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Pregnancy outcome after first trimester exposure to domperidone—An observational cohort study

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Abstract

Aim: To assess the teratogenic risk of domperidone by comparing the incidence of major malformation with domperidone to a control.

Methods: Pregnancy outcome data were obtained for women at two Japanese facilities that provide counseling on drug use during pregnancy between April 1988 and December 2017. The incidence of major malformation was calculated among infants born to women taking domperidone (n = 519), nonteratogenic drugs (control, n = 1673), or metoclopramide (reference, n = 241) during the first trimester of pregnancy. Using the control group as reference, the crude odds ratio (OR) of the incidence of major malformation in the domperidone and metoclopramide groups was calculated using univariable logistic regression analysis. Adjusted OR was also calculated using multivariable logistic regression analysis adjusted for various other factors.

Results: The incidence of major malformation was 2.9% (14/485, 95% confidence interval [CI]: 1.6–4.8) in the domperidone group, 1.7% (27/1554, 95%CI: 1.1–2.5) in the control group, and 3.6% (8/224, 95%CI: 1.6–6.9) in the metoclopramide group. The adjusted multivariable logistic regression analysis showed no significant difference in incidence between the control and domperidone groups (adjusted OR: 1.86 [95%CI: 0.73–4.70], p = 0.191) or between the control and metoclopramide groups (adjusted OR: 2.20 [95%CI: 0.69–6.98], p = 0.183).

Conclusions: This observational cohort study showed that domperidone exposure during the first trimester was not associated with increased risk of major malformation in infants. These results may help alleviate the anxiety of patients who took domperidone during pregnancy.

Key words: domperidone, first trimester, observational cohort study, pregnancy outcomes, teratogenicity.

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Introduction

Domperidone is an antidopaminergic benzimidazolone compound first synthesized by Janssen Pharmaceutica (Belgium) in 1974. Originally approved in Belgium in 1978, it has since been approved in over 100 countries, including in Japan in 1982. In Japan, domperidone has been widely used for the treatment of gastrointestinal symptoms such as nausea, vomiting, and anorexia.

In a study of domperidone administration during organogenesis in rats, skeletal and visceral malformations were observed in fetuses following an oral dose of 200 mg/kg or an intraperitoneal dose of ≥15 mg/kg. These observed malformations in rats occurred at approximately 300 times the daily oral dose for humans based on body weight. Due to these results, the package insert for domperidone in Japan states that it is contraindicated for use in pregnant women or women suspected of being pregnant.

In some cases, however, domperidone is prescribed for gastrointestinal symptoms such as nausea and vomiting to women who do not yet know they are pregnant due to the pregnancy being unplanned. In such cases, patients often become anxious when they find out they are pregnant and learn that domperidone is contraindicated.

Domperidone and metoclopramide are commonly used as antiemetic drugs in general clinical practice in Japan. Large-scale epidemiological studies have shown that metoclopramide does not increase the risk of malformation[1,2]. On the other hand, teratogenic risk with domperidone has been reported in only a few small-scale, cohort studies. A report by JS Choi et al. investigated 120 pregnancies treated with domperidone in the first trimester and concluded that domperidone is unlikely to be a major human teratogen[3]. Also, in an abstract, J Cottin et al. compared 124 pregnancies exposed to domperidone during organogenesis with those exposed to other antiemetics or nonteratogenic drugs[4]. There was no significant difference between the three groups in the incidence of major congenital malformations, but the authors commented that the small sample size was a limitation. A report on drug use during pregnancy in the French population stated that about 13% of all pregnant women were using domperidone[5]. Although the teratogenic risk of domperidone was not analyzed in that survey, it suggests that the drug is widely used by pregnant women in some countries.

In the present study, we evaluated the teratogenic risk of domperidone exposure during the first trimester. This is based on highly precise data about drug use by pregnant women, derived from interviews conducted by healthcare professionals at medical facilities that provide counseling on drug use during pregnancy.

Methods

Subjects

This study included women who consulted the Counseling Clinic for "Pregnancy and Medicine" of Toranomon Hospital or the Japan Drug Information Institute in Pregnancy of National Center for Child Health and Development regarding the safety of drugs during pregnancy. Pregnancy outcome data were extracted from the clinical databases of these facilities.

The inclusion criteria were pregnant women who consented to the study and with known pregnancy outcomes who took domperidone (domperidone group), or control drugs (control group) in the first trimester. Among these, women who used domperidone in combination with metoclopramide were excluded from the study. First trimester exposure was defined as drug use between the 28th and 97th days (4th week to 13th week of pregnancy) after the last menstrual period. Experts discussed and selected control drugs considered to be nonteratogenic, referring the report by F. Habermann et al.[6] Control drugs included acetaminophen, antihistamines that were reported in previous studies to have no increased risk of teratogenicity, anti-infectives like penicillins and cephalosporins, histamine H2-receptor (H_2) blockers, digestive enzyme preparations, and topical drugs (e.g., eye drops, ointment, or cream). Metoclopramide is a similar drug and is expected to be used for the same diseases. In addition, it has been commonly used as an antiemetic drug in pregnant women. Therefore, although statistical comparison with the domperidone group was not performed, patients who took metoclopramide were defined as the reference group.

Data collection

For Toranomon Hospital, women who consulted the Counseling Clinic for "Pregnancy and Medicine" during pregnancy between April 1988 and December 2016 were included in the study. People who wished to make a counseling appointment were first required by the clinic to complete a pre-appointment

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questionnaire regarding information such as the names and dosages of drugs taken during pregnancy and expected delivery date, and to return it by mail. At the time of counseling, subjects were interviewed to confirm their expected delivery dates and to obtain other information, including previous medical history, pregnancy and reproductive history, alcohol use, smoking, and family history. We asked patients who provided informed consent for study participation to complete a study questionnaire regarding pregnancy outcomes and any abnormalities during delivery, as well as sex, length, and weight at birth, and any abnormalities of the neonate, and to submit it by mail. If patients provided unclear answers about pregnancy outcomes, an obstetrician contacted their attending physician to obtain clarification. Information on pregnancy outcomes was collected about 1 month after delivery, and the survey was considered complete when this information was obtained.

At the National Center for Child Health and Development, women in pregnancy who sought consultation the Japan Drug Information Institute in Pregnancy between October 2005 and December 2017 were included in the study. The Japan Drug Information Institute in Pregnancy was established under a program of the Ministry of Health Labour and Welfare in October 2005. People who wished to make a counseling appointment were required to complete a pre-appointment questionnaire and to return it by mail. The pre-appointment questions were on age, use of drugs during pregnancy, history of present illness, previous medical history, experience of pregnancy, reproductive history, alcohol use, smoking, and intake of folic acid. Approximately a month after their expected delivery date, patients who provided informed consent for participation in the study were sent a postcard-type questionnaire on pregnancy outcomes and the 1-month checkup results of their infants. In cases where pregnancy outcomes were unclear, research assistants, doctors or pharmacists contacted the women's attending obstetricians to confirm their pregnancy outcome by telephone. The survey was concluded when information on pregnancy outcomes had been obtained.

Primary endpoint and statistical analysis

The primary endpoint of this study was the incidence of major malformation. To assess the teratogenic risk of domperidone, we compared the incidence of major malformation in the domperidone group with the control group. Major malformations were defined according to the European Surveillance of Congenital Anomalies (EUROCAT)[7]. In cases of congenital abnormalities not included in EUROCAT, a specialist in congenital abnormalities provided diagnoses. Two of the authors concluded that congenital abnormalities could be defined either as surficial malformations or as those requiring surgical treatment. Finally, two independent specialists confirmed the diagnoses.

The incidence of major malformation was analyzed in liveborn, single-birth infants, and was calculated by dividing the number of liveborn singletons with congenital malformation by the number of all liveborn singletons analyzed in each group. This incidence was compared between the domperidone and control groups. Using the control group as the reference of odds ratio (ORs), the crude ORs of the incidence of major malformations in the domperidone group were calculated using univariable logistic regression analysis. In addition, adjusted ORs were calculated using multivariable logistic regression analysis adjusted for alcohol intake, smoking, maternal age, use of concomitant drugs other than the control drugs during the first trimester of pregnancy, facility, and the year of counseling. Similarly, the crude and adjusted ORs of the incidence of major malformations in the metoclopramide group were calculated. In a subgroup analysis, adjusted ORs were calculated for each facility. The significance level of the test was 5%.

Ethics statement

This study was approved by the Ethics Committee of National Center for Child Health and Development and that of Toranomon Hospital. It was conducted according to the Declaration of Helsinki, and informed consent was obtained from all participants. Information collected from questionnaires was entered into the database and de-identified by an information administrator. Therefore, the investigators were unable to identify individuals based on the analysis data.

Results

Patient characteristics

At Toranomon Hospital, 12 074 women consulted the Counseling Clinic for "Pregnancy and Medicine" between April 1988 and December 2016. Of these, 1422 who met the inclusion criteria and did not meet the exclusion criteria were included in the analysis. At National Center for Child Health and Development,

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12 971 women consulted the Japan Drug Information Institute in Pregnancy between October 2005 and December 2017. Of these, 1011 who met the inclusion criteria and did not meet the exclusion criteria were included in the analysis. In total, the number of participants was 519 in the domperidone group, 1673 in the control group, and 241 in the metoclopramide group (Figure 1).

The median age of the subjects at the time of counseling was 30 years in all groups and the groups showed no difference in age distribution. There were no notable differences between groups in either alcohol use or smoking habits, as shown in Table 1.

Delivery outcomes and incidence of major malformations

Delivery outcomes were aggregated for all subjects. The percentage of liveborn infants was 94.0% (488 cases) in the domperidone group, 93.8% (1570 cases) in the control group, and 94.2% (227 cases) in the metoclopramide group. There were no notable differences in the incidences of stillbirth, miscarriage or abortion between the three groups (Table 2).

Major malformations in liveborn, single-birth infants occurred in 14 cases in the domperidone group, 27 in the control group, and 8 in the metoclopramide group (Table 3). There was no pattern of malformation types between the three groups.

Risk of major malformation

The incidence of major malformation in liveborn, single-birth infants (95% confidence interval [CI]) was 2.9% (14/485, 95%CI: 1.6–4.8) in the domperidone group, 1.7% (27/1554, 95%CI: 1.1–2.5) in the control group, and 3.6% (8/224, 95%CI: 1.6–6.9) in the metoclopramide group.

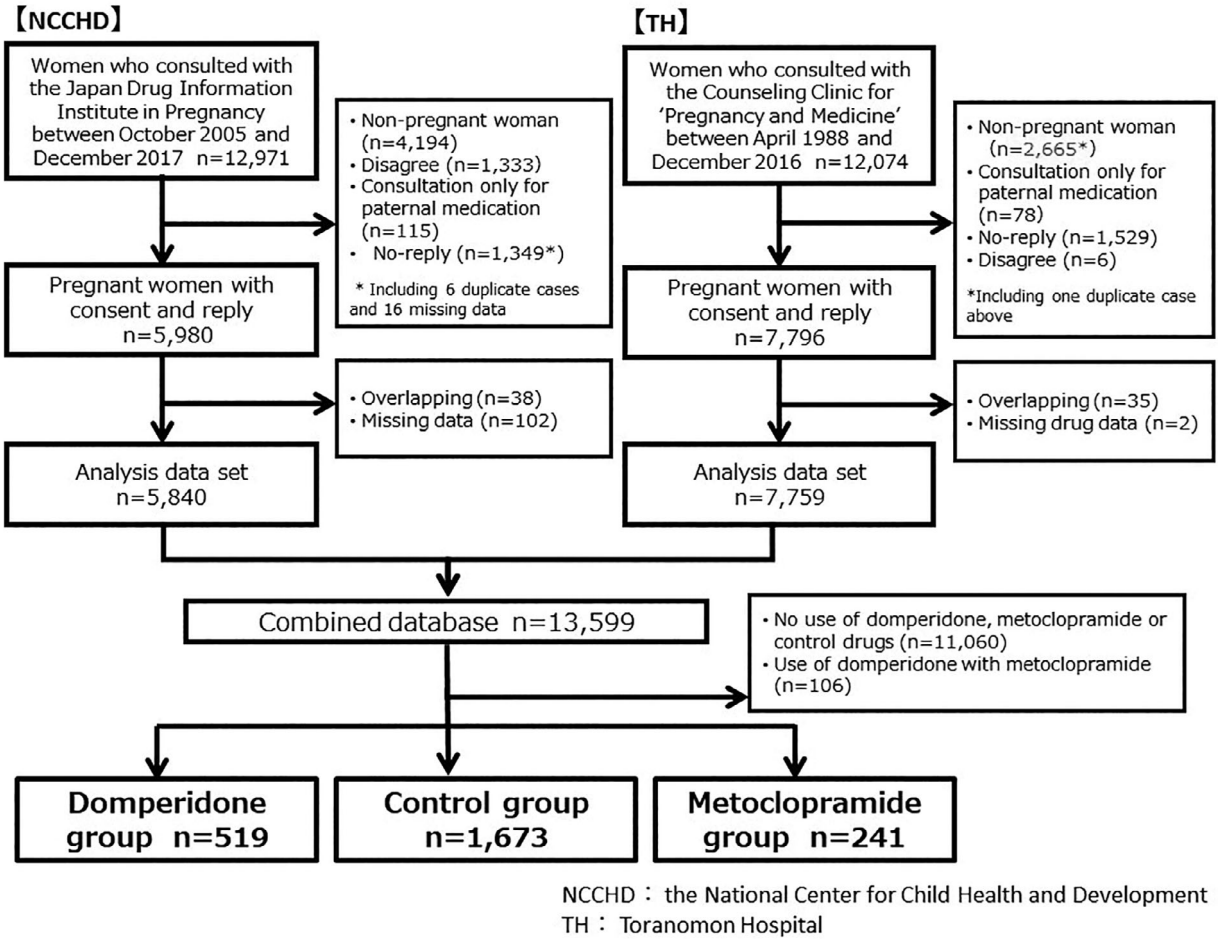

Figure 1 Flowchart

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Table 1 Patient characteristics

	Domperidone group	Control group	Metoclopramide group
n	519	1673	241
Age (year), *n* (%)			
50% [25%, 75%]	30 [26, 33]	30 [27, 34]	30 [27, 34]
≦24	79 (15.2)	160 (9.6)	30 (12.4)
25–29	170 (32.8)	548 (32.8)	81 (33.6)
30–34	167 (32.2)	628 (37.5)	83 (34.4)
35–39	84 (16.2)	288 (17.2)	40 (16.6)
40≦	18 (3.5)	46 (2.7)	6 (2.5)
NA	1 (0.2)	3 (0.2)	1 (0.4)
Alcohol, *n* (%)			
No use	292 (56.3)	861 (51.5)	125 (51.9)
Stop before pregnancy	7 (1.3)	45 (2.7)	13 (5.4)
Stop after pregnancy	84 (16.2)	305 (18.2)	48 (19.9)
Ongoing	3 (0.6)	16 (1.0)	5 (2.1)
Unknown stop time	75 (14.5)	250 (14.9)	28 (11.6)
NA	58 (11.2)	196 (11.7)	22 (9.1)
Smoking, *n* (%)			
No habit	390 (75.1)	1244 (74.4)	176 (73.0)
Stop before pregnancy	9 (1.7)	36 (2.2)	10 (4.1)
Stop after pregnancy	25 (4.8)	56 (3.3)	16 (6.6)
Ongoing	16 (3.1)	59 (3.5)	10 (4.1)
Unknown stop time	32 (6.2)	122 (7.3)	13 (5.4)
NA	47 (9.1)	156 (9.3)	16 (6.6)

Abbreviation: NA, not available.

Table 2 Pregnancy outcomes

	Domperidone group	Control group	Metoclopramide group
n	519	1673	241
Outcome, *n* (%)			
Live birth	488 (94.0)	1570 (93.8)	227 (94.2)
Stillbirth[a]	3 (0.6)	7 (0.4)	0 (0.0)
Miscarriage	18 (3.5)	80 (4.8)	8 (3.3)
Abortion	10 (1.9)	15 (0.9)	6 (2.5)
Other	0 (0.0)	1[b] (0.1)	0 (0.0)
Number of infant, *n* (%)			
1	506 (97.5)	1627 (97.3)	234 (97.1)
2≦	1 (0.2)	9 (0.5)	3 (1.2)
NA	12 (2.3)	37 (2.2)	4 (1.7)

Abbreviation: NA, not available.; [a]Fetal death after 22 weeks gestation was defined as stillbirth. and [b]Ectopic pregnancy.

Univariable logistic regression analysis showed no significant difference in the incidence of major malformation between the domperidone and control groups (OR: 1.68 [95% CI: 0.87–3.23], $p = 0.119$). Additionally, multivariable logistic regression analysis adjusted for alcohol intake, smoking, maternal age, use of concomitant drugs other than the control drugs during the first trimester of pregnancy, facility, and the year of counseling also showed no significant difference in the incidence of major malformation between the domperidone and control groups (adjusted OR: 1.86 [95% CI: 0.73–4.70], $p = 0.191$) (Table 3). Similar results were obtained when comparing the metoclopramide and control groups (OR: 2.09 [95% CI: 0.94–4.67], $p = 0.071$; adjusted OR: 2.20 [95% CI: 0.69–6.98], $p = 0.183$).

Subgroup analysis

For the cases at Toranomon Hospital, the adjusted OR (95%CI) of the incidence of major malformation was 2.54 (95%CI: 0.68–9.46, $p = 0.164$) in the domperidone group and 2.54 (95%CI: 0.47–13.82, $p = 0.282$) in the

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Table 3 Risk of major malformation

	Major malformation						
	No	Yes	95%CI	Crude OR (95%CI)	p-Value[a]	Adjusted OR[b] (95%CI)	p-Value[a]
Control group (n = 1554)	1527	27[c] (1.7%)	(1.1–2.5)	1	-	1	-
Domperidone group (n = 485)	471	14[d] (2.9%)	(1.6–4.8)	1.68 (0.87–3.23)	0.119	1.86 (0.73–4.70)	0.191
Metoclopramide group (n = 224)	216	8[e] (3.6%)	(1.6–6.9)	2.09 (0.94–4.67)	0.071	2.20 (0.69–6.98)	0.183

Risk of major malformation was analyzed in liveborn, single-birth infants.; Abbreviations: CI, confidence interval; OR, odds ratio.; [a]Significance level $p < 0.05$, *<0.05.; [b]Adjusted for alcohol intake, smoking, maternal age, use of concomitant drugs other than the control drugs during the first trimester of pregnancy, facility, and the year of counseling.; [c]Ventricular septal defect (6); ventricular and atrial septal defect (1); tetralogy of Fallot (1); pulmonary stenosis (1); peripheral pulmonary stenosis (1); endocardial cushion defect (1); complete transposition of great arteries (1); double outlet right ventricle (1); esophageal atresia (1); cleft lip (1); diastasis recti (1); adhesion of scrotum and penis (1); hydronephrosis (2); imperforate anus (1); talipes varus (1); polydactyly (3); a combination of coarctation of the aorta and ventricular septal defect (1); a combination of single ventricle and pulmonary stenosis (1); a combination of ventricular septal defect, pulmonary stenosis and syndactyly (1).; [d]Ventricular septal defect (5); ventricular and atrial septal defect (1); atrial septal defect (1); tetralogy of Fallot (1); pulmonary stenosis (1); cleft lip and palate (1); double vagina (1); hydroureteropathy (1); hydronephrosis (1); a combination of duodenal obstruction, heart disease, upper aortic malposition and pulmonary artery occlusion (1). and [e]Ventricular septal defect (1); endocardial cushion defect (1); myelomeningocele (1); lissencephaly (1); hypospadias (1); talipes varus (1); polydactyly (1); scalp defect (1).

metoclopramide group, indicating no significant difference for either group compared with the control group.

For the cases at National Center for Child Health and Development, the adjusted OR (95%CI) of the incidence of major malformation was 1.45 (95%CI: 0.38–5.54, p = 0.583) in the domperidone group and 2.06 (95%CI: 0.43–9.98, p = 0.370) in the metoclopramide group, again indicating no significant difference for either group compared with the control group (Supporting Information, Table SS1).

We also compared the adjusted OR of risk of major malformations by the year of counseling (Table SS2). To rule out the year of counseling as a possible confounding factor, we compared the first half of the data from Toranomon Hospital (1988–2004), to the second half (2005–2016) (adjusted OR: 0.79 [95%CI: 0.26–2.39], p = 0.680) and to the data from the National Center for Child Health and Development (2005–2017) (adjusted OR: 1.34 [95%CI: 0.69–2.60], p = 0.381), and found no significant differences in the adjusted OR.

Discussion

Although there are prior reports[3,4] of domperidone administered to pregnant women, those studies lacked sufficient detection power to ensure that domperidone exposure is not harmful to the fetus. Therefore, no information has been available to ensure the safety of using domperidone in pregnant women.

In this study, the 485 patients who received domperidone during the first trimester of pregnancy showed no increase in the incidence of major malformation compared with patients in the control group, who received drugs that are considered to have no teratogenicity. In addition, no difference was found in the results of a sensitivity analysis that assessed teratogenic risk by excluding patients who used teratogenic drugs defined by the clinical guidelines for gynecology and obstetrics[8].

This study enrolled pregnant women who consulted at Toranomon Hospital or the National Center for Child Health and Development. We therefore performed a subgroup analysis to determine if there were any discrepancies in results between the facilities. There were no such differences, and the incidence of major malformation in the domperidone group did not higher than that in the control group at neither facility.

This study analyzed participants who received counseling at Toranomon Hospital after April 1988 and at National Center for Child Health and Development after October 2005. The use of imaging modalities to detect visceral malformations began in 1997. Therefore, it is presumed that since then it has been possible to detect even minor malformations, such as inconsequential heart defects. However, there was no significant difference in the incidence of major malformation at Toranomon Hospital between 1988 to 2004 and 2005 to 2016. Also, the data from National Center for Child Health and Development (2005–2017) yielded similar results as those from Toranomon Hospital (1988–2004). Thus, the timing of counseling is unlikely to be associated with the detection rate of malformation.

The package insert for domperidone states that it is contraindicated for use in pregnant women and in

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women suspected of being pregnant, due to teratogenicity observed in reproductive toxicity studies. This has led to the problem of pregnant women becoming anxious when they discover they have taken domperidone before finding out they were pregnant.

This observational cohort study was based on highly precise data about drug use by pregnant women, derived from interviews conducted by healthcare professionals at medical facilities that provide counseling on drug use during pregnancy. It showed that the risk of major malformation was not increased in women who received domperidone during pregnancy. However, it should be noted that a limitation of the study is that women could cancel their counseling if they had a miscarriage or abortion beforehand, resulting in underreported miscarriage or abortion cases.

In future counseling, this information is clinically very useful because it can reduce or eliminate the anxiety of patients who have taken domperidone during pregnancy. The Japanese clinical guidelines for obstetrics and gynecology (obstetrics portion) list domperidone as one of the "drugs that may be used by women in early pregnancy without having a clinically significant adverse effect on the fetus, even though the package inserts state that they are contraindicated in pregnant women."[8] The results of this study support this statement in the guidelines.

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Conflict of interest

Atsuko Murashima received lecture fees from Chugai Pharmaceutical Co.Ltd and Astellas Pharma Inc.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Subgroup analysis by the facility

Table S2 Subgroup analysis by the year of counseling

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