



Evaluation of Gastrointestinal Complications in Lebanese Pregnant Females

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ABSTRACT

Purpose: The aim of this study is to evaluate the knowledge, awareness, and treatment of gastrointestinal complications encountered by females during gestation in Lebanon.

Methods: A community based retrospective multicenter observational study was conducted. Information regarding frequency, severity, and treatment taken for nausea, vomiting, heartburn, and constipation in pregnant females was recorded.

Results: We retrieved data for 381 females. The incidence of nausea and vomiting was 77.1%, of whom 53.8% had everyday symptoms and 72% had moderate to severe ones. Medical therapy was sought by 15% of the patients who were prescribed mostly pyridoxine (35.1%) and barely ondansetron (1.4%). Heartburn was reported in 70.9%, who were prescribed antacids (25.2%), histamine 2 receptor antagonists (12.1%), and proton pump inhibitors (10.2%). Constipation was encountered by 33.3% of the females and 11.8% received laxatives to lessen their symptoms.

Conclusion: Our data show that the management is not very well understood and entails a risk in terms of adequacy and safety.

Keywords: gastrointestinal; pregnancy; complications; Lebanon

INTRODUCTION

Complications of pregnancy are health problems that arise during the gestational period.^[1] They can involve the mother's health, baby's health, or both. Most of the complications can be simply managed, and a few are critical. The most common encountered complications are those related to the gastrointestinal system, including nausea and vomiting (N/V), heartburn, and constipation.^[1-5]

N/V during pregnancy is commonly referred to as "morning sickness", and affects 70 to 80 % of pregnant women. It is estimated that 50 to 90 % experience nausea, while 25 to 55 % of pregnant females experience vomiting.^[6-8] Even though N/V symptoms are limited to the first trimester, a small percentage of pregnancies have a prolonged course where symptoms could extend until delivery.^[9] It is generally mild and may be controlled by traditional

measures however; some females may have a profound course and develop hyperemesis gravidarum.^[10] Subsequently, heartburn or gastroesophageal reflux disease (GERD) is estimated to occur in 30 to 50% of pregnancies, reaching 80 % in some populations^[11]. More than 80% experience heartburn in the third trimester but only a few have symptoms in early pregnancy^[12-14]. Usually GERD is associated with N/V which could have serious negative effects on the quality of life.^[15]

The third common gastrointestinal complaint in pregnancy is constipation. It is a widespread problem that affects approximately half of all women at some point during their pregnancy.^[16] Reported prevalence rates of constipation vary from 9% to 39%. Multiple factors can trigger constipation, including hormonal changes (high progesterone and low motilin levels), medications (antacids, iron supplements...), stress, anxiety, and minimal physical exercise.^[17-22] During

late pregnancy, the enlarged uterus presses upon the intestine and rectum; this physiological change also increases the risk of experiencing constipation.^[16]

Maternal lifestyle habits are essential modifiable risk factors, which can be avoided to prevent or lessen these complications.^[23] Accordingly, assessing the frequency and degree of awareness of pregnancy related gastrointestinal complications in Lebanese females is important, in order to perceive the gaps in dealing with these problems that can negatively affect the daily lives of women during gestation. The aim of this study is to evaluate the knowledge, awareness, and treatment of females about the gastrointestinal complications that they might have encountered during gestation in Lebanon.

METHODS

Study Design and Setting: A cross sectional survey of postpartum women was performed. This was a multicenter observational study conducted between November 2014 and April 2015 in a community setting. Medical information was obtained from patients in different clinics to construct an observational study from the females who were pregnant in the last 10 years. The study protocol was reviewed and approved by the institutional review board of the school of pharmacy at the Lebanese International University. The study offered no physical or social risks to the participants; their privacy and confidentiality were respected and abided by.

Study Population: A total of 381 patients were assessed for their knowledge of pregnancy complications. Eligible participants were pregnant females and those who have had at least one child in the past ten years. Exclusion criteria were males, nulliparity females, last pregnancy for more than 10 years, and females of age more than 48 years.

Covariates: Three gastrointestinal complications were assessed and they included: N/V, heartburn, and constipation. Patients were asked the following questions for each complication: frequency, severity, initiation of symptoms, medical consultant for their symptoms, and the pharmacological and non-pharmacological treatment that was followed. Additionally, patients were questioned about the following variables: age, body weight, age of marriage, number of living children, number of pregnancies, smoking during gestational period, education and family income level. The following comorbidities were also identified: hypertension 3.4% HTN, 2.6% thyroid abnormalities, and 0.5% DM (**Table 1**).

(HTN), thyroid abnormalities, diabetes mellitus (DM), dyslipidemia (DL), urinary incontinence, irritable bowel syndrome (IBS), coronary artery disease (CAD), chronic renal failure (CRF), peptic ulcer disease (PUD), and GERD.

Study Outcomes: The primary outcome of this study was to assess the frequency, severity, and knowledge about the gastrointestinal related symptoms among pregnant Lebanese females. As for the secondary outcome, it included the evaluation of the treatment followed by the females to relieve these complications.

Statistical Analysis: Statistical analysis included calculation of frequencies and percentages for discrete variables, and means, standard deviations (SD), minimum and maximum values for continuous variables. Bivariate analysis was then performed; relationship between categorical variables whether dichotomous or multinomial qualitative variables were examined using Pearson's Chi square or Fisher's exact tests when normal or abnormal distribution was assumed, respectively. Statistical analysis was performed using the Statistical Package for Social Sciences software (SPSS) version 20.0 and two-tailed P-value less than 0.05 was considered to indicate statistical significance.

RESULTS

Patient Characteristics and Baseline Demographics: A cross sectional survey for 381 females, who had been pregnant at least once, was carried out from November 2014 to April 2015. The baseline characteristics of females enrolled are presented in **Table 1**. The mean age of the females was 29.32 years, the youngest women being 16 years old and the oldest being 48 years old. The majority of patients' weight was between 56 kilograms and 80 kilograms (64.3%). The average ages of marriage and last pregnancy were 21.73 and 26.54 years respectively.

Out of the enrolled patients, 117 (30.7%) reported smoking but not during gestation, 213 (55.9%) females never smoked, and 51 (13.4%) smoked during pregnancy. Of the 381 females, 53% received university education. Approximately, the income of the majority of the patients was between 1 and 3 million (65.9%). As for comorbidities, 25.6% of the patients who have been questioned reported having had a certain disorder. The percentage of documented diseases were 7% for PUD, 6.3% IBS, 5.8% GERD,

Nausea and Vomiting: N/V symptoms have been experienced by 294 (77.1%) patients. Of these, 53.8% suffered from the symptoms daily, and 22.3% had intermittent symptoms. Additionally, the symptoms were mild in 28% and moderate to severe in 72% (**Figure 1**). Patients have reported following some non-pharmacological and pharmacological treatment strategies in order to relieve their symptoms. For the non-pharmacological treatment, 4.7% took ginger, 13.4% had citrus fruits and 8.1% drank peppermint (**Figure 2**). The pharmacological treatment that was taken by the patients was as follows: combination of pyridoxine and doxylamine (35.1%), metoclopramide (15.5%), domperidone (6.2%), dimenhydrinate (3.4%), ginger tablets (1.4%), and ondansetron (1.4%) (**Figure 3**).

Heartburn: Patients who experienced heartburn during pregnancy were 270 (70.9%), whereby 111 (29.1%) had no symptoms. The frequency of heartburn occurrence was as follows: 16% had the symptoms only during their first trimester, 30.2% during the second, 23.6% in the third, and only 1% had their symptoms all through their pregnancy (**Figure 4**). Medical advice was sought by 73.7% of the females. The non-pharmacological treatment that was followed included avoiding spicy food (27%), meals before sleep (17.3%), and carbonated/caffeinated/heavy meals (17.1%). Moreover, 13.1% reported eating cucumbers to relieve their symptoms, 11.8% slept with their upper body elevated, 5.2% wore loose fitting clothes, and 4.2% had cold milk (**Table 2**). Additionally, some females preferred pharmacological treatment to alleviate their heartburn. Most females received antacids (25.2%), H2RAs like ranitidine (12.1%), and 10.2% took proton pump inhibitors (PPIs). Among the females who received antacids, 39.59% were prescribed calcium carbonate containing antacids, 31.25% aluminum hydroxide/magnesium hydroxide, and 29.16% calcium carbonate/magnesium carbonate. Moreover, the types of PPIs taken were as follows, omeprazole (51%), rabeprazole (18%), pantoprazole (15%), esomeprazole (13%), and lansoprazole (3%) (**Table 2**).

Constipation: Constipation is a frequent problem during pregnancy. Amongst the included sample, 127 (33.3%) experienced constipation, 54 (14.2%) had symptoms throughout their pregnancy, whereas 254 (66.7%) had no complaints (**Table 3**). As non-pharmacological treatment, patients followed more than one life style modification to relieve their symptoms, out of which 57.4% increased the fiber intake. Also, 8.6% of the females performed some physical activity to lessen their constipation. As for

the pharmacological treatment, 45 (11.8%) females had received medications to lessen their symptoms. The medications that were taken by these patients were as follows: bisacodyl (15%), lactulose (22%), glycerin (15%), castor oil (2%), and an herbal product (46%) (**Table 4**).

DISCUSSION

Interpretation of Main Findings

Nausea and Vomiting: Several safe and effective treatments are available to lessen N/V symptoms.^[24] Many women ignore taking treatment because their symptoms might have been minimized by other factors, or they have been informed that it is a normal part of pregnancy and something they have to tolerate.^[1, 25] Management of N/V has to be tailored for each female given that these symptoms are manifested differently in each individual. The study obtained data on symptoms and treatment of N/V in pregnant women of varying parity, age and socioeconomic status. It was found that 28% experienced moderate to severe symptoms. Ginger was taken by only a small percentage of females (4.70%) which could be due to wrong beliefs, because patients thought that it might lead to severe uterine cramps. In a double blinded randomized controlled trial which evaluated the effectiveness and safety of ginger in the management of pregnancy induced N/V, it was an effective and safe treatment.^[26] Another recent study also showed similar results.^[27] In regards to pharmacological treatment received by the patients, the combination of doxylamine with pyridoxine showed the highest percentage among all (35.10%). According to a study done by Koren G et al, the combination of doxylamine with pyridoxine was effective in mild to moderate nausea in pregnant females, however it didn't significantly reduce vomiting.^[28] Moreover, only 1.4% of the patients used ondansetron. Oliveira LG et al compared ondansetron versus doxylamine/pyridoxine and concluded that the first was shown to be superior in controlling N/V during pregnancy.^[29] Yet still, human data on the safety of ondansetron for the treatment of hyperemesis are still unclear. A study evaluating ondansetron and metoclopramide use demonstrated a similar antiemetic and anti-nausea effect in hyperemesis gravidarum, but the safety profile was better with ondansetron.^[30] In our study the use of metoclopramide was 15.50% which is eleven times more than ondansetron. This is due to the fact that metoclopramide is significantly less expensive than ondansetron and remains a reasonable antiemetic choice.

Heartburn: Heart burn is a normal physiological problem that a pregnant female might experience. In this sample, the start of heartburn symptoms was the highest in the second trimester (30.20%) as compared to the first and third trimesters. This could be due to the significant changes that occur in the growing fetus that impose a pressure on the lower esophageal sphincter throughout this trimester.

The first line therapies for these patients are life style modifications. Therefore, females were asked about the details of their behaviors to control the symptoms. The highest percentage of non-pharmacological treatment that was followed by the patients was the avoidance behaviors. Spicy food (27%), meals before sleep (17.30%), carbonated/caffeinated beverages (17.1%), and heavy meals (17.1%) were listed among elements that were avoided. A consensus document has recommended that lifestyle and dietary modifications should remain the first-line treatment for heartburn.^[31] However, if heartburn is severe enough, a medication should be initiated after consultation with a healthcare professional.

In our study, patients used antacids, H2RAs, and PPIs to relieve the heartburn symptoms. Antacids were the most common medication used by the pregnant females (25.2%). The greater part (39.59%) used calcium carbonate, followed by aluminum hydroxide/magnesium hydroxide (31.25%), and calcium carbonate/magnesium carbonate (29.16%). A study found that calcium-based antacids had the added benefit of increasing calcium supplementation to prevent the hypertension and pre-eclampsia associated with pregnancy.^[32] With regards to H2RAs, ranitidine was the only one used and taken by (12.1 %). With respect to PPIs, they were used by 10.2%. Out of the patients who used PPIs, 51% used omeprazole which is classified as a pregnancy category C. It should be noted that this is a prescription drug has been prescribed by gynecologists to pregnant ladies instead of giving them better pregnancy category medications like pantoprazole and lansoprazole (both are pregnancy category B). This means that gynecologists also need to be updated concerning the safest choices when it comes to pregnancy.

A multicenter prospective controlled study done by Lalkin A et al showed that exposure to omeprazole throughout pregnancy is not associated with an increased risk of spontaneous abortions, decreased birth weight, or prenatal complications.^[33] However, in another multicenter prospective case controlled study by Diav-Citrin et al that identified 295 women exposed to omeprazole during pregnancy, the median

dose was 20 mg (20-40 mg) and median duration of use was 22 days (4-47 days). The incidence of congenital anomalies in this study population was not greater than the one observed in the control group. This sample size was noted to have an 80% power to detect a 2.72-fold increase of major malformations.^[34]

Constipation: Constipation is a frequent and debilitating complication during pregnancy. Patients with mild constipation can be treated by lifestyle modifications. In our study, 57.4% of patients who suffered from constipation increased their daily dietary fiber intake to soften their stool. In a study done by Anderson AS, an increase in the number of bowel movements and a change to a softer stool consistency was observed in patients who improved the fiber intake.^[35] Medications are best avoided but if necessary should be taken under supervision using the best available evidence. In our findings, an herbal product had the highest percentage of use (46%) as compared with other laxatives. Women who are unable to increase their dietary fibers may benefit from supplemental fibers.^[36] Moreover, lactulose was also used during pregnancy by 22% of the patients. Ramkumar D et al showed that there is good evidence to support the use of lactulose. It is relatively safe during pregnancy. Reproduction studies performed in mice, rats, and rabbits at doses up to 3 or 6 times the usual human oral dose have revealed no evidence of impaired fertility or harm to the fetus due to lactulose solution.^[37] However, no adequate and well-controlled studies have been conducted in pregnant women.

Study Limitations: Although the research has reached its aims, there were some unavoidable limitations. Recall bias was one of the limitations of this study, since patients may fail to remember the severity and frequency of complications that occurred during their previous pregnancies, along with the medications that they might have taken. Most of the collected data relied on the information given by the pregnant women. So females may over or under estimate their condition severity. In this study it was not possible to determine which pregnancy incident might have contributed to the reported complication and whether the complications recurred in subsequent pregnancies. Also, some risk factors for the development of these pregnancy complications were not identified including genetic mutations, family history, and obesity. Finally, the current study was conducted only in Beirut area which excluded other cities in Lebanon. Given the potential difference with other regions, the generalization of our findings should be done with caution.

Implications and Further Research: The findings of this study have many implications for further research, in prenatal, primary care practice, and public health. The described studies only considered the prenatal phase. Follow-up of these women and their children may not only provide more insight into the underlying mechanisms, but also provide information on the long-term consequences of adverse maternal lifestyle habits.

CONCLUSION

The majority of patients were unaware of lifestyle modifications that could alleviate their symptoms. This could be due to the lack of knowledge or to wrong beliefs about fetal harm or probability of miscarriage. The results of this study have the

potential to inform the public and try to formulate a plan about the awareness needed to deal with the complications. Educational campaigns to increase awareness about managing pregnancy complications by lifestyle modifications could be developed. This could involve posters and conferences encouraging women to speak to health care providers about any complication encountered. These posters could be placed in areas frequently visited by women during pregnancy such as hospitals and clinics.

CONFLICTS OF INTEREST

The authors report no conflicts of interest. They have no financial or proprietary interest in the subject matter or material discussed.

Table 1: Baseline demographics and clinical characteristics

Characteristics		Number of patients N (%)	Mean (SD)
Age (years)	16-24	95 (25)	29.23 (6.137)
	25-39	251 (66)	
	40-48	35 (9)	
Weight (kg)	38 -55	98 (25.7)	64.59(12.19)
	56 -80	245 (64.3)	
	81-105	38 (10)	
Smoking	Non smokers	213 (55.9)	
	During pregnancy	51 (13.4)	
	Prior to pregnancy	117 (30.7)	
Education	School	179 (47)	
	University	202 (53)	
Income	< 1 million	67 (17.6)	
	1-3 million	251 (65.9)	
	>3million	63 (16.5)	
Average age of marriage (SD)			21.73 (3.86)
Average age of last pregnancy (SD)			26.54 (5.32)
Average number of pregnancies (SD)			2.52 (1.6)
Average number of abortion (SD)			0.36 (0.72)
Comorbidities			
HTN		13(3.4)	
Thyroid		10(2.6)	
DM		2(0.5)	
IBS		24(6.3)	
PUD		27(7)	
GERD		22(5.8)	

Abbreviations: N: Number; %: Percentage; SD: Standard Deviation; kg: Kilogram; HTN: Hypertension; DM: Diabetes Mellitus; IBS: Irritable Bowel Syndrome; PUD: Peptic Ulcer Disease; GERD: Gastroesophageal Reflux Disease

Table 2: Non pharmacological & pharmacological treatment of GERD

Non pharmacological Treatment	N (%)		
Sleeping with upper body elevated	45(11.8)		
Wearing loose fitting clothes	20(5.2)		
Avoiding spicy food	103 (27)		
Avoiding heavy meals	65 (17.1)		
Avoiding carbonated/caffeinated beverages	65 (17.1)		
Avoiding meals before sleep	66 (17.3)		
Eating cucumber	50(13.1)		
Drinking cold milk	16(4.2)		
Pharmacological Treatment	N (%)	Specific Drug	N (%)
Antacids	96 (25.2)	Calcium carbonate	38(39.59)
		Aluminum hydroxide/Magnesium hydroxide	30(31.25)
		Magnesium carbonate/calcium carbonate	28(29.16)
H2RA	46 (12.1)	Ranitidine	
PPI	39 (10.2)	Omeprazole	20 (51)
		Rabeprazole	7 (18)
		Pantoprazole	6 (15)
		Esomeprazole	5 (13)
		Lansoprazole	1 (3)
Total	181 (47.5)		

Abbreviations: N: Number; %: Percentage; H2RA: Histamine 2 Receptor Antagonist; PPI: Proton Pump Inhibitor

Table 3: Frequency of constipation in pregnancy

Frequency of Constipation	N (%)	
No	254 (66.7)	
Yes	1 st trimester	17 (4.5)
	2 nd trimester	28 (7.3)
	3 rd trimester	28 (7.3)
	All through pregnancy	54 (14.2)
	Total	127 (33.3)

Abbreviations: N: Number; %: Percentage

Table 4: Treatment of constipation

Non Pharmacological Treatment	N (%)
Increase fiber intake	73 (57.4)
Exercise	11 (8.6)
Water	75 (59)
Pharmacological Treatment	N (%)
Bisacodyl	7 (15)
Glycerin	7 (15)
Lactulose	10 (22)
Castor oil	1 (2)
Herbal product*	21 (46)
Total	49(100)

*Herbal product contains: *Rhamnus alpine*, liquorice extract, alfalfa, calcium phosphate, artichoke, rhubarb, zedoary turmeric, rose hip, rosa gallica extract

Abbreviations: N: Number; %: Percentage

Figure 1: Frequency and severity of nausea and vomiting

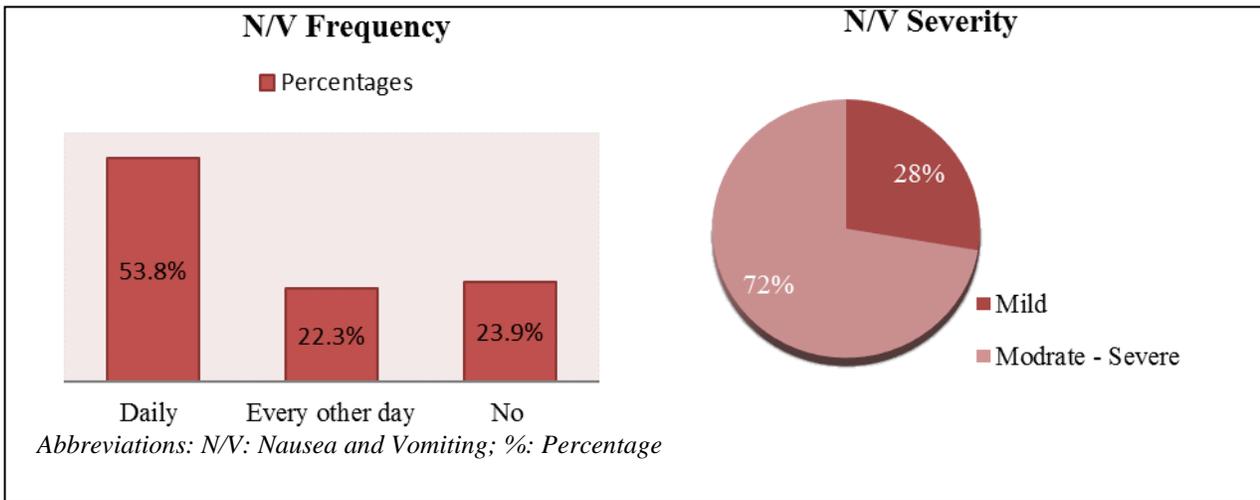
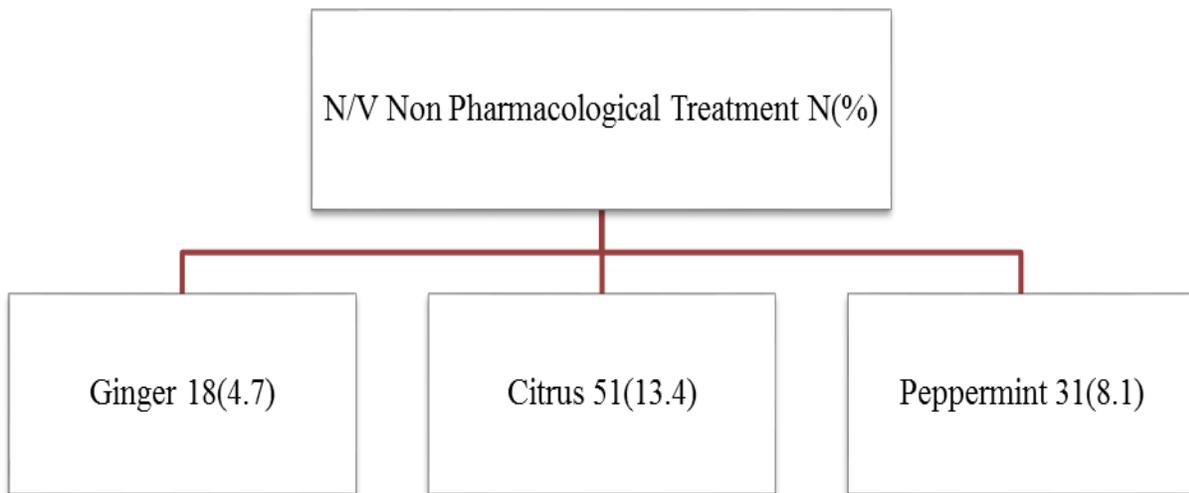
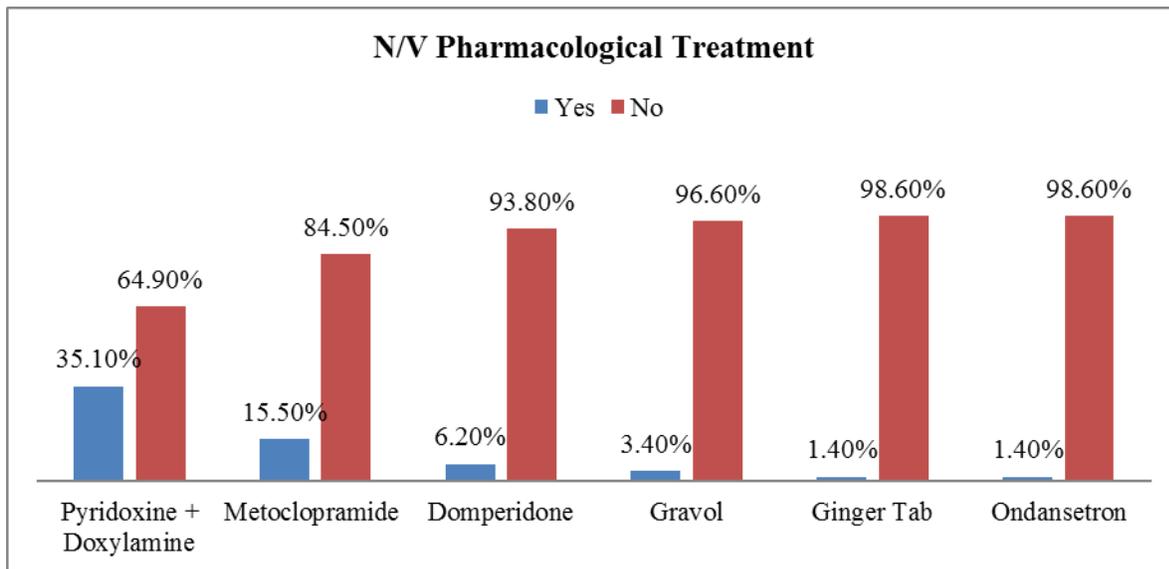


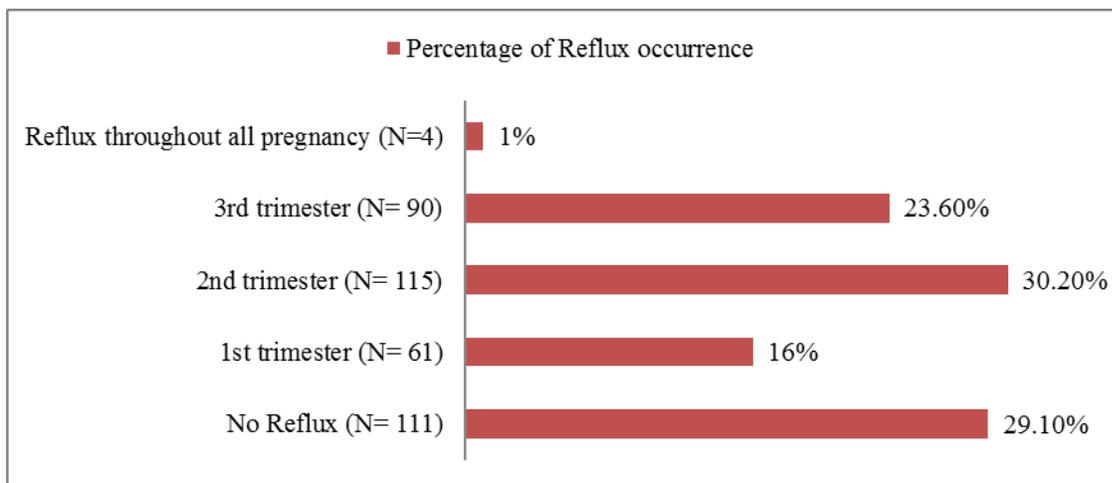
Figure 2: Non pharmacological treatment of nausea and vomiting



Abbreviations: N/V: Nausea and Vomiting; N: Number; %: Percentage

Figure 3: Pharmacological treatment of nausea and vomiting

Abbreviations: N/V: Nausea and Vomiting; %: Percentage

Figure 4: Percentage of reflux occurrence

Abbreviations: N: number; %: Percentage

REFERENCES

1. Pregnancy Complications, Compilation prepared by Centers for Disease Control and Prevention (CDC).
2. Niebyl J. N Engl J Med. 2010;363(16):1544-1550.
3. Koch K. Am J Obstet Gynecol. 2002;186(5):S198-S203.
4. Kassebaum N, Bertozzi-Villa A, Coggeshall M, Shackelford K, Steiner C, Heuton K et al. Int J Obstet Anesth. 2015;35(4):196-197.
5. Masson GM, Anthony F, Chau E. Br J Obstet Gynaecol. 1985;92:211-215.
6. Davis M. J Perinatal Neonat Nurs. 2004;18:312-328.
7. Buckwalter JG, Simpson SW. Am J Obstet Gynecol. 2002;186:S210.
8. Aka N, Atalay S, Sayharman S, Kiliç D, Köse G, Küçüközkan T. Aust N Z J Obstet Gynecol. 2006;46:274-277.
9. Gill SK, Maltepe C, Koren G. Can J Gastroenterol. 2009;23:270.

10. Einarson A, Maltepe C, Boskovi R, Koren G. *Can Fam Physician*. 2007;53(12), 2109-2111.
11. Rochelson B, Vohra N, Darvishzadeh J, Pagano M. *J Reprod Med*. 2003;48:422–424.
12. Richter JE. *Gastroenterol Clin North Am*. 2003;32: 235–61.
13. Weyermann M, Brenner H, Addler G, Yasar Z, Handke-Vesely A, Grab D et al. *Am J Obstet Gynecol*. 2003;189:526–31.
14. Richter, J.E. *Aliment Pharmacol Ther*. 2005;22(9):749-57.
15. Marrero JM, Goggin PM, de Caestecker JS, Pearce JM, Maxwell JD. *Br J Obstet Gynaecol*. 1992; 99(9):731-4.
16. Van Thiel DH, Gavaler JS, Joshi SN, Sara RK, Stremple J. *Gastroenterology*. 1977;72(4 Pt 1):666-8.
17. Cullen G, O'Donoghue D. *Best Pract Res Clin Gastroenterol*. 2007;21(5):807-18.
18. Trottier M, Erebara A, Bozzo P. *Can Fam Physician*. 2012;58(8):836-8.
19. Mirghafourvand M, Homayouni Rad A, Mohammad Alizadeh Charandabi S, Fardiazar Z, Shokri K. *Iran Red Crescent Med J*. 2016;18(11):e39870.
20. Longo SA, Moore RC, Canzoneri BJ, Robichaux A. *Clin Colon Rectal Surg*. 2010;23(2):80-9.
21. Keller J, Frederking D, Layer P. *Nat Clin Pract Gastroenterol Hepatol*. 2008;5(8):430-43.
22. Joo JS, Ehrenpreis ED, Gonzalez L, Kaye M, Breno B, Wexner SD et al. *J Clin Gastroenterol*. 1998;26(4):283–6
23. Lewis JH, Weingold AB. *Am J Gastroenterol*. 1985; 80: 912–23.
24. Kallen B, Lundberg G, Aberg A. *Acta Obstet Gynecol Scand*. 2003; 82:916–920.
25. Baron TH, Ramirez B, Richter JE. *Annals of internal medicine*. 1993; 118(5), 366-375.
26. Borrelli F, Capasso R, Aviello G, Pittler MH, Izzo AA. *Obstet Gynecol*. 2005; 105(4):849-56.
27. Viljoen E, Visser J, Koen N, Musekiwa A. *Nutr J*. 2014;13:20.
28. Koren G, Maltepe C. *J Obstet Gynaecol*. 2004; 24:530.
29. Oliveira LG, Capp SM, You WB, Riffenburgh RH, Carstairs SD. *Obstet Gynecol*. 2014;124(4):735-42.
30. Abas MN, Tan PC, Azmi N, Omar SZ. *Obstet Gynecol*. 2014;123(6):1272-9.
31. Kaltenbach T, Crockett S, Gerson LB. *Arch Intern Med*. 2006;166(9):965-71.
32. Thomas M, Weisman SM. *Am J Obstet Gynecol*. 2006;194(4):937-45.
33. Lalkin A, Loebstein R, Addis A, Ramezani-Namin F, Mastroiacovo P, Mazzone T et al. *Am J Obstet Gynecol*. 1998;179(3 Pt 1):727-30.
34. Diav-Citrin O, Arnon J, Shechtman S, Schaefer C, van Tonningen MR, Clementi M et al. 2005;21(3):269-75.
35. Anderson AS, Whichelow MJ. *Hum Nutr Appl Nutr*. 1985;39(3):202-7.
36. Prather, CM. *Curr Gastroenterol Rep*. 2004;6(5):402-4.
37. Ramkumar D, Rao SS. *Am J Gastroenterol*. 2005;100(4):936-971.