

The comparison of early gestational complications and perinatal outcomes of the pregnant women who used metoclopramide and dimenhydrinate

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Abstract

Objective: Metoclopramide and dimenhydrinate are used commonly in the treatment of nausea-emesis and hyperemesis gravidarum during the first trimester.

Methods: This retrospective study included 233 pregnant women who were diagnosed as hyperemesis gravidarum during first trimester between July 4, 2005 and May 27, 2009 at the Clinic of Obstetrics and Gynecology, Simav State Hospital (Simav, Kütahya, Turkey). The pregnant women were separated into groups according to their metoclopramide or dimenhydrinate use. The pregnant women included in the study were chosen from the pregnant women who were healthy and had singleton pregnancy.

Results: While 113 pregnant women were treated by metoclopramide and 120 pregnant women by dimenhydrinate. Spontaneous abortion was found as 6.2% in the pregnant women who used metoclopramide and as 4.2% who used dimenhydrinate, and stillbirth rate was 1.8 and 0.8%, respectively. Low birth weight rates were 8.0% in metoclopramide group and 5.8% in dimenhydrinate group, and preterm labor rates were 5.3% and 5.0%, respectively.

Conclusion: We have found that there was no difference between the pregnant women who used metoclopramide and dimenhydrinate in terms of early period complications and perinatal outcomes.

Keywords: Nausea, emesis, pregnancy, first trimester.

Özet: Metoklopramid ve dimenhidrinat kullanan gebelerin erken gebelik komplikasyonları ve perinatal sonuçlarının karşılaştırılması

Amaç: İlk trimesterde, bulantı-kusma ve hiperemesis gravidarumun tedavisinde metoklopramid ve dimenhidrinat yaygın olarak kullanılmaktadır. Metoklopramid ve dimenhidrinat kullanan gebelerin erken gebelik komplikasyonları ve perinatal sonuçlarının karşılaştırılması planlandı.

Yöntem: Bu retrospektif çalışma 4 Temmuz 2005 – 27 Mayıs 2009 tarihleri arasında Simav Devlet Hastanesi (Simav/Kütahya) Kadın Hastalıkları ve Doğum Kliniğinde ilk trimesterde hiperemesis gravidarum tanısı alan 233 gebeden oluştu. Gebeler tedavide metoklopramid veya dimenhidrinat kullanımına göre gruplara ayrıldı. Çalışmaya alınan gebeler, sağlıklı anne ve tekil gebeliği olan gebelerden seçildi.

Bulgular: Yüz on üç gebe metoklopramid, 120 gebe dimenhidrinat ile tedavi edildi. Grupların demografik verileri arasında istatistiksel olarak fark yoktu. Spontan düşük oranı, metoklopramid kullanan gebelerde %6.2, dimenhidrinat ile tedavi edilen gebelerde %4.2, ölü doğum oranları %1.8 ve %0.8 olarak bulundu. Düşük doğum ağırlığı oranları, metoklopramid kullanan grupta %8.0, dimenhidrinat kullanan gebe grubunda %5.8, preterm doğum oranları ise %5.3 ve %5.0 olarak hesaplandı.

Sonuç: Metoklopramid ve dimenhidrinat kullanan gebelerin erken dönem komplikasyonları ve perinatal sonuçları arasında fark olmadığı bulundu.

Anahtar sözcükler: Bulantı, kusma, gebelik, ilk trimester.

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Introduction

Nausea and emesis are common complaints seen during pregnancy. They are seen in approximately 80% of pregnant women.^[1] Hyperemesis gravidum (HG) is defined as severe nausea and emesis during pregnancy. Since it is a severe and resistive condition resulting in ketosis, dehydration and loss of weight, it is differed from nausea and emesis during regular pregnancy.^[2,3] The frequency of hyperemesis gravidum is between 0.3% and 10% in pregnancies.^[4,5]

If not treated, serious complications may arise in mother due to severe emesis such as dehydration, disorder in electrolyte-fluid balance, significant loss of weight, Wernicke's encephalopathy, renal failure, hepatic function disorder and secondary depressions.^[3,6]

Doxylamine, pyridoxine, antihistamines, H1 receptor blockers and phenothiazines are all reliable and effective drugs for slight, mild and severe nausea and emesis during pregnancy.^[4,7]

In Australia, methoclopramide is the first choice for hyperemesis gravidarum treatment, and methoclopramide is prescribed to 86% of pregnant women.^[8] Intravenous rehydration and thiamine may be needed together with antiemetic drugs (doxylamine, methoclopramide and chlorpromazine) in the treatment of hyperemesis gravidarum.^[4,9]

In our study, we studied whether there is difference between early period complications and perinatal outcomes of pregnant women who were treated with methoclopramide and dimenhydrinate during first trimester.

Methods

As the study group, the medical files of 233 pregnant women were analyzed retrospectively who admitted to the Clinic of Obstetrics and Gynecology, Simav State Hospital between July 4, 2005 and May 27, 2009, had nausea and emesis, could not nourished orally, found to be positive for ketone in the urine analysis, and treated by methoclopramide and dimenhydrinate. The study groups consisted of the pregnant women who used methoclopramide and dimenhydrinate.

The women who had nausea and emesis during 6-12 weeks of gestation, needed medical treatment and had singleton intrauterine pregnancy were included in the study. Since fetal and maternal results would be affected, those who had kin marriage, habitual abortion, cervical insufficiency, pregnant women who miscarried voluntar-

ily, molar pregnancies, those who had labor history with fetal anomaly in their previous pregnancy, those established with the diagnosis of preeclampsia, spontaneous preterm labor risk, hyperthyroidism, gastroenteritis, hepatitis and urinary tract infection, those who had psychiatric therapy, had an underlying medical disease and those not married were excluded from the study. The pregnant women who were included in the study were not smoking, drinking alcohol or using narcotic drugs. All pregnant women staying in the hospital were applied routinely hemogram, biochemical tests, urine analysis, Hepatitis B virus surface antigen, free T4, TSH and ultrasound examination. In the ultrasound examination, singleton pregnancy with positive fetal cardiac activity between 6 and 12 weeks of gestation according to CRL was observed. Also, general obstetric ultrasonography was carried out for major anomaly screening between 20 and 22 weeks of gestation.

Abortion^[10] was defined as stillbirth for fetuses under 20 weeks or below 500 g, and intrauterine fetal death^[11] was defined as deliveries after 200 weeks or above 500 g with no fetal cardiac activity at intrauterine period. Low birth weight^[12] was described as the births below 2500 g and those born before 37 weeks of gestation were defined as premature labor.^[13] Pregnancy-induced hypertension^[14] was described as the condition for pregnant women who have arterial blood pressure at and above 140/90 mmHg at 20 weeks of gestation.

Treatment Protocol

The pregnant women hospitalized in the clinic for pregnancy nausea-emesis and HG were had rehydration treatment by 0.9% NaCl and 10% dextrose solution.^[3,5,6,9] Vitamin complex (Bemiks C) was applied by intravenous administration once a day. Dimenhydrinate and metoclopramide were used in the treatment since they are widely used in the treatment of nausea and emesis during pregnancy,^[1,3] reliable,^[2,4] effective,^[7] cost-efficient and easily accessible. Dimenhydrinate^[15,16] 50 mg was administered intravenously twice a day and metoclopramide^[2,17,18] 5 mg ampoule intravenously four times daily.

The pregnant women were discharged by being prescribed oral tablets of the drugs administered parenterally to take them at home as 7-10 days treatment.^[2]

Statistical Analysis

In the statistical analysis, definitive test, Student-t test, chi-squared test and Fisher's exact test were used for the

comparison of two groups. A p value <0.05 was considered significant statistically.

Results

The medical files of 233 pregnant women, who were treated by metoclopramide and dimenhydrinate for pregnancy nausea-emesis or HG in the first trimester, were analyzed retrospectively. It was found that 113 pregnant women used metoclopramide and 120 pregnant women used dimenhydrinate. There was statistically no significant difference between two groups in terms of mean ages of the pregnant women and birth weights of their babies (**Table 1**). The rate of spontaneous abortion was 6.2% (n=7) in the group treated by metoclopramide, and 4.2% (n=5) in the group treated by dimenhydrinate (p=0.484). In both groups, spontaneous abortion occurred after 8 weeks of gestation. We found the rate of intrauterine fetal death (IUFD) as 1.8% (n=2) in the pregnant women using metoclopramide and as 0.8% (n=1) in the pregnant women using dimenhydrinate (p=0.62). Low birth weight was found as 8% (n=9) in the pregnant women using metoclopramide and as 5.8% (n=7) in the pregnant women using dimenhydrinate (p=0.52). The preterm labor rate was 5.3% (n=6) in those treated by metoclopramide and 5.0% (n=6) in those treated by dimenhydrinate (p=0.58). Fetal anomaly rate was 2.7% (n=3) in metoclopramide group and 2.5% (n=3) in dimenhydrinate group, and there was statistically no significant difference between the groups (p=0.91). For both groups, there was no statistical difference between early period gestational complications and perinatal gestational outcomes (**Table 2**).

Discussion

We have compared early period complications and perinatal outcomes of two groups consisted of the pregnant women having nausea and emesis or diagnosed as HG and treated either by metoclopramide or dimenhydrinate. We have found that there was statistically no difference between the rates of abortion, intrauterine death, premature labor, low birth weight, fetal anomaly and pregnancy-induced hypertensive diseases.

In all pregnant women, abortion rate after 8 weeks of gestation varies between 3.2% and 6%.^[10,19,20] We have found that there was no statistical difference between the abortion rates (6.2% and 4.2%) of those treated by metoclopramide and dimenhydrinate. At the same time, observing same abortion rate in the general

Table 1. Distribution of maternal age and birth weights.

	Metoclopramide n=113	Dimenhydrinate n=120	p value
Maternal age (year)	26.00±5.36	26.25±4.57	0.16*
	n=106	n=115	
Birth weight (g)	3105.44±470.11	3137.13±581.61	0.332*

*Student t-test

Table 2. Early period gestational complications and perinatal outcomes of control and study groups.

	Metoclopramide n (%)	Dimenhydrinate n (%)	p value
Abortion	7 (6.2)	5 (4.2)	0.484*
Anomaly	3 (2.7)	3 (2.5)	0.91*
IUFD	2 (1.8)	1 (0.8)	0.62†
LBW	9 (8.0)	7 (5.8)	0.52†
Preterm labor	6(5.3)	6 (5.0)	0.58†
Pregnancy-induced hypertensive disease	2 (1.8)	2 (1.7)	1†

IUFD: Intrauterine fetal death, **LBW:** Low birth weight. *Fisher's exact test, †Chi-squared test

pregnancy population has made us to consider that both drugs have no effect on abortion.

In the literature, there are publications reporting that there is no relationship between HG and IUFD.^[21-23] In two studies carried out, it was reported that there was no increase in IUFD risk in the pregnant women treated by metoclopramide.^[18,22] In the study published by Matok et al. in 2009, metoclopramide was used during the first trimester in 3458 pregnant women and perinatal death rate was found as 1.5% in those treated by metoclopramide and as 2.2% in the control group. It was reported that metoclopramide did not cause any increase in perinatal death rate.^[18] In our study, we found the IUFD rate as 1.8% in metoclopramide group and as 0.8% in dimenhydrinate group. The findings of our study are similar to other studies and we determined that both drugs did not cause any change in IUFD rate.

We have found the rate of low birth weight as 8.0% and 5.8% in metoclopramide and dimenhydrinate groups, and there was statistically no significant difference between the groups. There are publications in the literature providing different findings between low birth weight and pregnant women having antiemetic treatment.^[24,25] In some studies, it has been reported that antiemetic drugs may cause low birth weight.^[2,21,26] In

another study, it was concluded that there was no increase in the risk of low birth weight by antiemetic drugs.^[27] In two studies, the relationship between pregnant women treated by metoclopramide and control group not used any drug was analyzed in terms of low birth weight, and it was concluded that there was no increase in the risk of low birth weight by metoclopramide.^[17,18] However, in the studies of Mullin et al., Dodds et al. and Bailit et al., it was reported that HG caused low birth weight.^[6,23,28] In the study of Mullin et al., it was stated that nausea and emesis of pregnant women continued even after 27 weeks of gestation.^[6] Dodds et al. included pregnant women whose nausea and emesis continued up to 24 weeks of gestation into their study group.^[23] In their study, they reported that low birth weight increased in pregnant women with HG who gained weight less than 7 kg totally during pregnancy.^[23] In our study group, the nausea and emesis of pregnant women did not continue after 14 weeks of gestation. The emesis duration and weight gaining are different in the literature^[6,27] than our study. In other studies of the literature, it was reported that HG did not cause low birth weight.^[25,28,29] In our study, we have found that there was no difference among the groups in terms of the rates of newborns with low birth weight.

The preterm labor rate was 5.3% in the group treated by metoclopramide and 5.0% in the group treated by dimenhydrinate. There was statistically no significant difference between the groups.

In the literature, there are various data on preterm labor and the role of HG.^[27] Czeizel and Puho^[25] and Klebanoff et al.^[29] showed in their studies that preterm labor risk decreased. Hallak et al.^[22] and Depue et al.^[30] reported in their studies that HG had no impact on premature labor. Dodds et al. reported in their studies on HG published in 2006 that the preterm labor risk increased in pregnant women who gained weight less than 7 kg during pregnancy, but preterm risk did not increase in pregnant women who gained weight more than 7 kg.^[23] While premature birth rate in pregnant women using metoclopramide for HG treatment during first trimester was 5.8%, it was found as 6.0% in the control group who used no drug.^[15] Matok et al. found premature labor rate as 6.3% in metoclopramide group and as 5.9% in the control group.^[18] It was reported that metoclopramide has no impact on premature labor.^[15,17,18] In other publications, it was stated that premature labor risk was not increased.^[29,30] In our study group, there were no pregnant women who have smoking, alcohol and drug

addiction. Also, it was seen that gestational follow-ups were made regularly. Although there is no difference between the groups in terms of preterm labor rate, we found similar rates compared to other publications in the literature.^[15,17,18,29,30]

Antihistaminic drugs block the receptor in the nausea center of vestibular system. After histamine 1 receptor is blocked, the stimulation of nausea center decreases.^[31] Dimenhydrinate is widely used in pregnant women in North America.^[31] By many epidemiological studies, it was found that dimenhydrinate has no teratogenic impact on human fetuses.^[24] In animal trials carried out by antihistaminic drugs, it was found that they are teratogenic; however, it was used in the treatment of more than 200.000 pregnant women as of 1950 and reported to be non-teratogenic on human fetuses. In the same study, anomaly was observed in 1-3% of the babies of pregnant women who used antihistaminic drugs.^[31] Czeizel and Vargha reported in their case-control study that there was no increase in congenital anomalies of fetuses of the pregnant women who were treated by dimenhydrinate during their pregnancies.^[16] In a large scaled research study carried out between 2000 and 2004, it was shown that using antihistaminic drug in the treatment of nausea and emesis during pregnancy is safe.^[32] Metoclopramide is in group A among the safety categories for pregnancy.^[2] Sorensen et al. treated 309 pregnant women with hyperemesis by metoclopramide during first trimester. They found fetal anomaly in 5.8% of treated pregnant women and in 5.2% of control group, and reported that metoclopramide did not cause any fetal anomaly.^[17] In the research study performed by Matok et al., it was found that there was no difference between the pregnant women who used metoclopramide and the control group in terms of fetal anomaly.^[18]

In our study, we did not find any difference between pregnancy groups treated by metoclopramide and dimenhydrinate in terms of the rates of pregnancy-induced hypertensive diseases. The study of Kuru et al. showed no relationship between HG and pregnancy-induced hypertensive diseases.^[27] In another study, it was reported that hyperemesis gravidarum seen during the first trimester slightly increased preeclampsia risk; however, HG seen during the second trimester had a strong relationship with placental dysfunction diseases.^[33]

Conclusion

It is known that severe complications occur if severe HG is not treated. Antiemetic drugs are widely used in order

to prevent complications that may appear in mother. There is no difference between using metoclopramide and dimenhydrinate during first trimester in terms of gestational outcomes.

Conflicts of Interest: No conflicts declared.

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