The Turkish Journal of Pediatrics 2018; 60: 298-305
DOI: 10.24953/turkjped.2018.03.010

Original

Birth outcomes after inadvertent use of category X drugs contraindicated in pregnancy: Where is the real risk?

Zeynep Öztürk[1,2] Ercüment Ölmez[3], Tuğba Gürpınar[3], Kamil Vural[3]

[1]Department of Clinical Pharmacology and Toxicology, Izmir Ataturk Research Hospital, Izmir; [2]Department of Healthcare Management, İzmir University of Economics, İzmir; [3]Department of Pharmacology, Celal Bayar University, Manisa, Turkey. E-mail: dr.zeyneb@hotmail.com

Received: 4th April 2017, Revised: 7th November 2017, Accepted: 28th November 2017

SUMMARY: Öztürk Z, Ölmez E, Gürpınar T, Vural K. Birth outcomes after inadvertent use of category X drugs contraindicated in pregnancy: Where is the real risk? Turk J Pediatr 2018; 60: 298-305.

Drugs contraindicated in pregnancy are medicines that should be avoided by pregnant women, since they carry a concern for teratogenicity or there is no indication for their use during pregnancy. It does not mean that exposures to these drugs always cause harm. The aim of the present study was to investigate the risk of adverse outcomes following maternal exposure to the drugs contraindicated in pregnancy. We retrospectively analyzed prenatal drug exposure records of the pregnant patients referred to the clinical pharmacology consultation service in a tertiary-level university hospital from January 2007 until December 2012. Exposures to category X drugs (CXD) contraindicated in pregnancy were evaluated. After the expected date of delivery, we collected data about pregnancy complications and the outcomes. For comparison the women in the exposed group (N=52) were matched with a control group (N=162) of pregnant women without teratogenic exposure. We observed only one baby born with a birth defect (congenital cryptorchidism) in CXD group (2.6%) and four in control group (RR 0.91; 95% CI 0.10- 7.94). The rates of adverse pregnancy outcomes including miscarriage, preterm birth and congenital abnormality were not significantly different from controls. However, the rate of elective termination of pregnancy was higher in women exposed to CXD while pregnant (RR 2.54; 95% CI 1.11- 5.80, p = 0.027). Contraceptive failure and unintended pregnancy are the reasons for inadvertent drug exposure and choosing abortion. The high perception of teratogenic risk among pregnant women may cause terminations of pregnancies. Individual risk assessment and avoiding the phrase 'CXD' or 'contraindicated in pregnancy' in counseling may help to reduce maternal concerns about medication use in pregnancy.

Key words: contraindications; medication; newborn; birth outcome.

A number of medications in common clinical use are contraindicated in pregnant patients, since there is no indication for use during pregnancy or they carry a concern for teratogenic risk. To evaluate the drug-related risk in pregnancy, some resources such as the United States-Food and Drug Administration's (US- FDA) pregnancy categories, medication package inserts or electronic databases containing specific drug safety information can be used.[1] FDA pregnancy categories (A, B, C, D, and X) provide short and practical data, but this category system is not sufficient when used alone.[2] An overall classification for pregnancy may not accurately or consistently communicate differences in degrees of fetal risk. To help health care providers in counseling patients of reproductive potential, the pregnancy letter categories have recently been removed and replaced with an evidence-based approach.[3,4]

Contraindicated drugs are 'pregnancy category X' drugs that are considered to have a high

The study was presented at the 81st Annual Congress of the German Society for Experimental and Clinical Pharmacology and Toxicology (10-12 March 2015, Kiel, Germany) as an oral presentation.

teratogenic risk to fetus, based on data from animal studies or marketing experience in human. Risk statements must be found in medication package inserts provided by the manufacturer, and if the drug is contraindicated in pregnancy, it must be stated first.[5] Reliance on inserts can result in poorly informed clinical decision making, because adequate safety data are often not available. Additionally, warning information including contraindications and drug adverse reactions may also create worries and questions in patients.[6] Therefore, patients exposed to drugs and known teratogens during pregnancy should be clearly informed of the potential side effects, and the physician should avoid negative comments that increase anxiety.

Pregnant women should not use drugs contraindicated in pregnancy. However, it does not mean that exposures to these drugs always cause harm.[2] There are a few studies that have investigated prescriptions for contraindicated category X drugs (CXD).[7-10] However, none of the studies have information about outcomes of pregnancies exposed to these drugs.

The aim of this study was to investigate obstetric and neonatal outcomes in women exposed to CXD contraindicated in pregnancy.

Material and Methods

Pregnant women exposed to drugs known as contraindicated in pregnancy were identified from medical records of patients referred for medication safety counseling to the Pharmacology Department in Manisa Celal Bayar University Hospital between January 2007 and December 2012. Patient data are documented through the risk consultation.

We retrospectively evaluated the patients' data including information about maternal demographics, obstetric history, medical history, family history, consanguineous marriage, smoking, alcohol consumption and all drug exposures after conception (dose, time, and duration in pregnancy). After the expected day of delivery, we conducted telephone interviews with the woman and/or the woman's physician. We collected data about complications during pregnancy and details of the outcomes (live birth, preterm birth, birth defect, stillbirth, miscarriage, elective termination of pregnancy). This study was approved by the Ethics Committee of the Celal Bayar University, Turkey. All patients were informed that their medical information would be stored and used for scientific research.

For comparison, the women exposed to CXD (N=52) were matched with a control group (N=162) of pregnant women who had been counseled during pregnancy about exposures to drugs not known to be teratogenic. 162 controls were sampled, matched on year of counseling, in order to obtain a ratio 1:3. The control group data were collected and analyzed using the same procedure.

Statistical analysis

The results were expressed as number and percentages. For calculating rates of miscarriages, elective terminations of pregnancy (ETOP) were excluded (number of miscarriages/number of exposed pregnancies, ETOP excluded). Risk ratios with 95% confidence intervals were calculated with the use of SPSS V.16 (SPSS, Chicago, Illinois, USA). For the comparison of continuous variables, Student's t-test was used. Proportions were compared using the chi-square test or Fisher's exact test, as appropriate. The results were considered statistically significant when p values were <0.05.

Results

From January 2007 till December 2012, we had a total of 52 queries on maternal exposure to CXD. The control group consisted of 162 pregnant women not exposed to known teratogens. The maternal characteristics of the women in the drug-exposed and control groups are presented in Table I. There were no statistically significant differences for maternal characteristics between cases and controls. However, the control group women were more likely to be pregnant for the first time, and the women in CXD group smoked less.

As shown in Table II, most pregnancies were exposed to hormonal contraceptives (N=28), ergotamine (N=10), isotretinoin (N=6) and atorvastatin (N=5). Treatment indications (N=52) were contraception (22/52), secondary amenorrhea (6/52), migraine (10/52), acne (6/12), hyperlipidemia (5/52) and others (3/52).

Drug exposures occurred in 6 pregnancies during the first and second trimester, and others

Table I. Maternal Characteristics.

Characteristics	CXD (N = 52)	Control (N = 162)
Maternal age (years)		
Median age	29	29
Min-max	20-45	18–44
Smoking		
No	41/52 (78.9%)	111/162 (68.6%)
≤5 cigarettes/day	6/52 (11.6%)	19/162 (11.7%)
>5 cigarettes/day	5/52 (11.5%)	32/162 (19.7%)
Alcohol		
No	51/52 (98.1%)	159/162 (98.2%)
≥ drink/day	1/52 (1.9%)	3/162 (1.8%)
Previous pregnancies		
0	15/52 (28.8%)	60/162 (37.0%)
1	16/52 (30.8%)	46/162 (28.4%)
2	15/52 (28.8%)	33/162 (20.4%)
≥3	6/52 (11.6%)	23/162 (14.2%)
Previous parities		
0	15/52 (28.8%)	68/162 (41.9%)
1	25/52 (48.1%)	61/162 (37.7%)
2	7/52 (13.5%)	22/162 (13.6%)
≥3	5/52 (9.6%)	11/162 (6.8%)
Previous miscarriages		
0	45/52 (86.6%)	139/162 (85.8%)
1	5/52 (9.6%)	20/162 (12.3%)
2	2/52 (3.8%)	3/162 (1.9%)
Weeks at first consultation		
Median	7	7
Min-max	4-20	3-32

CXD: Category X drugs.

in the first trimester. In 75% of pregnancies, treatment was initiated before pregnancy. One out of every four women in the exposed group was already pregnant when the treatment was started. Medical treatments were discontinued in all recognized pregnancies. Pregnancy outcomes associated with drug exposures are given descriptively in Table II.

Of the children exposed to CXD in-utero, 1 child was diagnosed congenital cryptorchidism. The 34-year-old mother received a monthly intramuscular injection of norethisterone enanthate and estradiol valerate (50 mg/5 mg) when she was already pregnant. Drug exposure occurred in the fifth week of the pregnancy.

Of 52 pregnancies with CXD exposure, 38 resulted in live birth, and 5 in miscarriage. Miscarriages were reported in 3 gestations exposed to hormonal contraceptives (3/28), 1 to ergotamine (1/10) and 1 to atorvastatin (1/5). Two children (2/38) were born premature (before 37 weeks of pregnancy), and the mothers of both premature infants smoked over half a package of cigarettes a day while pregnant. For details of unhealthy pregnancy outcomes see Table III.

The proportion of live births was lower in CXD group than in controls (73.0% vs. 85.8%). As

Table II. Drug Exposures and Pregnancy Outcomes.

Drug (route)	Exposed pregnancies	Live births	ETOP	SA	PD	BD	Comments
Hormonal contraceptives							
MPA (PO)	11	9	1	1	-	-	Pregnancy loss in week 8
EE/LNG (PO)	5	4	1	-	-	-	
EV/NG (PO)	5	3	1	1	-	-	Pregnancy loss in week 24
LNG (PO)	1	1	-	-	-	-	
EB/P (IM)	1	1	-	-	1	-	
EE/DRSP (PO)	1	-	1	-	-	-	
EE/DSG (PO)	1	-	-	1	-	-	Pregnancy loss in week 10
EV/NE (IM)	2	1	1	-	-	1	Congenital cryptorchidism
NE (PO)	1	1	-	-	-	-	
Other drugs							
Ergotamine (PO)	10	9	-	1	1	-	Pregnancy loss in week 20
Isotretinoin (PO)	6	3	3	-	-	-	
Atorvastatin (PO)	5	3	1	1	-	-	Pregnancy loss in week 7
Misoprostol (PO)	2	2	-	-	-	-	
Acitretin (PO)	1	1	-	-	-	-	

BD: birth defect, EB/P: estradiol benzoate combined with progesteron, EE/DRSP: ethinyl estradiol combined with drospirenone, EE/DSG: ethinyl estradiol combined with desogestrel, EE/LNG: ethinyl estradiol combined with levonorgestrel, ETOP: elective termination of pregnancy, EV/NE: estradiol valerate combined with norethisterone, EV/NG: estradiol valerate combined with norgestrel, LNG: levonorgestrel, IM: intramuscular, MPA: medroxyprogesterone acetate, NE: norethisterone, PD: preterm delivery, PO: per oral, SA: spontaneous abortion.

can be seen in Table IV, there was no statistically significant difference in rates of miscarriages, preterm deliveries and birth defects between the two groups. However, the rate of elective abortions was significantly higher in CXD group (17.3% vs. 7.3%; RR 2.54; 95% CI: 1.11- 5.80; p=0.027).

Discussion

We found no significant association between exposure to CXD during pregnancy and risk of adverse pregnancy outcomes, including miscarriage, preterm birth and congenital abnormality. However, there was a significant association with the elective termination of pregnancy.

This study covered 52 cases with gestational exposure to CXD that were followed by our clinical pharmacology consultation service. More than half of the cases (28/52) received hormonal contraceptives for the prevention of pregnancy and for the treatment of menstrual irregularities. Symptoms of menstrual irregularities can mask early symptoms of pregnancy or miscarriage. Some women may experience light bleeding or spotting that can occur 1 to 2 weeks following conception.[11] Because pregnancy is the most common cause of secondary amenorrhea, a pregnancy test is usually recommended for women whose menstrual periods have stopped.[12] In our study, 6 of 28 pregnant women receiving hormonal contraceptives were diagnosed with secondary amenorrhea and no pregnancy tests were done before treatment.

Based on our results, ergotamine was the second most commonly reported medication in

Table III. Characteristics of Unhealthy Outcomes.

Outcome	Age (years)	Drug(s), route	Dose (mg/d), route	Exposure in weeks after LMP	Obstetric history	Alcohol/ smoking	Comments
SA1 (week 8)	34	MPA	5, oral	4-5	Pr. Preg.: 7 Pr. Par.: 2 SA: 0 ETOP: 5	-	Treatment indication: irregular menstruation. Additional drugs (week 0- 8): acetylsalicylic acid 300 mg/d, oxerutin 500 mg/d (venous insufficiency)
SA2 (week 24)	31	EV/NG	2/0.5, oral	2-6	Pr. Preg.: 2 Pr. Par.: 1 SA: 1 ETOP: 0	-	Treatment indication: irregular menstruation
SA3 (week 10)	34	EE/DSG	0.03/0.15, oral	4-7	Pr. Preg.: 1 Pr. Par.: 1 SA: 0 ETOP: 0	-	Treatment indication: contraception
SA4 (week 20)	45	Ergotamine (combined with mecloxamine, caffeine, paracetamol)	0.75, oral	0-5	Pr. Preg.: 5 Pr. Par.: 4 SA: 0 ETOP: 1	-	Treatment indication: migraine. Additional drugs (week 0- 20): levothyroxine 50 mcg/d (hypothyroidism)
SA5 (week 7)	33	Atorvastatin	80, oral	0-5	Pr. Preg.: 0 Pr. Par.: 0 SA: 0 ETOP: 0	-	Treatment indication: hypertension. Additional drugs (week 0- 5): epoetin beta 100 mcg/month, acetylsalicylic acid 300 mg/d, carnitine 3 g/ week, paricalcitol 15 mcg/week, calcium acetate 750 mg/d (renal insufficiency)
PD1	33	EB/P	2.5/ 12.5, IM	7-8 (once)	Pr. Preg.: 0 Pr. Par.: 0 SA: 0 ETOP: 0	40 cigarettes/d	Treatment indication: irregular menstruation. Additional drugs (week 7-8): amoxicillin 2000 mg/d, naproxen sodium 550 mg/d, loratadine 10 mg/d (pneumonia). Additional drugs (week 7-11): alprazolam 0.5 mg/d (anxiety)
PD2	38	Ergotamine (combined with mecloxamine, caffeine, paracetamol)	0.75, oral	0-4	Pr. Preg.: 1 Pr. Par.: 1 SA: 0 ETOP: 0	10 cigarettes/d	Treatment indication: migraine
BD1	34	EV/NE	5/50, IM	4-5 (once)	Pr. Preg.: 4 Pr. Par.: 4 SA: 0 ETOP: 0	-	Treatment indication: contraception. Additional drugs (week 7- 8): cetirizine 10 mg/d, pseudoephedrine hydrochloride 40 mg/d, levofloxacin 750 mg/d, flurbiprofen 200 mg/d (sinusitis)

BD: birth defect, d: day, EB/P: estradiol benzoate combined with progesterone, EE/DSG: ethinyl estradiol combined with desogestrel, ETOP: elective termination of pregnancy, EV/NE: estradiol valerate combined with norethisterone, EV/NG: estradiol valerate combined with norgestrel, g: gram, LMP: last menstrual period, mcg: microgram, MPA: medroxyprogesterone acetate, PD: preterm delivery, Pr. Par.: previous parities, Pr. Preg.: previous pregnancies, SA: spontaneous abortion.

CXD group (10/52). Ergotamine tartrate (0.75 mg/day, oral) in combination with caffeine, mecloxamine and paracetamol was used for the treatment of migraine. All treatments were initiated before pregnancy, continued until the diagnosis of pregnancy, and drug exposure occurred only during the first trimester. Many women have migraines before they become pregnant. Hormonal changes and the increase in blood volume can also cause headaches during first trimester, but most of the headaches improve or disappear during the second and third gestation trimester.[13] Therefore, non-pharmacologic interventions are recommended as the initial strategy for managing migraines during pregnancy.[14] Pregnancy use of ergotamine has not been demonstrated to increase the risk of congenital anomalies.[15] Some investigators have reported an association of low birth weight and preterm birth with maternal use of ergotamine in pregnancy.[16] We observed healthy babies (8/10) born to mothers who used ergotamine after conception.

In this study, we evaluated maternal characteristics of the groups, and we found that the rate of previous pregnancies was higher in CXD group (71.2%) than in control (63.0%). Most of the women in CXD group used hormonal contraception, and they became pregnant unexpectedly. Worldwide, approximately 40% of pregnancies are unintended.[17] Unplanned or mistimed pregnancies are the main reason for accidental use of medication in early pregnancy. Compared to controls, the pregnant women in CXD group smoked less, but it is not surprising, because more than half of the cases received hormonal contraceptives. It is well known that smoking cigarettes while using hormonal contraception increases the risk of cardiovascular problems and aggravates the stage of arterial disease, especially in women older than 35 year.[18]

Our results showed that 25% of pregnancies began before the start of the contraindicated-drug medication and 75% during treatment. Since many women are unaware of their pregnancy status, the use of medications is very common in the first trimester, which is a critical period for organogenesis.[19,20] Among 52 pregnancies with CXD exposures, we observed 6 exposures in second trimester, and all treatments were discontinued after the diagnosis of pregnancy. The pregnancies with exposure to atorvastatin, isotretinoin, misoprostol, acitretin, medroxyprogesterone acetate, estradiol and levonorgestrel in second trimester resulted in healthy live births. As shown in Table III, all unhealthy outcomes were found to be associated with exposure of CXD in early pregnancy. Drug exposure during late pregnancy can affect the functional fetal development, however not usually associated with major congenital malformations.[21]

When compared the rate of birth defects, we found no remarkable difference between the groups. We observed only one birth defect, congenital cryptorchidism, in our exposed group. The mother of the infant was a 34-year-

Table IV. Pregnancy Outcomes.

Outcomes	CXD (N= 52)	Control (N= 162)	CXD vs. Control	
	N (%)	N (%)	RR (95% CI)	p-value
Live births	38 (73.0)	139 (85.8)		
Miscarriage *	5/52 (9.6)	12/162 (7.4)	1.29 (0.47-3.51)	0.39
ETOP	9/52 (17.3)	11/162 (7.3)	2.54 (1.11- 5.80)	0.027
Preterm births (<37 weeks)	2/38 (5.2)	7/139 (5.0)	1.03 (0.22- 4.79)	0.61
Birth defects	1/38 (2.6)	4/139 (2.8)	0.91 (0.10- 7.94)	0.70

CI: confidence interval, CXD: Category X drugs, ETOP: elective termination of pregnancy
*: ETOP excluded

old woman, who received estradiol valerate combined with norethisterone IM once in week 5. Congenital cryptorchidism, also known as undescended testis, and is a common birth defect especially in premature infant boys. As in our patient, undescended testis occurs in only about 2% to 5% of full-term infants.[22] Progestins or estrogen in oral contraceptives may interfere in some way with testicular descent. A study of the risk factors for undescended testis has reported an odds ratio of 3.6 (95% CI 1.0-12.5) for mothers using oral contraceptives in pregnancy.[23] Androgenic progestins such as norethisterone may exert masculinizing effects on 1% of exposed fetuses. Clitoral hypertrophy in female fetuses and hypospadias in male fetuses have been attributed to progestin or hormonal contraceptive exposure during early pregnancy.[24-26] Some authors have reported an increase in nongenital anomalies such as heart defects[27], limb reduction deformities[28], urinary tract abnormalities[29] and bladder exstrophy[30] associated with the use of sex hormones in pregnancy. By contrast, other studies have found no association between nongenital anomalies and inadvertent exposure to hormonal contraceptives in first trimester.[31,32]

In this study, we found a higher rate of ETOP in CXD group when compared to controls. Hormonal contraceptives and isotretinoin were the most common used medication in women who decided to terminate the pregnancy. All terminations were performed because of fear of maternal medication. Package inserts that indicate an increased risk after CXD exposure in pregnancy might trigger the patients' concerns. Despite the higher rate of ETOP in CXD group, the women using ergotamine decided to continue their pregnancies. Since ergotamine is an over-the-counter drug, it is not surprising that the patients have no strong concerns about the possible adverse effects in pregnancy.

Kaplan et al.[33] reported a lower teratogenic risk perception of the Turkish pregnant women and a lower likelihood of ETOP after teratology counselling. We could not confirm this finding in our study, because a higher rate of our patients using a CXD decided to terminate their pregnancies when compared with the controls. In his study, Kaplan et al.[33] did not analyze the risk categories of medication exposures and the real pregnancy outcomes, but ETOP ideas via a cross-sectional survey study. Previous studies with similar findings from western countries have also reported that maternal-rated likelihood to terminate the pregnancy does not necessarily reflect a mother's actual future action.[34]

National studies about pregnancy outcomes following medication exposure are very limited. To our knowledge, the present study includes the first outcomes of unintended pregnancies following use of CXD in Turkey. Similar to our findings, a recent publication reported on a higher rate of ETOP among Turkish pregnant women taking psychotropic medications when compared a control group.[35] The researchers concluded that underlying psychiatric disease and fear of medication's effect on pregnancy outcome may play a role in making the decision to terminate the pregnancy.

Our findings show that there is a tendency to terminate pregnancy for women using a CXD while pregnant. Contraceptive failure and unintended pregnancy are the reasons for inadvertent medical exposure and choosing abortion. The high perception of teratogenic risk among pregnant women may lead to terminations of pregnancies. Individual risk assessment and avoiding the phrase 'CXD' or 'contraindicated in pregnancy' in counseling may help to reduce maternal concerns.

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