ONDANSETRON USE DURING PREGNANCY: A CASE SERIES

E Ferreira[1], M Gillet[2], J Lelièvre[2], J-F Bussières[3]

[1]Pharmacy Department, CHU Sainte Justine, Faculty of Pharmacy, Université de Montréal, Montréal, Quebec, Canada; [2]Pharmacy Department and Pharmacy Practice Research Unit, CHU Sainte-Justine, Montreal, Quebec, Canada; [3]Pharmacy Department and Pharmacy Practice Research Unit, CHU Sainte-Justine, and Faculty of Pharmacy, Université de Montréal, Montreal, Quebec, Canada

Corresponding Author: *ema.ferreira@umontreal.ca*

ABSTRACT

This is a descriptive retrospective case series of 14 pregnant women treated with ondansetron for hyperemesis gravidarum (HG) at CHU Sainte-Justine, from January 2002 to October 2011. Two of the patients received ondansetron during two separate pregnancies. Both pregnancies were analyzed separately for the purposes of this study. Another woman had twins who were included in the analysis. Therefore, the outcomes of 16 pregnancies and 17 newborns are presented. The patients were on average 28.1 ± 4.6 years old and were admitted to the hospital 5.0 ± 4.0 times. All patients who received ondansetron had previously been treated using the standard HG protocol to which they had not optimally responded. Ondansetron was initiated on average at 11.8 ± 4.8 weeks' gestation. In seven cases, administration was carried out during organogenesis. We observed 16 live births, including a set of twins, and one minor birth defect (isolated atrial and ventricular septal defects) reported after a second trimester exposure. Mean gestational age at birth was 36.9 ± 3.4 weeks and mean birth weight was 2.85±0.86 kg. We also noted six other pregnancy or neonatal outcomes (intrauterine growth retardation [IUGR] for each twin and a in a single pregnancy, a transient tachypnea, a mild hydrocele, and an extrarenal pelvis). Furthermore, we noted two premature births, one at 24 weeks of gestation and her infant died in the first weeks of life due to complications of prematurity and a second birth at 36 $^{2/7}$ weeks of gestation. Teratogenicity associated with the use of ondansetron has so far not been shown in humans. This case series adds information on ondansetron use during pregnancy. However, until we have more published data, ondansetron should be used as a second-line agent for the management of HG.

Key Words: *Ondansetron, pregnancy, hyperemesis gravidarum, case series, birth defects*

Up to 80 % of pregnant women suffer from nausea and vomiting, which usually begin by the 4th week and subside by the 16th week of pregnancy. However, in more than 20% of women, the condition persists after the 16th week, and in about 1% to 3% it presents as *hyperemesis gravidarum* (HG).[1] HG is defined as persistent vomiting accompanied by weight loss exceeding 5 percent of pre-pregnancy body weight, hypokalemia and ketonuria unrelated to other causes. HG tends to improve in the last half of pregnancy, but may persist until delivery.[2] Excessive vomiting during pregnancy can lead to maternal complications including elective terminations of pregnancy (ETOP).[3,4] HG combined with a pregnancy weight gain less than 7 kg is associated with an increased risk of prematurity and low birth weight.[5,6]

The pathogenesis of HG is unknown but may include psychological factors (e.g. somatization disorder), hormonal changes (e.g. increased serum concentrations of estrogen, progesterone or human chorionic gonadotropin), abnormal gastric motility and others causes (e.g. nutrient deficiencies, alteration in lipid levels, genetic factors, infection with *Helicobacter pylori*, etc.).[4,7]

The treatment of HG depends on the severity of symptoms and their impact on the mother, and

whether maternal treatment is safe for the fetus. Treatment choices may include dietary/lifestyle changes, vitamins, antiemetics, and hospitalization. Usually, nausea and vomiting treatment starts with non-pharmacologic approaches and then drugs are added if symptoms do not improve. HG treatment includes hospitalization with intravenous rehydration with electrolytes to manage dehydration and electrolyte disorders and antiemetics.[8]

According to a systematic review on nausea and vomiting in early pregnancy conducted by Festin, there are no drugs likely to be beneficial in HG; of unknown effectiveness, there are corticosteroids, corticotrophins, diazepam, ginger, ondansetron and dietary interventions other than ginger; they did not find any study evaluating metoclopramide in the treatment of HG.[9] However, Lacasse et al. suggest that a combination of metoclopramide and diphenhydramine may be useful[10] as well as metoclopramide alone.[11] The use of corticosteroids and diazepam has been associated with an increased risk of oral clefts in two meta-analyses with an OR of 3.35 (1.97 to 5.69) for corticosteroids, and of 1.79 (1.13 to 2.82) for benzodiazepines considering a baseline risk of oral cleft is 1/1000.[12,13]

Ondansetron is a 5-hydroxytryptamine (5-HT_3) receptors antagonist. Stimulation of 5-HT_3 receptors located in the chemoreceptive trigger zone plays a major role in the genesis of nausea and emesis.[14-16] There are limited data about the safety and the efficacy of ondansetron in HG.[9] There are three case reports published using ondansetron during pregnancy without evidence of fetal harm; however, treatment was started after organogenesis.[17] The efficacy of ondansetron was similar to promethazine in two groups of pregnant women treated with ondansetron (n=15) or promethazine (n=15) for HG; pregnancy outcomes were not reported in this trial.[18] Einarson et al. has also published a prospective comparative observational study of three groups of 176 mothers exposed to ondansetron, to other antiemetics or to non teratogenic agents. The rate of major malformations and other pregnancy outcomes were similar between these three groups.[19] The American College of Obstetrics and Gynecology practice bulletin's algorithm on antiemetic pharmacotherapy for NVP suggests oxylamine then promethazine or dimenhydrinate, either orally or rectally, for the treatment of NVP. In women hospitalized for HG, intravenous dimenhydrinate, metoclopramide, or promethazine are recommended as first-line therapies with methylprednisolone or ondansetron as second line.

Tan et al. indicated that despite the lack of evidence of superiority and with only anecdotal literature, ondansetron is increasingly being used in HG driven by documented efficacy in chemotherapy-induced nausea and vomiting. They also believe ondansetron should be considered a second-line antiemetic.[11]

The aim of this study is to describe our clinical experience with the use of ondansetron in the treatment of HG.

METHODS

This is a descriptive retrospective case series. The centre hospitalier universitaire (CHU) Sainte-Justine is a mother-child teaching center that includes 80 ob-gyn beds in four patient care wards. It is a tertiary referral center for high-risk pregnancies. The in-house standard protocol for treating HG includes IV administration of D5% NaCl 0.9% solution with 100 mg of thiamine. Following one litre of hydration, IV diphenhydramine 50 mg every 6 hours is administered along with multivitamins. Then, thirty minutes later, IV metoclopramide 45 mg in D5% 250 mL at a rate from 1.8mg/h to 3.2mg/h is initiated. Vitamin B6 may be added when symptoms persist. Liquids and low-fat meals are re-introduced from day 2 on. Sequential oral treatment is begun two hours after the first low-fat meal is well tolerated and includes oral hydroxyzine 25 mg every 6 hours and metoclopramide 10 mg every 6 hours.[10] The HG treatment protocol involves a multidisciplinary team consisting of obstetricians, pharmacists, dieticians, nurses and other professionals when required.

The retrospective study included all pregnant inpatients at CHU Sainte-Justine treated for HG from January 2002 to October 2011 with at least one prescription for ondansetron. The patients were identified using the pharmacy software (Gespharx(R) – CGSI Solutions TI Inc, Québec, QC). Multiple births were included. Patients with

unknown pregnancy outcomes and those who had received ondansetron for other indications were excluded from the study. Demographic (age, last menstruation period date, and alcohol consumption, smoking, drugs, whenever available), clinical (obstetrical history, associated diagnoses, date of HG diagnosis, number of hospital admissions for HG), biological (kaliemia, ketonuria, proteinemia) and pharmaceutical (drug history) data were collected for each patient. Outpatient compliance after discharge could not be monitored. Demographic (date of birth, birth weight) and clinical (congenital and/or abnormal outcomes) data were collected for each newborn from the medical chart. Use of ondansetron was confirmed from medication administration records. Medical records were analyzed retrospectively using a standardized data collection sheet (MS Word, Seattle, WA). All compiled data were entered into a spreadsheet (MS Excel, Seattle, WA). Gestational ages were determined with the last menstruation period date. Descriptive statistical analyses (i.e., mean, standard deviation, median and interval) were carried out using a database program (MS Access, Seattle, WA) (mean ± standard deviation, median, [minimum-maximum]).

In addition, a review of the medical literature was performed using Medline. The Mesh terms "pregnancy" and "ondansetron" were used. Research was limited to French - and English - language articles focusing on humans from 1990 to 2011. Case reports and letters to the editor were also taken into account. None of the articles that referred to the use of ondansetron during the peripartum period were considered for the purposes of this analysis.

RESULTS

A total of 14 pregnant women who were treated with ondansetron for HG were identified at the CHU Sainte-Justine from January 2002 to October 2011. Two of the patients received ondansetron during two separate pregnancies. Both pregnancies were analyzed separately for the purposes of this study. Another woman had twins who were included in the analysis. Therefore, the outcomes of 16 pregnancies and 17 newborns are presented.

The patients were on average 28.1 ± 4.6 years old (median [min-max]: 26.0, [22-38]). Three women had had an ETOP due to HG previously. The patients were admitted to the hospital 5.0 ± 4.0 times (median [min-max]: 3.5, [1-15]) for HG. We identified ketonuria in 14 of the 16 pregnancies and an average of 3.5 ± 3.7 hypokaliemia episodes (K^+<3.5 mmol/L) (median [min-max]: 2.0, [0-11]) per patient.

All patients who received ondansetron had previously been treated using the standard HG protocol to which they had not optimally responded. In some cases, however, metoclopramide could not be prescribed to its maximum dosage because of extrapyramidal side effects. Ondansetron was initiated, on average, at 11.8 ± 4.8 weeks' gestation (median [min-max]: 10.5, [6.3-23.9]). In seven cases, administration was carried out during organogenesis (from the 4th to the end of the 10th week of pregnancy), whereas for the other, administration began after organogenesis. Out of the 16 pregnancies reviewed, 14 had a diagnosis of HG before the initiation of ondansetron. In two cases, the HG diagnosis was not precisely stated; however, nausea and vomiting were well documented. It should be mentioned that hydromorphone, for which nausea and vomiting are a frequent side effects, was used in 9 pregnancies to treat pain (Table 1).

TABLE 1 Summary of Pregnancies Data

Pregnancy (#)	Age (Yrs)	Gestational Age at Start of Ondansetron Treatment (week$^{days/7}$)	Hospital Admissions for Exacerbated NVP (n)	Hypokaliemia Episodes (n)	Other First Trimester Treatments**	Past and Present Medical History***
1*	29	$6^{2/7}$	3	0	Omeprazole	ETOP for HG
2*	24	$8^{1/7}$	4	3	Omeprazole	ETOP for HG
3	32	$18^{6/7}$	8	2	Acetylsalicylic Acid Citalopram Dalteparin Dicyclomine Hydromorphone Lorazepam Oxazepam	Depression, anxiety, gestational diabetes
4	31	$17^{1/7}$	7	1	Hydromorphone Lorazepam Tacrolimus	Cardiac transplant, psychiatric disorders
5	29	$9^{1/7}$	10	10	Acetylsalicylic Acid Cosyntropin (a single dose) Hydromorphone Aspart Insulin Regular Human Insulin Oxazepam Pantoprazole Sumatriptan	Gestational diabetes
6*	22	$14^{2/7}$	3	1	Hydromorphone	ETOP for HG
7	24	$13^{1/7}$	1	2	Hydromorphone	None
8	26	$13^{1/7}$	2	2	None	None
9	26	$23^{6/7}$	3	3	Doxylamine	Type 2 diabetes, obesity, depression, genital herpes

Pregnancy (#)	Age (Yrs)	Gestational Age at Start of Ondansetron Treatment (week$^{days/7}$)	Hospital Admissions for Exacerbated NVP (n)	Hypokaliemia Episodes (n)	Other First Trimester Treatments**	Past and Present Medical History***
10	36	$10^{5/7}$	1	0	Diclectin Pantoprazole Ranitidine Omeprazole Diphenhydramine Metoclopramide Hydromorphone Hydroxyzine	None
11	24	$7^{4/7}$	5	8	Metoclopramide Diphenhydramine Ranitidine Hydroxyzine Hydromorphone Pantoprazole Methylprednisone Sucralfate Omeprazole	None
12	38	$9^{2/7}$	2	8	Dimenhydrinate Diphenhydramine Docusate de Sodium Hydroxyzine Metoclopramide Omeprazole Pantoprazole Ranitidine Aspart insuline Regular human insuline Isophan human insuline	Type 2 diabetes
13*	24	$8^{3/7}$	15	11	Metoclopramide Diphenhydramine Ranitidine Hydroxyzine Hydromorphone Pantoprazole Omeprazole Acetaminophen Clotrimazole Ginger Domperidone Citalopram Docusate de sodium Glycerin Lactulose Codeine Indomethacin Methylprednisolone Prednisone	ETOP for HG, narcodependance

Pregnancy (#)	Age (Yrs)	Gestational Age at Start of Ondansetron Treatment (week$^{days/7}$)	Hospital Admissions for Exacerbated NVP (n)	Hypokaliemia Episodes (n)	Other First Trimester Treatments**	Past and Present Medical History***
14	32	$10^{2/7}$	10	5	Hydroxyzine Metoclopramide Diphenhydramine Ranitidine Acetaminophen Pantoprazole Omeprazole	Acute renal insufficiency during previous pregnancy
15	26	$6^{6/7}$	5	0	Citalopram Indomethacin Clonazepam Cephalexin Doxylamine+pyridoxine Olanzapine Hydromorphone Nicotine patch Propranolol Oxycodone Ampicillin Gentamicin Acetaminophen Ginger Oxazepam Cefazolin Docusate de sodium Sennosides a+b Clotrimazole Metoclopramide Diphenhydramine Ranitidine Acetaminophen + codeine	**Surgical**: phlebitis (saphenous vein), kidney x4, cholecystectomy, appendectomy **Medical**: acute renal insufficiency, migraine, depression, chronic pyelonephritis, urinary lithiasis **Gynecological**: condyloma, gestational diabetes
16	26	$12^{2/7}$	1	0	Levothyroxine Doxylamine+pyridoxine Metoclopramide Multivitamins Diphenhydramine Ranitidine Hydroxyzine Pantoprazole Ginger Omeprazole	Hypoglycemia, hypothyroidism

HG: *Hyperemesis gravidarum*
ETOP: Elective Termination of Pregnancy
NVP: Nausea and Vomiting of Pregnancy
*Pregnancies #1 and #2 relate to the same patient
Pregnancies #6 and #13 relate to the same patient
** While HG was clearly diagnosed in all except two cases (patient #4, 15), there were confounding factors that could have contributed to severe nausea in some cases (e.g. psychiatric disorders, use of narcotics, GERD, etc.).
*** Past and present medical history were collected from our medical records; in some cases, patient did receive treatment for other chronic medical conditions not necessarily documented in the hospital medical record.

TABLE 2 Summary of Newborns Data

Pregnancy (#)	Newborns	Gestational Age at Birth (Weeks)	Birth Weight (Kg)	Anomalies
1	1	38	3.56	Rapidly reversible transient tachypnea
2	2	37	3.31	None
3	3	38	3.30	None
4	4	24	0.66	Premature, died within the first weeks of life
5	5*	37	2.09	IUGR, hypoglycemia
5	6*	37	1.86	IUGR, hypoglycemia
6	7	38	3.07	Slight hydrocele
7	8	40	4.10	None
8	9	38	3.88	None
9	10	36	2.50	Heart murmur with ASD-VSD, ankyloglossia, icterus
10	11	37	3.87	None
11	12	39	2.99	None
12	13	38	2.34	None
13	14	38	3.06	Extrarenal pelvis
14	15	36	2.14	Premature, IUGR
15	16	38	2.83	None
16	17	37	2.95	None

IUGR: Intra-uterine growth retardation
ASD: Atrial septal defect
VSD: Ventricular septal defect
(*) Newborns #5 and #6 are twins

We observed 16 live births, including a set of twins, and one minor birth defect (isolated atrial and ventricular septal defects). Mean gestational age at birth was 36.9 ± 3.4 weeks (median [min-max]: 38.0 weeks, [24-40]), and mean birth weight was 2.8 5± 0.86 kg (median [min-max]: 3.07 kg, [0.66-4.10]). We also noted six other pregnancy or neonatal outcomes (intrauterine growth retardation [IUGR] for each twin and a in a single pregnancy, a transient tachypnea, a mild hydrocele, and an extrarenal pelvis). Furthermore, we noted two premature births, one at 24 weeks of gestation and the infant died in the first weeks of life due to complications of prematurity and a second birth at 36 $^{2/7}$ weeks of gestation. A summary of the findings regarding the newborns is presented in Table 2.

DISCUSSION

While a majority of pregnant women will suffer from nausea and vomiting, a minority experiences HG. Poursharif et al. demonstrated that, in a cohort of 808 women with HG, 15% of the patients underwent ETOP, which illustrates the major impact this pathology has on the course of pregnancy.[3]

At CHU Sainte-Justine, ondansetron is only considered as a second line agent for the treatment of HG. In the literature, teratogenicity studies of ondansetron have been conducted in rats and rabbits and they have not indicated any conclusive teratogenic risks.[20] In humans, Einarson et al. assessed the safety of ondansetron during the first trimester (most of the patients treated between five and nine weeks of gestation) of pregnancy in a controlled prospective study aimed at comparing pregnancy outcomes in three groups of 176 patients.[19] One patient group was exposed to ondansetron, the second to other antiemetics and the third to nonteratogenic medications. This study did not reveal any significant differences among the three groups with respect to birth defects, spontaneous abortions, stillbirths, ETOP and prematurity. Nevertheless, it did report the presence of three mild cases of hypospadias in children whose mothers received ondansetron. Asker et al. reported 65 patients exposed to ondansetron during pregnancy, 21 of whom were exposed during the first trimester. The authors did not observe birth defects and reported two preterm births.[21] Sullivan et al. conducted a randomized controlled study comparing the efficacy of ondansetron to promethazine in two groups of 15 patients who were suffering from HG.[18] Ondansetron was started at 11 ± 2.7 weeks' gestation. The authors concluded that there were no significant differences between the two groups in terms of efficacy; however, they did not describe pregnancy outcomes. Three case reports on the use of ondansetron during pregnancy were also published.[22-24] The three women received ondansetron after organogenesis was completed. All of them had a good response to the treatment and no anomaly was observed (Table 3).

TABLE 3 Case Reports of Ondansetron Use during Pregnancy

Siu et al.[22]	- 35-year-old female, HG - Ondansetron IV 8 mg 3 times begun at 12 weeks of pregnancy for 7 days followed by alternative treatment with oral ondansetron for 2 days (unspecified dosage) - Good response to ondansetron - Healthy newborn, caesarean delivery at 35 weeks of pregnancy
Tincello et al.[23]	- 29-year-old female, HG - Ondansetron IV 8 mg, 1 dose at 14 weeks' gestation followed by alternative treatment with oral ondansetron 8 mg 3 times day until 33rd week of pregnancy - Good response to ondansetron - Healthy newborn, labour at 39 weeks of pregnancy
Guikontes et al.[24]	- 21-year-old female, HG - Ondansetron 8 mg 3 times a day beginning in the 11th week of pregnancy for 14 days - Good response to ondansetron - Healthy newborn, term labour (unspecified gestational age)

In a prospective observational study, three doses of ondansetron 8 mg were administered in 41 patients who requested surgical termination of pregnancy at the first trimester. A significant amount of ondansetron was present in all embryonic compartments with a fetal/maternal ratio of 0.41 (0.31-0.52).[25]

There are still limited data published on the safety of ondansetron used at the first trimester of pregnancy. Our case series are in line with the current published data. We did not observe any major congenital anomalies in newborns whose mothers took ondansetron early in their pregnancy. A minor congenital defect of the atrial and ventricular septa was observed in one case but could not be related to ondansetron since it was started after organogenesis (i.e. 23 6/7 weeks). Moreover, the mother had type 2 diabetes. Benign reversible conditions were also observed, but they seemed not related with ondansetron use. IUGR

was observed in a singleton and a twin pregnancy and the management of the second case was particularly difficult due to significant under nutrition linked to persistent nausea and vomiting even after ondansetron use. As for the neonatal death, it was related to complications of prematurity.

This case series has important limitations due to its sample size and retrospective design, which did not allow us to evaluate the patient compliance on an outpatient basis. However, it does allow us to describe the use of ondansetron in a real clinical setting and to add information to what is already published.

CONCLUSION

Thus far, teratogenicity associated with the use of ondansetron has not been shown in humans. This case series adds information on ondansetron use during pregnancy. However, until more published data is available, ondansetron should be used as a second-line agent for the management of HG.

Acknowledgments

The authors wish to acknowledge Karine Touzin and Caroline Morin whose contributions helped to write this article.

REFERENCES

1. Miller F. Nausea and vomiting in pregnancy: the problem of perception--is it really a disease? Am J Obstet Gynecol 2002;186 (5 Suppl Understanding):S182-3.
2. Goodwin TM. Hyperemesis gravidarum. Clin Obstet Gynecol 1998;4:597-605.
3. Poursharif B, Korst LM, Macgibbon KW, Fejzo MS, Romero R, Goodwin TM. Elective pregnancy termination in a large cohort of women with hyperemesis gravidarum. Contraception 2007;76(6):451-5.
4. Goodwin TM. Hyperemesis gravidarum. Obstet Gynecol Clin North Am 2008;35(3):401-17.
5. Bailit JL. Hyperemesis gravidarium: Epidemiologic findings from a large cohort. Am J Obstet Gynecol 2005;193(3 Pt 1):811-4.
6. Dodds L, Fell DB, Joseph KS, Allen VM, Butler B. Outcomes of pregnancies complicated by hyperemesis gravidarum. Obstet Gynecol 2006;107(2 Pt 1):285-92.
7. Golberg D, Szilagyi A, Graves L. Hyperemesis gravidarum and Helicobacter pylori infection: a systematic review. Obstet Gynecol 2007;110(3):695-703.
8. Ismail SK, Kenny L. Review on hyperemesis gravidarum. Best Pract Res Clin Gastroenterol 2007;21(5):755-69.
9. Festin M. Nausea and vomiting in early pregnancy. Clin Evid 2009;6:1405-25.
10. Lacasse A, Lagoutte A, Ferreira E, Berard A. Metoclopramide and diphenhydramine in the treatment of hyperemesis gravidarum: Effectiveness and predictors of rehospitalisation. Eur J Obstet Gynecol Reprod Biol 2009;143(1):43-9.
11. Tan PC, Omar SZ. Contemporary approaches to hyperemesis during pregnancy. Curr Opin Obstet Gynecol 2011;23(2):87-93.
12. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology 2000;62(6):385-92.
13. Dolovich LR, Addis A, Vaillancourt JM, Power JD, Koren G, Einarson TR. Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. BMJ 1998;317(7162):839-43.
14. Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. Pharmacotherapy: A pathophysiologic approach. 3rd edition. Stamford: Appleton and Lange, 1997. 751-65.
15. Hornby PJ. Central neurocircuitry associated with emesis. Am J Med 2001;111 Suppl 8A:106S-112S.
16. Moore KL, Persaud TVN. Before we are born: Essentials of embryology and birth defects. 6th edition. Philadelphia: Saunders, Elsevier Science, 2003. 62-75.
17. Mazzotta P, Magee LA. A risk-benefit assessment of pharmacological and non-pharmacological treatments for nausea and vomiting of pregnancy. Drugs 2000;50(4):781–800.
18. Sullivan CA, Johnson CA, Roach H, Martin RW, Stewart DK, Morrison JC. A pilot study of intravenous ondansetron for hyperemesis gravidarum. Am J Obstet Gynecol 1996;174(5):1565-8.
19. Einarson A, Maltepe C, Navioz Y, Kennedy D, Tan MP, Koren G. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. BJOG 2004;111(9):940-3.
20. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation. 8th edition.

Philadelphia: Lippincott Williams and Wilkins, 2008. 1368.
21. Asker C, Norstedt Wikner B, Kallen B. Use of antiemetic drugs during pregnancy in Sweden. Eur J Clin Pharmacol 2005;61(12):899-906.
22. Siu SS, Yip SK, Cheung CW, Lau TK. Treatment of intractable hyperemesis gravidarum by ondansetron. Eur J Obstet Gynecol Reprod Biol 2002;105(1):73-4.
23. Tincello DG, Johnstone MJ. Treatment of hyperemesis gravidarum with the 5-HT3 antagonist ondansetron (Zofran). Postgrad Med J 1996;72(853):688-9.
24. Guikontes E, Spantideas A, Diakakis J. Ondansetron and hyperemesis gravidarum. Lancet 1992;340(8829):1223.
25. Siu SS, Chant MT, Lau TK. Placental transfer of ondansetron during early human pregnancy. Clin Pharmacokinet 2006;45(4):419-23.