

Teratogenic evaluation of drugs used by pregnant patients with gastrointestinal system diseases

Duygun Altintas Aykan, Yusuf Ergun

Kahramanmaraş Sutcu Imam University, Faculty of Medicine, Department of Pharmacology, Kahramanmaraş, Turkey

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Abstract

Aim: Drug use may be necessary in pregnant women due to chronic diseases or digestive disorders. However, safety of the use of many medications during pregnancy remains limited. The purpose of this study is to evaluate the safety of digestive system drugs during pregnancy.

Material and Methods: In this observational study, we collected data of pregnant women who used gastrointestinal agents between 2014 and 2018. Data regarding the medications, exposure to other agents and co-morbidities were documented. Our Teratology Information Service assessed the teratogenic risk of drugs. To investigate the pregnancy outcomes, a follow-up was conducted on the women after delivery to obtain whether there had been any major and/or minor congenital malformations and/or adverse neurodevelopmental effects in the infant.

Results: Twelve pregnant women (age 27-34 years), whose gestational age were between 4 and 24 weeks at admission time, were followed up. Among patients, one woman with ulcerative colitis used azathioprine; two women with hepatitis B using tenofovir; three women with nausea and abdominal pain used metoclopramide, hyoscine, ondansetron; six women with dyspepsia and gastritis used alginate acid, antacids, lansoprazole, rabeprazole, pantoprazole, trimebutine, alverine and pancreatin. After delivery, no congenital anomalies were detected. Two infants had low birth weights for gestational age, and one was born preterm.

Conclusion: Data in our study contributes to the literature on safety of gastrointestinal system medications in pregnancy. This permits decreasing the number of potential elective terminations related to the concerns about digestive system drugs.

Keywords: Teratogenesis; Digestive System; Pregnancy.

INTRODUCTION

Drug use is frequent among pregnant women due to chronic diseases or digestive disorders. The number of studies on drug risks during pregnancy has improved in recent years, based mostly on animal studies, case reports, retrospective studies and a small number of prospective studies. The unavailability of pregnant patients in randomized clinical trials limits data about the possible teratogenic risks of many medications. As a result of the impossibility to plan prospective interventional studies of drug use in pregnant women for ethical and legal reasons, information on the use of many drugs during pregnancy remains limited (1,2).

Medication use or exposure in pregnancy is a complex issue for both the pregnant women and physicians. The

concerns on drugs result in the avoidance of a necessary treatment during pregnancy or termination of a desired pregnancy (3). Individualized risk information is required for the clinical decision-making. However, there is uncertainty in the way of concluding the available data and clinical experience is still insufficient for the majority of drugs to verify their safety in pregnancy.

According to the Anatomical Therapeutic Chemical Classification (ATC) coding system, digestive system drugs are classified as antacids, anti-ulcer drugs, anti-emetics, drugs for intestine and/or gall bladder disorders, etc. Few drugs have been defined as definitely teratogenic in humans but numbers of congenital defects attributed to them are limited. Hence prevention for these defects is possible and women of reproductive age who use these

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Corresponding Author: Duygun Altintas Aykan, Kahramanmaraş Sutcu Imam University, Faculty of Medicine, Department of Pharmacology, Kahramanmaraş, Turkey, E-mail: altintasduygun_dr@yahoo.com

drugs should be carefully informed about the possible adverse effects. However 40% of pregnancies are not planned so that usage of such drugs may be enforced under strict medical control. Furthermore, when necessary, the duration of a waiting period prior to conception may be indicated (4).

We aimed to evaluate the safety of digestive system drugs in pregnancy and expand the human data. In this study, pregnant women who admitted to the Teratology Information Service of Pharmacology for digestive system drug analysis were evaluated.

MATERIAL and METHODS

Study design and settings

This is an observational study conducted in the Research Hospital of Faculty of Medicine of Kahramanmaraş Sutcu Imam University, Kahramanmaraş, Turkey. The inclusion criteria for the exposed cohort were the usage of digestive system drugs at any time from conception to delivery. Therapy may have started earlier and could have lasted longer. Patients with acute malignancies were excluded. Prior to the study, ethics approval was obtained from the Medical Faculty Ethics Committee for Clinical Investigations (date: 04.07.2018, no: 2018/11/02).

Participants and data enrolment

A total of twelve pregnant women who had admitted to the Teratology Information Service (TIS) for digestive system drugs analysis between the years 2014 and 2018 were included in the study. Data were recorded using structured questionnaires as a written form. All relevant data with respect to medication, exposure to other agents and comorbidities were documented. The primary questionnaire included maternal characteristics (age, place of birth, body mass index, occupation, and educational achievement), medical and obstetric history, chronic diseases, smoking, alcohol, ionized radiation exposure, concurrent drugs and herbal consumption. The commercial names and active ingredients of each drug were questioned along with the exposure period, medication dose, intervalance and clinical indications. Gestational age at admission time to TIS was calculated using ultrasound-based measures during the first trimester or, if not available, the date of the last menstrual period.

To investigate the pregnancy outcomes, a follow-up was conducted by a structured telephone interview with the women after the expected date of delivery. Details on pregnancy and delivery section, and neonatal outcome parameters such as birth weight, gestational age at delivery and postnatal disorders were obtained.

The survey also obtained whether there had been any major and minor congenital malformations or adverse physical and neurodevelopmental effects in the infant discovered either at birth or during routine family physician visits.

Outcome variables

The primary objective of this study was to estimate the risk of major birth defects. Secondary endpoints were to evaluate the low birth weight, incidence of preterm delivery, pregnancy complications (preeclampsia, abruptio placentae) and the rate of electively terminated pregnancies. Birth defects were categorized as major and minor congenital defects according to Malformation Coding Guides of European Surveillance of Congenital Anomalies (EUROCAT) (5). Miscarriage was defined as the spontaneous loss of a pregnancy before 20th gestational week, elective termination was defined as the voluntary abortion for non-medical reason, stillbirth was defined as the birth with no signs of life after 20th gestational week, preterm birth was defined as the birth before 37th gestational week and low birth weight was defined as the birth weight less than 2500 g.

Statistical analysis

The data was analyzed using the SPSS 17.0 program. Continuous variables were expressed as median (range).

RESULTS

Baseline characteristics of pregnant women

Between 2014 and 2018, twelve cases with exposure to gastrointestinal drugs during pregnancy were identified. Among patients, one woman with ulcerative colitis used azathioprine (50 mg/day); two women with hepatitis B used tenofovir (245 mg/day); three women with nausea and abdominal pain used metoclopramide (10 mg/day), hyoscine (20 mg/day), ondansetron (4 mg/day); six women with dyspepsia and gastritis used alginate acid (500 mg/day), antacids (2280 mg/day), lansoprazole (40 mg/day), rabeprazole (20 mg/day), pantoprazole (40 mg/day), trimebutine (100 mg/day), alverine (180 mg/day), and pancreatin (170 mg/day).

The ages of pregnant women range between 27 and 34 years. We found that ten women used the drugs in the first trimester, one woman in the third trimester and one in the preconception period. All pregnancies were treated at therapeutic and standard doses, and the medications were prescribed by specialist doctors. In addition, there was no exposure to ionizing radiation, cigarette, alcohol or herbal. But some of the patients have used concomitant prescription drugs other than digestive system drugs. Detailed maternal characteristics are presented in Table 1.

Pregnancy outcomes and neonatal characteristics

The median gestational age at admission was 6 (range: 4 - 24) weeks. The median start time of exposures was 4 weeks (range: before conception - 23 weeks) and median duration of drug exposure was 10 days (range: 1 day- throughout pregnancy). Patterns of exposure and exposed co-medications are presented in Table 2. Of the 12 pregnancies with known outcomes, all were live births. Two infants were reported to have low birth weights for gestational age and one was born preterm.

Table 1. Maternal characteristics of pregnant women

Indication	Gestational age (week)	Drugs	Gestational period	Dose (mg/day)
Ulcerative colitis	6	Azathioprine	1st trimester	1x50 mg
Hepatitis B	6	Tenofovir	1st trimester	1x245 mg
Hepatitis B	4	Tenofovir	1st trimester	1x245 mg
Gastritis	7	Alginic acid Lansoprazole	1st trimester	1x500 mg 1x40 mg
Gastritis	5	Lansoprazole Trimebutine	1st trimester	1x40 mg 1x100 mg
Gastritis	6	Antacid Metoclopramide Pantoprazole	1st trimester	3x760 mg 1x10 mg 1x40 mg
Dyspepsia	6	Alginic acid	Before conception	1x500 mg
Dyspepsia	12	Alverine Pancreatin	1st trimester	3x60 mg 1x170 mg
Dyspepsia	6	Rabeprazole	1st trimester	1x20 mg
Nausea	24	Ondansetron	3rd trimester	1x4 mg
Nausea	6	Metoclopramide Hyoscine	1st trimester	2x10 mg 1x20 mg
Abdominal pain	11	Metoclopramide Hyoscine	1st trimester	1x10 mg 1x20 mg

Table 2. Patterns of exposure and exposed co-medications

Exposed drugs	Start time(week)	Duration (day)	Administration routine	Comedications
Azathioprine	Before conception	43	p.o	-
Tenofovir	Before conception	Throughout pregnancy	p.o	-
Tenofovir	Before conception	Throughout pregnancy	p.o	-
Alginic acid Lansoprazole	6 6	7 7	p.o p.o	Cyproheptadine NSAID Flunarizine
Lansoprazole Trimebutine	4 4	2 2	p.o p.o	Ergotamine Flunarizine Citalopram
Antacid Metoclopramide Pantoprazole	1 1 1	10 10 10	p.o p.o p.o	Trazodon Duloxetine NSAID Miconazole / metronidazole Ciprofloxacin / ornidazole Diflucortolone / isoconazole
Alginic acid	6	1	p.o	Adalimumab
Alverine Pancreatine	Before conception	86 86	p.o p.o	Fluconazole Levetiracetam Carbamazepine Ciclopirox
Rabeprazole	Before conception	36	p.o	Levonorgestrel / ethinyl estradiol
Ondansetron	23	10		
Metoclopramide Hyoscine	4 4	14 5	p.o p.o	Levocetirizine NSAID
Metoclopramide Hyoscine	8 8	7 7	i.v i.v	Metronidazole Betahistine

p.o: per oral; i.v: intravenous; NSAID: nonsteroidal anti-inflammatory drugs

DISCUSSION

In this study, we evaluated the safety of digestive system drugs to expand human data about their use during pregnancy. We found that twelve pregnant women, who had been exposed to various drugs related to gastrointestinal system (GIS) disorders, gave birth to healthy infants. The pregnant women in this study had diagnosis and/or symptoms of ulcerative colitis, hepatitis B, nausea, abdominal pain, dyspepsia and gastritis at the time of their admission to TIS. The medications prescribed by specialist physicians were azathioprine, tenofovir, metoclopramide, hyoscine, ondansetron, alginate acid, antacids, lansoprazole, rabeprazole, pantoprazole, trimebutine, alverine, and pancreatin in this study.

Among these agents, azathioprine is an immunosuppressant agent used in the treatment of inflammatory bowel diseases such as Crohn disease and ulcerative colitis. Adverse events including skeletal defects and visceral anomalies in rats and mice and multiple anomalies in exposed rabbit fetuses have been observed in animal studies (6,7). In human studies, azathioprine has been reported to cause immunosuppression, hematologic toxicities and intrauterine growth retardation when used during third trimester (8).

Therefore women of childbearing potential should avoid pregnancy under this regimen. When clinically indicated, guidelines recommend doses ≤ 2 mg/kg/day during pregnancy for rheumatoid arthritis, lupus nephritis or post renal transplant (9-11). Although most controlled studies involving azathioprine found no increased risk of congenital anomalies, one study reported an increase in atrial and ventricular septal defects and preterm delivery (12). In our study, azathioprine was used in the first six weeks by a pregnant woman with ulcerative colitis. She gave birth to a healthy infant with a weight of 2000 g at 36 weeks. It is not clear if growth restriction and shortened gestation are due to azathioprine, concomitant medications or the underlying maternal illness.

Tenofovir, which is an antiviral agent and often prescribed in patients with hepatitis B, is an acyclic analog of adenosine-5'-monophosphate with activity against viral reverse transcriptase. No increased risk of congenital malformations was reported following first trimester exposure of tenofovir in the previous studies (13). Tenofovir is one of the most preferred antivirals that have been studied in pregnant women. However, there is data about the potential growth restrictive effects of tenofovir disoproxil fumarate later in infancy following maternal use. Antiretroviral medications may cause mitochondrial dysfunction so long-term follow-up is recommended for all infants whose mother had used antiretroviral medications during gestation in terms of systemic anomalies such as central nervous system or heart (14). Guidelines suggest antiviral therapy to reduce the risk of perinatal transmission of hepatitis B in HBsAg-positive pregnant women with an HBV DNA $>200,000$ units/mL (15). In this study, two pregnant women with a history

of tenofovir usage due to the diagnoses of hepatitis B, delivered healthy, term and normal weight babies.

Sucralfate and antacids are the first line treatment options for gastroesophageal reflux in pregnancy. In patients who fail to respond, histamine 2 receptor antagonists and then proton pump inhibitors (PPIs) are advised. Most antacids, except sodium bicarbonate and magnesium trisilicate, are considered safe in pregnancy (16,17). Among PPIs, omeprazole, lansoprazole and pantoprazole have been more widely used in pregnancy so are recommended rather than other PPIs. No significant increase in the risk for major congenital birth defects, spontaneous abortions or preterm delivery among women exposed to PPIs during pregnancy was found in a large number of studies and meta-analysis when compared with control groups (18,19). In this study, pregnant women with dyspeptic complaints used lansoprazole, rabeprazole and pantoprazole. Each woman exposed to these agents in the first trimester and there was no congenital anomaly or complication at delivery.

Pregnancy-related vomiting is frequently seen during pregnancy. Previous studies have demonstrated that antiemetic drug therapy does not increase the incidence of congenital anomalies and the use of doxylamine-pyridoxine was recommended for vomiting women without hypovolemia (20-25). If doxylamine and pyridoxine has been ineffective, antihistamines such as dimenhydrinate, meclizine, and diphenhydramine may be used as second-line agents for treatment of nausea and vomiting in pregnancy. A number of studies and meta-analysis reported that H1 receptor blockers have protective effects on the risk of major congenital malformations (26-29). On the other hand, the three main classes of dopamine receptor antagonists, benzamides (metoclopramide), phenothiazines (promethazine and prochlorperazine), and butyrophenones (droperidol) may be used for the treatment of nausea and vomiting in pregnancy, since these drugs exert action on the dopaminergic mechanisms involved in the regulation of gastrointestinal motility. Pregnant women who had nausea had used ondansetron, metoclopramide and hyoscine in our study. One of these pregnancies resulted in low birth weight infant after using ondansetron in the third trimester.

When women are given prescription medication for chronic diseases or acute disorders related to GIS, the pregnancy status or pregnancy plan of women should be considered. Only drugs with proven safety should be used during pregnancy. It is prudent to use those drugs if clinical experience is available because new pharmaceuticals may be teratogenic. With regard to women who have inadvertently used drugs during the initial stages of pregnancy, it is advisable to refer them to TIS. These services can evaluate any risk on the drug use during pregnancy, and advice on the field of reproductive risk factors when necessary.

It is important to note the limitations of our study. We have a limited sample size and lack comparison group, so it can

not be attributed to the general population. However, this study may be considered as a small contribution to the available safety data of GIS drugs until epidemiological studies are completed.

CONCLUSION

Our findings support the evidence that digestive system drugs are not major teratogens. Moreover, our findings do not indicate a substantial risk of the GIS disorders for major birth defects or other adverse pregnancy outcomes. This allows decreasing the number of many unnecessary elective terminations related to the drug concerns.

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