of gestation, no antiemetics were used before enrollment and the woman could not have any allergies to the study drugs. Exclusions were made if the women were in need of hospitalization or could not participate in follow up meetings or if the nausea and vomiting started before the pregnancy. After ethical considerations were met randomization was conducted and the study drugs were prepared in advance. Blinding of the different drugs was generated by use of identical capsules and the 4mg ondansetron capsule was accompanied by a placebo so all participants had two capsules per dose. One dose was taken every 8 hours for 5 days.

Before medication started each participant graded the nausea and vomiting frequency during the past week, using VAS-scales from 0-100. Following up grading of nausea and vomiting were conducted at 5-7 days after initiating the medications. Adverse effects were also investigated and compliance to the regime was controlled.

Statistical analysis by Strata 13 was preformed, intention to treat principle was used and the level of significance was set at $P < 0.050$. Wilcoxon rank sum test compared demographic and mean differences of the groups, and Fisher exact test was performed to assess the difference in proportion of patients showing significant improvements as adverse effects. Five women failed to report follow up data four from the ondansetron group and one from the doxylamine-pyridoxine group.

Table 7: Showing the median (interquartile range) of demographics before any medication regimes were started and baseline VAS-scores pre-medication.

<table>
<thead>
<tr>
<th></th>
<th>Ondansetron</th>
<th>Doxylamine-pyridoxine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravidity</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>Parity</td>
<td>1 (0-1)</td>
<td>0.5 (0-1)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>8 (7.1-8.9)</td>
<td>8.1 (7.2-9.9)</td>
</tr>
<tr>
<td>Nausea (VAS baseline)</td>
<td>73mm (67-84)</td>
<td>81mm (68-93)</td>
</tr>
<tr>
<td>Vomiting (VAS baseline)</td>
<td>53mm (26-74)</td>
<td>64mm (26-89)</td>
</tr>
</tbody>
</table>

No significant differences between the groups were found before any of the treatments were started.

The study showed that after utilization of ondansetron the reported reduction in nausea was greater than for those who were using doxylamine-pyridoxine. The median reduction on the VAS were 20 mm (interquartile range from 8–51) for doxylamine-pyridoxine
treated women compared to 51 mm (interquartile range between 37–64) for ondansetron treated women (P= 0.019). Indicating that on the VAS, women estimated their nausea 31mm less severe after utilization of ondansetron.

The frequency of vomiting was also more reduced on the VAS-scale in the ondansetron group with a reduction of 41 (interquartile range from 17 to 57) compared to the doxylamine-pyridoxine group where the reduction was 17 (interquartile range from 24 to 38) (P= 0.049)

The ondansetron group showed clinical significant reduction in nausea (set to >25mm reduction on the VAS) in 12 out of 13 women, and reduction of emesis in 10 out of 13 women. In the doxylamine-pyridoxine group only 7 out of 17 showed a clinical significant reduction of nausea (P= 0.007) and 6 out of 17 reported reduction in emesis (P= 0.033)

Table 8: Showing the number of women reporting sedation and/or constipation.

<table>
<thead>
<tr>
<th>Secondary outcomes</th>
<th>Ondansetron</th>
<th>Doxylamine-Pyridoxine</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>4</td>
<td>7</td>
<td>P=0.707</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>3</td>
<td>P=0.412</td>
</tr>
</tbody>
</table>

No significant differences in the secondary outcomes of sedation and constipation were found. Four patients reported sedation in the ondansetron group compared to seven patients in the doxylamine-pyridoxine group. For reported constipation there were five patients in the ondansetron group compared to three patients in the doxylamine-pyridoxine group. The compliance was similar both groups with a mean of seven pills remaining at follow-up (P= 0.906).

The study has limitations to whereas the economic aspects of treatment regimens were not considered and the authors mention that there is no known validated tool for quantifying nausea and vomiting in pregnancy available.

In conclusion, this study compared ondansetron with the first-line treatment of pyridoxine and doxylamine and concluded that ondansetron is superior to this invention regarding nausea using VAS-scores and might well be a possible first line treatment for NVP/HG [2].

4.1.3 Study 3. Promethazine Compared with Metoclopramide for Hyperemesis Gravidarum by Tan P C et al. 2010 [19]

This study was conducted as a randomized controlled trial where promethazine was compared with metoclopramide in hospitalized women with HG. The primary outcomes were well-being and frequency of vomiting. Secondary outcomes to investigate were adverse effects, ketonuria status, total doses of iv antiemetics, time needed for iv rehydration and discharges from hospitalization.

All ethical considerations were met before starting the trial which was conducted from 25th of November 2008 until 14th of august 2009. Women who were in need of antiemetics when hospitalized for the first time due to HG was approached and included into the selection of participants. Other inclusion criteria were HG with electrolyte imbalances, ketonuria and gestational age of 16 weeks or less. Exclusions were made if the
women were expecting twinning, had preexisting medical conditions with nausea and vomiting as symptoms, or allergy to either of the test drugs. The sample size for the study was calculated from hypothesis of visible results by at least one unit at a 10-point numerical scale with a SD of 2 and 80% power to detect the difference, for these calculations 64 women in each trial group were needed, an extra 10% for not normal distribution and another 10% drop-out made the study population to be at least 158 women. The chosen women were randomized by computer generated randomization into either promethazine 25mg or metoclopramide 10mg, blinded as drug A and drug B prepared in advance for the trial. A total of 160 women were enrolled. 79 randomized to metoclopramide and 80 to promethazine. 10 women were excluded after randomization (6 from metoclopramide group and 4 from promethazine group) 149 patients started treatment with either study drug. Parameters such as liver and renal function, blood counts etc. were all similar between the groups.

The medication was administered by slow injection into an intravenous catheter at trial start, thereafter at 8, 16, and 24 hours later. Participants had a diary to fill in periods of vomiting alongside nausea on a 0-10 scale at every eighth hours. After 24hours a questionnaire was filled by the women.

Data were entered in SPSS16 and the analysis was made by intention to treat model generated by graphic software. Continuous data were checked with the Kolmogorov-Smirnov test for normal distribution and analyzed by the students t-test. Ordinal data and non-normally distributed continuous data were analyzed by the Mann-Whitney U-test. P< .05 was considered significant.

Table 9: Showing results for the primary outcomes on vomiting frequency and well-being score. Data are median (interquartile range).

<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Metoclopramide</th>
<th>Promethazine</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting frequency</td>
<td>1 (0-5)</td>
<td>2 (0-3)</td>
<td>P=0.810</td>
</tr>
<tr>
<td>Well-being score</td>
<td>8 (6-10)</td>
<td>7 (5.25-9)</td>
<td>P=0.240</td>
</tr>
</tbody>
</table>

The results of the study’s primary outcomes showed no significant difference between the study drugs regarding vomiting frequency which was one for metoclopramide ranging from 0-5, and 2 ranging from 0-3 for promethazine indicating a difference too small to be significant. Neither did the well-being score on a 1-10 scale indicate any significant differences with a median score of 8 ranging from 6-10 in the metoclopramide group compared to a median score of 7 ranging from 5.25 to 9 in the promethazine group.

The well-being score were also calculated for a mean-value and standard deviation resulting in mean score for metoclopramide 7.6 (+/- 2.2) compared to mean score of promethazine 7.1 (+/-2.3) (P= 0.810).

Secondary outcomes were; length of hospitalization, persistence of ketonuria, overall treatment curtailment, duration of iv fluids, total doses of antiemetics and were showing no differences between the groups.
Table 10: Data from questionnaire on adverse effects.

<table>
<thead>
<tr>
<th></th>
<th>Metoclopramide</th>
<th>Promethazine</th>
<th>P-values</th>
<th>NNTb4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>58.6%</td>
<td>83.6%</td>
<td>P=0.001</td>
<td>5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>34.3%</td>
<td>71.2%</td>
<td>P=0.001</td>
<td>3</td>
</tr>
<tr>
<td>Dystonia</td>
<td>5.7%</td>
<td>19.2%</td>
<td>P=0.020</td>
<td>8</td>
</tr>
</tbody>
</table>

Other adverse effects such as difficulty in sleeping, dry mouth, diarrhea, headache and skin rashes were reported with the same frequency in both trial groups. 13 women did not complete all doses (4 from the metoclopramide group and 9 from promethazine group) hence Metoclopramide was less likely to be associated with less compliance due to adverse effects. (P= 0.014).

Limitations of the study according to the authors were that primary outcomes were measured with in a 24h window, the enrollment were based on presumed HG and further testing was not conducted on the diagnosis.

The study concludes that there are similar therapeutic effects between metoclopramide and promethazine in women hospitalized for HG, but adverse effects were better with metoclopramide. Therefore, is intravenous metoclopramide preferred over intravenous promethazine in this study for the treatment of HG [19].

4.2 Results from original studies on ondansetron and safety:

4.2.1 Study 4. Ondansetron in Pregnancy and Risk of Adverse Fetal Outcomes by Pasternak et al. 2013 [1]

This study was conducted by using information from the Danish Medical birth register and National patient register for pregnancies during the period 1st January 2004 through 31th of March 2004. The National prescription registry and the central person register were used to identify drug use during pregnancy. Exclusion of pregnancies were done when the gestational age was unclear; spontaneous abortion before six weeks gestation.

The exposure to ondansetron was concluded to be the date the prescription was recorded, women who were exposed to ondansetron within a window that did not match the first trimester (12 weeks of gestation) was categorized as unexposed.

The National Patient register was used to find cases of major birth defects and spontaneous abortions. Major birth defects were defined by EUROCAT© classification except for children born with chromosomal abnormalities and known causes of birth defects. The statistical methods used in the research to conclude hazard ratios were the Cox-proportional-hazards regression model.

4 NNTb = number needed to treat to benefit

5 A European network of population-based registries for the epidemiologic surveillance of congenital anomalies. [27]
Confounders were accounted for. Ondansetron exposed women were then matched to unexposed women in a ratio of 1:4. The study of was then restricted in the analysis for exposure to ondansetron during the weeks 4-10 in gestation. Results from this database study comprised in total 608,385 women where ondansetron exposure was reported in 1970 of these women.

Table 11: Chart showing percentage of exposed contra unexposed women reporting any of the following outcomes of the pregnancy.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ondansetron exposed women</th>
<th>Unexposed women</th>
<th>Adjusted hazard ratio</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous abortion week 7-12</td>
<td>1.1%</td>
<td>3.7%</td>
<td>0.49</td>
<td>0.27-0.91</td>
</tr>
<tr>
<td>Spontaneous abortion week 13-22</td>
<td>1.0%</td>
<td>1.8%</td>
<td>0.60</td>
<td>0.29-1.21</td>
</tr>
<tr>
<td>Still birth</td>
<td>0.3%</td>
<td>0.4%</td>
<td>0.42</td>
<td>0.10-1.73</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>4.1%</td>
<td>3.7%</td>
<td>0.79</td>
<td>0.51-1.13</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>10.4%</td>
<td>9.2%</td>
<td>1.13</td>
<td>0.89-1.44</td>
</tr>
<tr>
<td>Major birth defects</td>
<td>2.9%</td>
<td>2.9%</td>
<td>1.12</td>
<td>0.69-1.82</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>6.2%</td>
<td>5.2%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The risk of spontaneous abortion was not increased among ondansetron exposed women in weeks 7 to 12. The adjusted hazard ratio suggests that 51% of the women were less likely to have a spontaneous abortion compared to the unexposed women. Nor did they find any increased risks for spontaneous abortion from week 13 to 22. The adjusted hazard ratios of 0.60 give an estimate of how approximately 40% of the women were less likely to suffer from spontaneous abortion compared to the unexposed women.

Neither were there any increased risks in still-birth, low birth weight, babies too small for gestational age or any major birth defects. The study did however find a slight association between ondansetron exposed women and preterm delivery. Ondansetron exposed women gave birth preterm in 6.2% of the recorded cases compared to 5.2% of unexposed women.

The study concluded that in this cohort, based on available registries there were no associations between use of ondansetron for treating NVP/HG and any significant increased risks of spontaneous abortions, still birth, unhealthy babies according to size and weight nor any higher risks for birth defects. Even though the possibility of adverse
effects in ondansetron exposed women cannot be completely ruled out the study and authors claim that this study at least provides reassurance regarding ondansetron use in women suffering from NVP/HG [1].

4.2.2 Study 5. Use of ondansetron during pregnancy and congenital malformations in the infant by Danielsson et al. (2014) [21]

In this retrospective cohort study investigated teratogenic risks after exposure to ondansetron. Two sources were used for including exposed women into the study; midwife interviews around week 10-12 of the pregnancy and the Swedish Prescription Register linked to the Medical Birth Register. Mid-wife interview data were available from 1998-2002 and the Swedish Prescription Register had data available from 2006-2012.

Mild malformations registered were excluded and the remaining malformations were labeled as relatively severe. The odds ratios (OR) were calculated by Mantel-Haenszel analysis and 95% CI's were estimated by Miettinen's technique. Adjustments were made for confounders such as year of birth, maternal age, parity, exposure to smoking and BMI.

Tabel 12: Chart showing how many infants born with any malformation, how many of these were severe and out of the severe malformations how many were cardiovascular in general and cardiac septum defects in particular.

<table>
<thead>
<tr>
<th></th>
<th>Ondansetron</th>
<th>Odds ratio</th>
<th>CI 95%</th>
<th>Meclizine</th>
<th>Odds ratio</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any malformation</td>
<td>49 infants</td>
<td>0.95</td>
<td>0.72-1.26</td>
<td>1782 infants</td>
<td>0.96</td>
<td>0.90-1.02</td>
</tr>
<tr>
<td>Severe malformation</td>
<td>38 infants</td>
<td>1.11</td>
<td>0.81-1.53</td>
<td>1228 infants</td>
<td>0.95</td>
<td>0.90-1.00</td>
</tr>
<tr>
<td>Cardiovascular defect</td>
<td>19 infants</td>
<td>1.62</td>
<td>1.04-2.14</td>
<td>441 infants</td>
<td>1.02</td>
<td>0.92-1.12</td>
</tr>
<tr>
<td>Cardiac septum defect</td>
<td>17 infants</td>
<td>2.50</td>
<td>1.19-3.28</td>
<td>315 infants</td>
<td>1.03</td>
<td>0.92-1.15</td>
</tr>
</tbody>
</table>

The results from the study showed that out of the total number of births (1,501,434) 43,658 reported malformations classified as major (2.9%). And among these 2.9% there were 14,872 children who had a cardiovascular defect (1%) and 0.7% of those had a cardiac septum defect. The investigation identified 1349 infants who were exposed to ondansetron (435 from mid-wife interviews and another 914 from the registers). Comparisons were then made from ondansetron exposed infants and meclizine exposed infants (being the first over the counter option in Sweden).

The sex ratio after maternal need for ondansetron was 0.83 (CI 95% 0.75-0.93) and for meclizine 0.93 (CI 95% 0.90-0.93) females in excess, which could confound the results due to an overall excess of female infants born with cardiac septum defect (0.88, CI 95% 0.84-0.93)

The authors claims that a final question of teratogenicity is not provided from one study alone, rather repeated studies must be undertaken to evaluate the risks of teratogenicity associated with the use of ondansetron. The suggested teratogenicity could be related to a
potential QT prolongation seen in ondansetron. Ondansetron could inhibit human Ether-à-go-go-Related Gene channels (hERG)\(^6\) incorporated in the cardiac rhythm regulation which could affect and limit oxygen flow to the more sensitive developing heart in the fetus. Other QT-prolongation drugs, e.g. erythromycin, have shown teratogenic effects in animal studies where ventricular septal defects were the most easily induced malformation.

The study concludes that ondansetron was not associated with high risk of congenital malformations, possibly a higher risk of cardiac septum defects could exist. And the authors stress that the off-label use of ondansetron should not be used until larger prospective studies are available even though the results only showed a possible increased risk for cardiac septum defects, which are not seen as very severe malformations [21].

4.2.3 Study 6. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study by Einarsson et al. 2004 [20]

This prospective comparative study enrolled women within a two-year period calling Motherisk service in Canada and the Mothersafe services in Australia who were exposed to ondansetron and were less than three months pregnant. The comparison groups of women also suffering from HG but were not using ondansetron and women suffering from HG using other antiemetics were also enrolled in with the same method. Oral consent forms were taken from each enrolled woman after thorough explanation of the study purpose.

Interviews were conducted and information collected. PUQE-scores were taken. The enrolled women were then contacted again 4-6 months after delivery to obtain follow-up data from a standardized form along with a verification request sent to the women’s physicians. Comparisons were made on the basic characteristics of the women (age, smoking, alcohol, gestational age) All groups were then analyzed regarding live births, miscarriages, therapeutic abortions, still births, gestational age at birth, weight at birth and any major malformations. X2, Fishers exact and ANOVA were the statistical tests used to compare the outcomes.

188 women were enrolled in the ondansetron group, 12 failed to follow through. 176 women were then used in the analysis in each group. No significant differences in the maternal characteristics between the three groups were found.

Table 13: Maternal characteristics between groups. Data are mean [SD] or n (%).

<table>
<thead>
<tr>
<th></th>
<th>Ondansetron</th>
<th>Other antiemetics</th>
<th>Non-exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32.3 [4.4]</td>
<td>31.5 [4.3]</td>
<td>31.7 [4.4]</td>
</tr>
<tr>
<td>Smoking status</td>
<td>1 (0.5%)</td>
<td>5 (2.8%)</td>
<td>15 (8.5%)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>2 (1.1%)</td>
<td>1 (0.5%)</td>
<td>3 (1.7%)</td>
</tr>
</tbody>
</table>

\(^6\) The “hERG-channel” is a potassium channel that contributes to the electrical activity of the heart.
Table 14: Study outcomes, values are given as mean [SD] or n (%).

<table>
<thead>
<tr>
<th></th>
<th>Ondansetron</th>
<th>Other antiemetics</th>
<th>Non-exposed</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live births</td>
<td>169 (96.8%)</td>
<td>169 (91%)</td>
<td>162 (92%)</td>
<td>P=0.68</td>
</tr>
<tr>
<td>Miscarriages</td>
<td>5 (2.9%)</td>
<td>13 (7.5%)</td>
<td>14 (8%)</td>
<td>P=0.46</td>
</tr>
<tr>
<td>Still birth</td>
<td>0 (0%)</td>
<td>1 (0.5%)</td>
<td>0 (0%)</td>
<td>P=0.70</td>
</tr>
<tr>
<td>Therapeutic abortion</td>
<td>2 (1.3%)</td>
<td>2 (0.5%)</td>
<td>0 (0%)</td>
<td>P=0.89</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3362 [525]</td>
<td>3372 [608]</td>
<td>3490 [606]</td>
<td>P=0.08</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.7 [1.7]</td>
<td>38.7 [1.9]</td>
<td>39.4 [1.6]</td>
<td>P=0.57</td>
</tr>
<tr>
<td>Major malformations</td>
<td>6 (3.5%)</td>
<td>3 (1.8%)</td>
<td>3 (1.8%)</td>
<td>P=0.52</td>
</tr>
</tbody>
</table>

The conclusion drawn from the results of the 176 women who used ondansetron during the first trimester of pregnancy was no increased risk for major malformations nor any statistical differences between the ondansetron exposed neonates and the comparison group in any of the other study endpoints mentioned in table 14. The authors mention the small sample size and states that further investigations will be needed to make definite conclusions [20].

4.2.4 Study 7. Ondansetron in pregnancy and risk of adverse fetal outcomes in the United States by Fejzo et al. 2016 [22].

This study was a retrospective cohort study that was part of a larger study which aimed to evaluate the epidemiology of HG. Women were enrolled by advertisements on a website for HG between 2007-2014. Inclusion criteria for participating in the study was the diagnosis of HG in a one child pregnancy, treatments with intravenous fluids and/or total parenteral nutrition, an age >18 years and living in the USA. The matching women were asked to submit their medical records and also recruit one other women who have had two pregnancies without HG to participate as a control to eliminate the misclassification of control groups. A total of 772 women with HG reported 1070 ondansetron exposed pregnancies and 771 non-exposed. 90% of the exposed pregnancies were exposed during the first trimester and for the pregnancies not exposed to ondansetron 68.1% were treated with other common methods such as metoclopramide or promethazine. 563 women who did not experience HG during pregnancy reported on 1555 un-exposed for any medication pregnancies as control.

The participating women filled an online form regarding symptoms, treatments, and outcomes of these. The women were then categorized according to ondansetron exposure. Fisher’s exact test was used to evaluate differences between categorical variables in the groups and unpaired t-tests were used for the numerical variables. Logistic regression was used to derive estimated odds ratios.
The results from the study showed that women with a history of HG who used ondansetron were less likely to terminate the pregnancy (p<0.010; OR=0.18, CI 95% =0.11-0.28) than those who experienced HG and did not take ondansetron. Among the women who experienced HG and did not use ondansetron and terminated the pregnancy 54% reported that the reason was that they were not offered any medication, 15% could not endure the symptoms and 8% reported termination due to any of the following: declined medication, nothing worked, fear for life or doctor’s recommendation.

Women who used ondansetron for their HG were less likely to report miscarriages both compared to the HG/no ondansetron group (p < 0.010; OR = 0.09, 95% CI = 0.06–0.13) and the control group. (p < 0.010; OR = 0.29, 95% CI = 0.20–0.42)

Results showed no significant difference in risks for preterm deliveries for women with HG who did or did not use ondansetron, but a significant difference between the women who had HG compared to the controls were found p<0.010)

Women with HG who used ondansetron were more likely to report a live birth (88.97%) than both the HG/no ondansetron (57.20% OR = 6.03, CI 95% = 4.73–7.73) and the control group (82.70% OR = 1.69, CI 95%= 1.33-2.15) (p < 0.010)

Birth defects were equally reported in both HG/ondansetron and HG/no ondansetron groups, but showed an increased risk compared to the control group without HG. Among 952 live births in the ondansetron group there were 33 reported birth defects (3.47%) which was similar to the HG/no ondansetron group (3.40%, p=1.000)

For major birth defects the reports were similar, for ondansetron exposed groups 5 heart defects, 1 cleft lip/palate was reported and for the control group 8 heart defects and 2 cleft lip/palate were reported.

This study did not show any statistically significant increase in the reported minor or major birth defects associated to the use of ondansetron but rather the history of HG could be a risk itself. Over-reporting could be a confounding factor for women experiencing HG during pregnancy, the overall results does not support any evidence that ondansetron has teratogenic effects. Ondansetron use could on the other hand be associated to decreased risk of termination of pregnancy, and they claim that ondansetron could be one of the more effective treatments for HG.

Limitations of the study was confounding factors between the groups which was close but not perfectly matched, self-selection of the control groups may not be the best way of choosing control groups. Also, the fact of recall bias could play part when conduction research on women in different stages of pregnancy or even long time after pregnancy. Also, no control for gestational age were done which could have an effect on the results.

To conclude the results there is no support for teratogenic risks for ondansetron use for HG, women who has experienced HG had a slight increased risk for reporting a child with malformations but this had no correlation to the exposure to ondansetron or not. Adding to these findings the women who experienced HG and were treated with ondansetron were much less likely to report termination of pregnancy, miscarriages and therefore more likely to report a live birth [22].
5. Discussion

5.1 Method

The study was a literature study where RCT’s, prospective studies and retrospective studies were all included in the final results to investigate the safety and effect of three antiemetics used in women suffering from HG and NVP. The study populations are relatively small due to the rare occurrence of HG (0.5-2% of pregnant women) and the phenomenon is hard to study due to ethical considerations. Therefore, the inclusion criteria for this study were set to exclude as few original studies as possible to have any available material to work with. Full texts had to be available and the publishing date had to be within the last 15 years. The articles also had to be written in English or Swedish. Other hits were excluded. In the chosen studies, the women were all >18 years of age and diagnosed with NVP/HG severe enough to be in need of pharmacological interventions. The gestational age had to be less than 12 weeks to fulfil the purpose of safety regarding teratogenicity during organogenesis. It would have been interesting to narrow the criteria down even further to get more precise results but because of the very few women experiencing the condition, studies are not available for more limited criteria.

Three original studies were chosen on the theme of effectiveness. These studies were chosen because each study compared one substance of interest with another intervention. More similar studies could strengthen the results and might have given a clear indication to whether one treatment regime is actually superior to another.

Four studies were chosen on the theme of safety, focusing on ondansetron which is the only substance which is currently an off-label prescription. The focus on ondansetron were chosen to answer the study question regarding whether HG/NVP should be considered indication for ondansetron. Post hoc the safety part maybe should have been broadened to include more studies on the other two substances as well.

Limitations to the method in this study were when the PubMed Advanced search was used and the combination of selected words generated more than 50 results. For these scenarios PubMed automatically sorted the articles by top hits and only the first 20 headings were read and assessed whether to be of interest or not. This method could be faulty and sort out articles of interest. The algorithm PubMed uses to sort by top hits are not accounted for. Another limitation is the use of RCT’s alongside with both prospective and retrospective studies. The RCT’s are of most interest and the highest standard compared to other study designs. Investigating these cases, RCT’s are unfortunately hard to undertake both because of ethical concerns and the rare occurrence of congenital malformations associated with medications for NVP/HG. Hence, the only way to include a larger number of participants is to go into different registers [11].

The relevance of the chosen studies is up to date and the studies were all registered for and no conflicts of interests have pointed the results in any direction of favor. The studies were all published in quality sources and were all considered trustworthy before included in this report.
5.2 Result

The study questions were as follows:
- Are promethazine, metoclopramide and ondansetron safe treatment options during pregnancy?
- Are promethazine, metoclopramide and ondansetron effective for treating NVP/HG?
- Is one therapy regime superior to another?
- Could NVP/HG be considered indication for ondansetron instead of an off-label option?

This study aimed to conclude results from previous studies and reviews regarding the safety and effect of drug-treated HG focusing on the three substances: promethazine, metoclopramide and ondansetron. Furthermore, the study aimed to investigate the reason to why out of these three substances ondansetron is the only off-label drug prescribed for treating HG, the reason for not having HG as indication and if there could possibly be taken into consideration to add this indication for the substance. This study tried to find out if any substance could be superior to another and associated with overall better outcomes when used for treating HG symptoms. All studies mentioned in the results of this study aimed to differentiate NVP/HG from differential diagnosis and nausea and vomiting which was present before conception.

NVP/HG peaks during the first trimester about week 7–12 and nausea that is experienced for the first time after the first trimester need further evaluation due to suspicion of differential diagnosis. These symptoms and their treatments are not included in this study and the substances studied might not be suited for that purpose.

According to the results all of the three interventions could be said to be safe for use in pregnant women. The studies are most often investigating a 24-hour exposure to the substance [3, 19] and more studies should be done on long-term effects of treatments. Otherwise, the results suggest that one regime could not be concluded to be superior to another between ondansetron, metoclopramide and promethazine [9] except in a study where ondansetron was said to be superior to other regimes due to less frequent vomiting, less nausea and milder side-effects than the compared substance [3]. Metoclopramide also seemed to be better than promethazine regarding adverse effects [19] suggesting that any of these agents should be used individualized and in dialog with the affected woman. However, ondansetron showed to be superior to standard treatment with pyridoxine and doxylamine [2] but treatment regimens should preferably start with pyridoxine + doxylamine because this option has the largest amount of evidence on efficacy and safety. [4].

For mild symptoms, non-pharmacological interventions could benefit, for moderate symptoms pyridoxine-doxylamine, promethazine and metoclopramide could be beneficial compared to placebo and ondansetron was associated with improvements for a range of symptoms and severity levels from mild to severe cases [17]. If NVP/HG is experienced and no non-pharmacological methods give symptomatic relief, monotherapy with pyridoxine should be tried, if it doesn’t give enough relief an addition of doxylamine could be given [4, 18, 25, 26]. What the next step will be is individual but studies suggest that ondansetron is a well-functioning agent and could be incorporated into the first-line treatments after non-pharmacological methods have failed [2, 3]. Thus, economical and individual prospects need to be considered before choosing any of the available substances for treating NVP/HG [3].

Results from the original studies and the conclusions from the reviews are mostly agreeing that ondansetron is not associated with any significant increase in malformations above baseline [1, 4, 17, 20, 22]. A possible correlation between cardiac septum defect was found [21] and this possible correlation need further larger studies and controlled trials to conclude any statistical significant increased risks.
However, the use of ondansetron and the possible risk of malformations -which was concluded to be low- could still be a better option for the fetus than not treating the woman at all [12, 22]. Ondansetron seemed to have better safety profile compared to metoclopramide [3] and better effect than standard treatment with pyridoxine/doxylamine [2] but ondansetron use should be reserved for those women who does not get symptomatic relief from any other method due to the lack of large controlled trials [27].

The fetal development is at its most sensitive period during the same weeks as the NVP/HG most often peaks. This period in the development is of most interest regarding the studies mentioned due to possible malformations in the cardiac septum associated with ondansetron treatment of NVP/HG. Any exposure to ondansetron after this stage should therefore be less likely to cause any malformations or teratogenic effects. The reasons for NVP/HG are also discussed and theories of an overall healthy pregnancy showing NVP/HG symptoms due to higher hormonal levels and a well-functioning placenta [10] associated with less frequent reporting of miscarriages and malformations are an interesting theory and should also be studied further.

The NVP/HG symptoms does however in most cases cease after mid-pregnancy when the sensitive developmental phases are undergone. For severe cases when the nausea does not subside, neither of the substances should cause any harm to the growing baby. Reasons for the non-subsiding NVP/HG could be due to other factors than the high hormonal fluctuations that could trigger the CRTZ [13] for example inputs from the GI-canal that shrinks as the uterus grows, the mother’s BMI, the sex of the fetus among other confounding factors in the studies [4, 9, 10].

5.3 Limitations

The studies and reviews have some limitations due to the classifying of first-trimester exposure. The first trimester starts at conception and lasts until the 12th week of gestation. Organogenesis and the formation of the heart happens during the 10 first weeks of gestation leaving the exposure window to ondansetron unclear to conclude that the ondansetron exposure was associated with cardiac malformations, which was the most frequent abnormality accounted for in the studies. Also, there is a higher risk for cardiac septum malformation in female fetuses generally and NVP/HG is also more frequently reported in women bearing female fetuses. These among other confounding factors were not always taken into consideration. Most studies except one [2] only exposed the women for study drugs for 24 hours then changed into open label treatment if continuation with anti-emetics were needed. Some suggestions for the short exposure window was that some women felt totally treated after the study doses every eight hours for a 24h period, and did not need further hospitalization or anti-emetic treatment but because of this designs the studies fail to conclude anything for long-term treatment with the studied drugs. Further controlled investigations on this matter is needed.

There are also ethical issues with studying pregnant women and therefore the number of randomized controlled trials (RCT’s) is not sufficient to establish a certainty of associations between malformations nor what treatment form is the most effective and safe. Studies often collect data from registers and retrospective studies always have a degree of recall bias and possibly a higher degree of reports in cases where malformations have occurred after NVP/HG treated with antiemetic drugs. The compliance to the prescriptions is also a confounder in database research because the prescription itself does not automatically mean that the women has followed the ordination or even taken the drugs at all. Most studies also mention that the sample size is quite small and conclusions could benefit from larger prospective investigations.
With all these results and conclusions made in both the available RCT’s and the systematic reviews it seems not to be a higher risk for any severe malformations in antiemetic exposed fetuses. The symptoms of NVP/HG suggest that the placenta is well functioning and the pregnancy healthy overall and the option of not treating the women for symptomatic relief is possibly causing more harm than any antiemetic will do. With that said the antiemetic drugs should not be used as absolute first line treatments; non-pharmacological methods have less questions marks to their effects in the fetus and the evidence available are not enough to make any definite assumptions on total safety for any antiemetic substance used during pregnancy. More and larger studies should be undertaken and more RCT’s are needed to make final conclusions of the safety of substances, but due to the rare occurrences of malformations, RCT’s are hard to accommodate. Also factors such as the absolute number of gestational weeks need to be assessed and studied in particular because of the organogenesis phases are limited in the fetus and exposure to medications after this stage could not possibly turn into organ-malformations. The possible mechanism of action for creating cardiac abnormalities in the baby are due to the QT-prolongation effect of ondansetron which in other drugs have shown tendencies to create malformations during pregnancy, if the QT-interval is prolonged an oxygen delicacy could have severe impacts on the fetal heart during development but when the heart is already formed this should not be considered a problem for the fetal development. However, the studies used for this literature based study were all registered and often cited in smaller studies and reviews suggesting that the results should matter for the evaluation of drug-treated HG.

5.4 Final summary

According to the results all of the three interventions could be said to be safe for use in pregnant women suffering from NVP/HG. Ondansetron exposed women reported adverse effects less frequently than women given metoclopramide or promethazine. Between metoclopramide and promethazine alone the effects were similar but the adverse effects were more frequent reported in women treated with promethazine. The choice of treatment should however be individualized and chosen in dialog with the affected woman.

The studies conclude that non-pharmacological options and pyridine/doxylamine alongside to metoclopramide and promethazine regimes have been used more frequently and for longer time than ondansetron. Most likely due to the off-label prescriptions and the lack of larger controlled studies on birth outcomes after ondansetron exposure. But all of the studies fail to show any statistically increased risks, and if there were one it should have been clear by now that the risk is higher. Nowadays ondansetron is one of the more frequently prescribed off-label drugs in the US [22] due to better adverse effect profile and are said to improve a range of symptoms in various degrees from mild to severe HG [17].
6. Conclusion

For conclusion, one can assume the safety and effect of promethazine, metoclopramide and ondansetron are validated for treating HG [1, 9, 20, 22] however, non-pharmacological interventions shall always remain the first-line treatment due to the sensitivity of the developing embryo especially the first 10 weeks of gestations and organogenesis [1, 4, 9, 18, 20, 22, 26].

One regime cannot be said to be superior to another in general [9] but rather individualized care shall be given. Studies do however suggest that ondansetron could be superior to other substances due to better profile regarding vomiting frequency and adverse effects [2, 17]. The association between ondansetron and cardiac malformations is unclear and larger studies should be undertaken on this matter. Regardless of the possible association between cardiac malformations and ondansetron exposure it seems like that one shall not hesitate to treat women suffering from severe HG after the 10th week of gestation with ondansetron because HG untreated is putting both mother and child in more danger than the risk of malformations after organogenesis [10, 21, 25]. HG after 10th week of pregnancy could possibly be considered an indication for ondansetron while NVP should remain off-label and an option only after other methods have failed.
7. Acknowledgements

Klara Harlin for being my beautiful daughter and inspiration for this study.

Dr. Anna Pohjanen, Head of Regional Department of Gynecology and Obstetrics, MD, senior consultant, for her support during my pregnancy, and for information well needed for this study.

Maria Gustafson, supervisor, for her fast correspondence and keeping the work together.

Norrbottens läns landsting, Sunderbys hospital for keeping me alive and placing my little Klara on my chest 3/9-17 after nine months of severe HG.
8. References


9. Appendix 1

PUQE-Scale [28]

Motherisk PUQE-24 scoring system:

<table>
<thead>
<tr>
<th>Question</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>In the last 24h, for how long have you felt nauseated or sick to your stomach?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the last 24h, have you vomited or thrown up?</td>
<td>7 or more times (5)</td>
<td>5-6 times (4)</td>
<td>3-4 times (3)</td>
<td>1-2 times (2)</td>
<td>I did not throw up (1)</td>
</tr>
<tr>
<td>In the last 24h, how many times have you had retching or dry heaves without bringing anything up?</td>
<td>No time (1)</td>
<td>1-2 times (2)</td>
<td>3-4 times (3)</td>
<td>5-6 times (4)</td>
<td>7 or more times (5)</td>
</tr>
</tbody>
</table>

Total score is sum of replies to each of the three questions.

Mild: 6 or less
Moderate: 7-12
Severe: 13-15

Additional questions:

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 (best you felt before pregnancy)

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