The Safety of Ondansetron and Chlorpromazine for Hyperemesis Gravidarum in First Trimester Pregnancy

Şafak ÖZDEMİRCİ[1,2], Funda AKPINAR[2], Melek BİLGE[3], Funda ÖZDEMİRCİ[4], Saynur YILMAZ[2]
Deniz ESİNLER[2], İnci KAHYAOĞLU[2]

Kütahya, Turkey

OBJECTIVE: To evaluate the pregnancy outcome of women with nausea and vomiting of pregnancy (NVP) who were treated with either ondansetron or chlorpromazine.

STUDY DESIGN: This retrospective study included 185 women who were hospitalized in the first trimester for treatment of NVP and treated with either ondansetron or chlorpromazine between January 2006 and March 2011 at Simav Government Hospital. We evaluated the pregnancy outcome including birth weight, pregnancy induced hypertension, preterm birth and major congenital malformations.

RESULTS: In the ondansetron group 4 (4%) low birth weight newborn, 9 (9%) preterm birth and 1 (1%) congenital anomaly, while in chlorpromazine group 1 (1.2%) low birth weight newborn, 9 (10.6%) preterm birth and 4 (4.7%) congenital anomalies were observed.

CONCLUSION: The malformation risk for both drugs found to be similar to baseline. Although the sample size was small, both drugs found to be safe to use in first trimester for NVP.

Keywords: Nausea and vomiting of pregnancy (NVP), Ondansetron, Chlorpromazine, First trimester pregnancy

Gynecol Obstet Reprod Med 2014;20:81-84

Introduction

Nausea and vomiting of pregnancy (NVP) affects up to 85% of pregnancies. In addition to physical effects, NVP interferes with social and psychological life. In literature the most severe form of NVP namely hyperemesis gravidarum (HG) reported to be a reason for elective termination of pregnancy in an otherwise a healthy gravidity.[1,2]

There is not much information about use of anti-emetics in first trimester pregnancy due to the fair of increased congenital malformation risks. Phenothiazines, such as chlorpromazine are commonly used antiemetics and antipsychotics. Continuous use of phenothiazines in the third trimester of pregnancy was reported to associate with withdrawal and extrapyramidal effects in neonate.[3] Ondansetron is a selective serotonin receptor antagonist approved for treatment of chemotherapy associated nausea and vomiting. Both drugs although not indicated are used for NVP.

The aim of this study was to evaluate and compare the pregnancy outcome of women with HG treated with either ondansetron or chlorpromazine in first trimester of pregnancy.

Material and Method

This retrospective study took place at Simav Government Hospital between January 2006 and March 2011. The computerized database of hyperemesis gravidarum (HG) patients analyzed. Pregnant women who were refractory to oral meclizine dihydrochloride-pyridoxine hydrochloride (Postadoksin®, Bilim Pharma, Istanbul, Turkey) BID tablets, unable to tolerate oral nutrition and required hospitalization for treatment of HG were included in the study if treated with either ondansetron (Zontron®, Ulagay Pharma, Istanbul, Turkey) or chlorpromazine (Largactil®, Eczacıbası Pharma, Istanbul, Turkey).

The study group consisted of N=185 singleton pregnancies less than 13 weeks of gestation according to last menstrual period with a positive fetal cardiac activity. Multiple gestations, molar pregnancies and missed abortions were excluded from the study. After complete blood count, urinary, serologic and

[1] *Simav Government Hospital, Kütahya*

[2] *Etlik Zübeyde Hanım Gynecology Education and Research Hospital, Ankara*

[3] *Dr Faruk Sükan Women Health and Child Hospital Konya*

[4] *Başkent University, Ankara Başkent Hospital Family Medicine Department, Ankara*

Address of Correspondence: *Şafak Özdemirci*
Etlik Zubeyde Hanim Maternity Hospital Division of Maternal Fetal and Medicine Ankara, Turkey
safakozdemirci@gmail.com

Submitted for Publication: *08. 04. 2014*
Accepted for Publication: *05. 06. 2014*

biochemical tests, pregnant women with infection (gastroenteritis, urinary tract infection, hepatitis) or systemic disease (hypertension, diabetes mellitus, hyperthyroidism, Addison's disease) were also excluded from the study.

All patients were intravenously hydrated and given pyridoxine once a day. The patients in ondansetron group treated with 8 mg ondansetron once a day intravenously. The patients in chlorpromazine group treated with 12.5 mg chlorpromazine twice a day intravenously. Pregnancy outcome including stillbirth, low birth weight, congenital anomaly, pregnancy complications (preterm birth, pregnancy induced hypertension) were evaluated.

Data analysis was performed by using SPSS for Windows, version 21.0 (SPSS Inc., Chicago, IL, United States). Data were shown as mean ± standard deviation or median (min-max), where applicable. Nominal data were expressed as number of cases and percentages. Nominal data were analyzed by Pearson's chi-square or Fisher's exact test, where applicable. A p value less than 0.05 was considered statistically significant.

Results

Demographic characteristics of 185 pregnant women enrolled in this study are summarized in table 1. Ondansetron group included 100 pregnant women, while chlorpromazine group contained 85 pregnant women. The mean maternal age was 26.02±4.56 years in ondansetron group and 25.96±4.55 years in chlorpromazine group (p=0.935). The mean birth weight of newborn was 3076.2±485.5 grams in ondansetron group and 2962.9±460.0 grams in chlorpromazine group (p= 0.107). The mean gestational week of fetuses at drug administration time were 7.7±0.94 weeks and 7.8±0.93 weeks in ondansetron and chlorpromazine groups; respectively (p= 0.888).

According to mean birth weight at the delivery time and administration of antiemetic drugs at the gestational weeks of neonates were no statistically significant difference for both groups (p=0.107 and p=0.888).

The rate of fetal anomaly was 4% in chlorpromazine group and 1% in ondansetron group (p= 0.108). Rates of stillbirth, low birth weight, preterm delivery and pregnancy induced hypertensive disorders were not significant between two groups (p=0.459, p=0.377, p=0.716, and p=0.501) (Table 2).

Discussion

The fear of congenital malformation risk in pregnancy often avoid health providers from using effective pharmacological treatment, that results a decrease in quality of life. Hyperemesis gravidarum is an example to this condition due to its nature of early pregnancy occurrence at the time of organogenesis. This study is designed to share our experience about safety of anti-emetics that are prescribed in first trimester of pregnancy. According to the findings of the present study, both ondansetron and chlorpromazine has been safe to be used in first trimester pregnancy with a 1-3% of congenital malformation risk which equals to baseline risk of a birth defect by chance alone.[4]

Ondansetron is a selective 5HT3 (serotonin) receptor antagonist authorized for prevention of nausea and vomiting induced by operation and chemo- or radiation therapy. Use of ondansetron for NVP is off-label. Teratogenic effect was not observed in animal studies. Placental transfer of ondansetron

Table 1: Demographic characteristics of the groups

	Ondansetron n = 100	Chlorpromazine n= 85	P Value
Maternal age (year)	26.02±4.56	25.96±4.55	NS
Gestational age at the administration of the drugs (weeks)	7.7±0.94	7.8±0.93	NS
Birth weight (grams)	3076.2±485.5	2962.9±460.0	NS

NS: Not significant

Table 2: Perinatal outcomes of the groups

	Ondansetron n=100	Chlorpromazine n=85	P Value
Stillbirth (n; %)	0 (0%)	1 (1.2%)	NS
Low birth weight (n; %)	4 (4%)	1(1.2%)	NS
Preterm delivery (n; %)	9 (9%)	9 (10.6%)	NS
Hypertension disorders (n; %)	2 (2%)	0 (0%)	NS
Fetal anomaly (n; %)	1 (1%)	4 (4.7%)	NS

NS: Not significant

during early human pregnancy was shown by Siu et al.[5] In a prospective randomized trial concerning safety of ondansetron for NVP Einarson et al. concluded that the drug was not associated with increased malformation risk.[6] And in a large cohort of 600.000 pregnancies in Denmark, Pasternak et al. reported use of ondansetron during pregnancy was not associated with a significantly increased risk of adverse fetal outcomes.[7] Consistent with the literature, we did not find any increase in congenital anomaly incidence in pregnant women using ondansetron for HG in early pregnancy.

Chlorpromazine is a phenothiazine group antipsychotic agent that is also licensed for control of nausea and vomiting. It is a centrally acting agent that blocks dopaminergic receptors in brain, depress reticular activating system; thus prevent emesis. In a prospective survey including 12 University hospitals in Paris, first trimester use of phenothiazines found to be associated with increased malformations.[8] However, potentially confounding factors like use of alcohol was not mentioned. Regarding use of chlorpromazine for NVP of pregnancy, other studies have not shown any significant increase in malformation risk.[3,9] Although the number was insignificant, we detected more fetuses with congenital anomaly in chlorpromazine group compared to ondansetron group (4.7% vs 1%). If we could perform this study with a larger population, the difference might be significant.

We did not find any increase in fetal loss in our study. In a study, Veenedal MV et al. reported hyperemesis gravidarum was not associated with perinatal fetal demise.[10] And Pasternak et al. reported frequency of intrauterine fetal death was not increased with use of ondansetron for hyperemesis gravidarum.[7] Our results were consistent with the literature.

In our study we found a low birth weight incidence of 4.78%. Jancevska et al. in their study reported incidence of low birth weight in a normal population is 5%.[11] Also Pasternak B et al. reported no increase in low birth weight incidence in pregnant women using ondansetron for HG.[7]

We found a preterm birth ratio of 9% in ondansetron group and 10.6% in chlorpromazine group. Ananth et al. found a preterm birth ratio of 12.3% in USA and 7.7 % in Canada.[12]

In their study Getahun et al. reported incidence of preeclampsia as 1.8% in white women.[13] When we consider our results rate of preeclampsia was significantly much lower. In another study by Bolin et al. rate of preeclampsia within population of hyperemesis gravidarum patients was slightly increased.[14] They observed a significant increase in placental dysfunction especially in women with a second trimester emesis. In our study emesis was observed only in first trimester at an average of 8 weeks of gestation which might explain our lower rate of preeclampsia.

And our cohort was not powerful enough which forms the major limitation of our study. As far as we know, there are no prospective studies evaluating the effects of these drugs on these adverse pregnancy outcomes.

Hyperemesis gravidarum is a challenging problem for both health providers and patients. Although these drugs are prescribed off-label for HG, we did not detect any increase in adverse pregnancy outcome including fetal congenital malformation risk. However, more prospective randomized controlled trials with larger cohorts are required to conclude as use of these drugs is safe in first trimester pregnancy.

İlk Trimesterde Hiperemesiz Gravidarumda Ondansetron ve Klorpromazin Kullanımının Güvenilirliği

AMAÇ: Gebeliğinde bulantı ve kusması olan ondansetron ve klorpromazin ile tedavi edilen gebelik sonuçlarının değerlendirilmesi.

GEREÇ VE YÖNTEM: Çalışma, Haziran 2006-Mart 2011 tarihleri arasında Kütahya Simav Devlet Hastanesi'nde retrospektif olarak yapıldı. Bulantı ve kusması ondansetron ve klorpromazin ile tadavi edilen 185 gebenin doğum ağırlıkları, gebeliğin indüklediği hipertansiyon, preterm doğum ve majör konjenital anomali sonuçlarını değerlendirdik.

BULGULAR: Ondansetron grubunda; düşük doğum ağırlığı 4 (%4), preterm doğum 9 (%9) ve konjenital anomali 1 (%1), klorpromazin grubunda ise düşük doğum ağırlığı 1 (%1,2), preterm doğum 9 (%10,6) ve konjenital anomaliler 4 (%4,7) olarak bulduk.

SONUÇ: Malformasyon riski için her iki ilaç kullanımında da benzer düzeyde olduğunu bulduk. Çalışma grubumuzun küçük olmasına ragmen her iki ilacın ilk trimesterdeki bulantı ve kusması olan gebelerde kullanımının güvenli olduğu bulundu.

Anahtar Kelimeler: Gebelikte bulantı ve kusma, Ondansetron, Klorpromazin, İlk trimester gebeliği

References

1. Mazzotta P, Stewart DE, Koren G, Magee LA. Factors associated with elective termination of pregnancy among Canadian and American women with nausea and vomiting of pregnancy. J Psychosom Obstet Gynecol 2001;22:7-12.
2. Mazzotta P, Stewart D, Atanakovic G, Koren G, Magee LA. Psyhosocial morbidity among women with nausea and vomiting of pregnancy: prevelance and association with anti-emetic therapy. J Psychosom Obstet Gynecol 2000;21:129-36.
3. Bottomley C, Bourne T. Management strategies for hyper-

emesis. Best Pract Res Clin Obstet Gynecol 2009;23(4): 549-64.

4. Nguyen P, Einarson A. Managing nausea and vomiting of pregnancy with pharmacological treatments. Women's Health 2006;2(5):753-60.
5. Siu SS, Chan MT, Lau TK. Placental transfer of ondansetron during early human pregnancy. Clin Pharmacokinet 2006;45(4):419-23.
6. 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.
7. Pasternak B, Svanström H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. N Eng J Med 2013;368(9):814-23.
8. Rumeau-Rouquette C, Goujard J, Huel G. Possible teratogenic effect of phenothiazines in human beings. Teratology 1977;15(1):57-64.
9. Shrim R, Boskovic C, Maltepe C, Navios Y, Garcia-Bournissen F, Koren G. Pregnancy outcome following use of large doses of vitamin B6 in the first trimester. J Obstet Gynecol 2006;26(8):749-51.
10. Veenendoal MV, Abeelen AF. Consequenes of hyperemesis gravidarum for off spring: A systematic review and metaanalysis. BJOG 2011;118(11):1302-13.
11. Jancevska A,Tasic V, Damcevski N, Danilovski D, Janavaska V, Gucev Z. Prilozi 2012;33(2):47-58.
12. Ananth CV, Joseph KS, Oyelese Y, et al: A comparison of feotal and infant mortality in the United States and Canada. Int Epidemiol 2009;38(2):480.
13. Getahun D, Ananth CV, Oyeese Y et al. Primary preeclampsia in secondary pregnancy. Obstet Gynecol 2007;110:1319.
14. Bolin M, Akerud H, Cnattinqius S, Stephansson O, Wikstrom A. Hyperemesis gravidarum and risks of placental dysfunction disorders: a population - based cohort study. BJOG 2013 Jan 30 doi.10.1111/1471-0528.12132