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Evaluation of pregnant women admitted to Dokuz Eylül University Teratogenicity Information Service due to use of medications affecting the cardiovascular system

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ABSTRACT

Objectives: This study aims to evaluate the demographic characteristics, maternal and neonatal outcomes of pregnant women receiving cardiovascular medications (CVMs) during pregnancy and admitted to the Teratogenicity Information Service (TIS).

Patients and methods: In this descriptive, cross-sectional, retrospective study, a total of 47 pregnant women (mean age: 34.0±5.5 years; range, 19 to 41 years) who were admitted to the TIS of Dokuz Eylul University were included between January 2014 and December 2016. Demographic characteristics, types of the CVMs, concomitant medication and/or substance use, medical and obstetric histories of cases, and maternal and neonatal outcomes were evaluated.

Results: The most commonly used drugs were beta-receptor antagonists. The mean gestational age at the time of delivery was 35.9±8.2 weeks and 42 infants (89.4%) were healthy. Five pregnancies (10.6%) ended in miscarriage or elective termination. No malformation was found in healthy live newborns.

Conclusion: The use of CVMs during pregnancy remains as a challenging issue, as their potential effects on the developing fetus are not fully known. Based on these study results, it is difficult to determine safety of CVMs during pregnancy and establish a causal relationship between maternal/neonatal outcomes and CVMs exposure.

Keywords: Cardiovascular system medicines, maternal and neonatal outcomes, pregnancy.

The use of medications during pregnancy is a common problem across the globe. In 80% of all pregnancies, prescription or non-prescription medications are used.[1] It has been estimated that malformation affects one to three in every hundred babies, and teratogenic drugs/substances can be only held responsible for less than 10% of these malformations.[2,3]

In developed countries, cardiac diseases are the most common causes of maternal mortality during pregnancy. According to the epidemiological studies, approximately every year 0.2% of all pregnant women die from cardiac reasons.[1-4] Additionally, in the United States, 11% of the maternal deaths during pregnancy are caused by cardiac diseases.[5] Physiological changes in pregnancy may adversely affect the prognosis of an existing cardiovascular disease and may alter the effects of medications which affect the cardiovascular system. Also, the effects of the cardiovascular medications (CVMs) on the fetus are not fully known. It is also an undeniable fact that ethical concerns limit the controlled studies on this subject. Thus, the data regarding the use of CVMs during pregnancy and their effect on pregnancy outcomes are limited in Turkey.

In the present study, we aimed to evaluate the demographic characteristics of pregnant women referred to the Teratogenicity Information Service (TIS) during pregnancy and to identify the characteristics of the CVMs exposures and the pregnancy outcomes.

PATIENTS AND METHODS

This descriptive, cross-sectional, retrospective study was conducted at Dokuz Eylul University, TIS

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between January 2014 and December 2016. Initially, a total of 491 pregnant women were admitted to the TIS for teratogenicity risk evaluation and 62 (12.6%) of these admissions were due to the use of CVMs during pregnancy. Fifteen cases with missing data were excluded from the study. Finally, a total of 47 pregnant women (mean age: 34.0±5.5 years; range, 19 to 41 years) were included in the study. Participants who exposed to CVMs alone and together with the other medicines and/or substances were also evaluated. A written informed consent was obtained from each participant. The study protocol was approved by the Dokuz Eylul University, Faculty of Medicine, Non-Interventional Research Ethics Committee (No: 3494-GOA/2017). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The data of the pregnant women included in the study were obtained from the registration forms filled out during the initial admission to TIS. The data collected from the registration forms were as follows: demographic data (age, educational status, presence of consanguineous marriage), medical, family and obstetric history (gestational week, last menstrual period, number of pregnancies, number of live/stillbirths in previous pregnancies, presence of anomalies in previous pregnancies), and CVMs and exposure characteristics (name, content, dose, total amount, and duration). The gestational week was calculated according to the ultrasound data or the last menstrual period. To obtain the verbal consent and investigate the pregnancy outcomes and confirm the data, a phone interview was conducted with each mother. In addition, data related to the

Table 1
Maternal demographic and obstetric characteristics

	n	%	Mean±SD
Gestational age at admission (week)			9.2±4.7
Age (year)			
≤35	21	44.7	
>35	26	55.3	
Consanguineous marriage			
2nd degree	2	4.3	
3rd degree	1	2.1	
None	44	93.6	
Maternal education status			
None	3	6.4	
Primary/secondary school	25	53.2	
High school/university	19	40.4	
Substance/illicit drug use			
Smoking	10	21.3	
Alcohol	4	8.5	
None	33	70.2	
Radiation exposure			
Direct graph	10	21.3	
CT	1	2.1	
None	35	76.6	
Gravidities/parities			
1	9/11	19.1/23.4	
2	18/32	38.3/68.1	
3 and more	20/4	42.6/8.5	
Previous miscarriages/elective terminations			
0	30	63.8	
1-2	15	31.9	
3 and more	2	4.3	

SD: Standard deviation; CT: Computed tomography.

pregnancy outcomes (term birth, preterm delivery, miscarriage, elective termination, stillbirth, baby healthy, presence/absence of anomaly) and possible complications during pregnancy were obtained by phone interviews. Pregnant women who did not give a verbal consent were excluded from the study. Pregnancy outcomes were classified using the International Classification of Diseases 10th revision (ICD 10) definitions of World Health Organization (WHO).[6] Elective termination was defined as the voluntary abortion, miscarriage as a pregnancy loss before 22 completed weeks of gestational age, stillbirth as the birth with no signs of life after 22 completed weeks of gestational age, and preterm birth was defined as the birth before 37 completed weeks of gestational age.[6]

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD) or median (min-max) for continuous variables and in number and frequency for categorical variables. In the comparison of the two groups, the chi-square (χ^2) test was used for categorical data. The Fisher's exact test was used, when the χ^2 assumption was not met. A p value of <0.05 was considered statistically significant.

RESULTS

Of the patients, the mean gestational age at the time of admission to the TIS was 9.2±4.7 (range, 5 to 25)

Table 2
The association between some properties of pregnants and pregnancy outcomes

	Pregnancy outcomes						
	Healthy birth		Abortus		Total		
	n	%	n	%	n	%	p
Having a baby with anomalies in previous pregnancies							
No	40	90.9	4	9.1	44	100	0.29
Yes	2	66.7	1	33.3	3	100	
Maternal age (year)							
≤35	20	95	1	5	21	100	0.3
>35	22	84.6	4	15.4	26	100	
Consanguineous marriage status							
No	40	90.9	4	9.1	44		0.70
2nd degree	2	100	-	-	2	100	
3rd degree	-	-	1	100		100	
Substance use							
No	28	84.8	5	15.2	33	100	
Cigarette	10	100	-	-	10	100	0.16
Alcohol	4	100	-	-	4	100	
Radiological examination							
No	30	85.7	5	14.3	35	100	
Direct graph	10	100	-	-	10	100	0.23
Computed tomography	1	100	-	-	1	100	
Magnetic resonance imaging	1	100	-	-	1	100	
Education status							
None	1	100	-	-	1	100	
Primary/secondary school	25	92.6	2	7.4	27	100	0.62
High school/above	16	84.2	3	15.8	19	100	

weeks. The rate of consanguineous marriage was 6.4% (n=3). The maternal and obstetric characteristics are summarized in Table 1.

There was no significant relationship between the presence of consanguineous marriage and pregnancy outcomes (χ^2=0.199, p=0.655) (Table 2).

When the presence of chronic disease was evaluated, it was found that 89.4% (n=42) of pregnant women had an existed chronic disease and the most commons were hypertension (HT, 28%), diabetes mellitus (DM) and hypothyroidism (11.9%, Figure 1). No statistically significant relationship between presence of a chronic disease and pregnancy outcomes was found (χ^2=0.032, p=0.858) (Table 2). The characteristics of illicit drug/alcohol use, radiation exposure or smoking are presented in Table 1.

Approximately one third of pregnant women (29.8%, n=14) used CVMs alone and 70.2% (n=33) reported concomitant medicine exposures (Table 3). The most frequently exposed concomitant medicines were central nervous system drugs (30.3%) and analgesics (18.2%). The proportion of the mothers who used only one group of CVMs and more than one group CVMs were 76.6% (n=36) and 23.4% (n=11), respectively (Table 3). There was no significant difference between using one or more than one group of CVMs and pregnancy outcomes (χ^2=2.787, p=0.095).

The most frequently exposed CVMs were beta adrenergic receptor antagonists (beta-blockers), diuretics, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers (CCB), angiotensin receptor blockers (ARB), antiaggregants, antilipidemics and antiarrhythmics (Table 2). There was no statistically significant difference between groups of CVMs exposed during pregnancy and the termination of pregnancies (p>0.05).

When gestational outcomes were examined, the mean gestational week at delivery was 35.9±8.2 weeks. Of all 47 pregnancies with CVMs exposure, 42 (89.4%) pregnancies resulted in live births. Three (6.4%) pregnancies ended in elective termination and two (4.3%) pregnancies ended in miscarriage (Table 4). No malformation was detected in any of the live births. Neonatal jaundice developed in four (9.8%) infants and one (2.1%) infant needed incubator care.

There was no statistically significant difference between pregnancy outcome and educational status, substance use of radiation exposure during pregnancy (p>0.05). It is stated that while the 21 (44.7%) pregnant women's age was under 35 years, the 26 (55.3%) pregnant women's age was over 35 years. There was no significant difference between maternal age and the termination of pregnancies (χ^2=0.140, p=0.308) (Table 2).

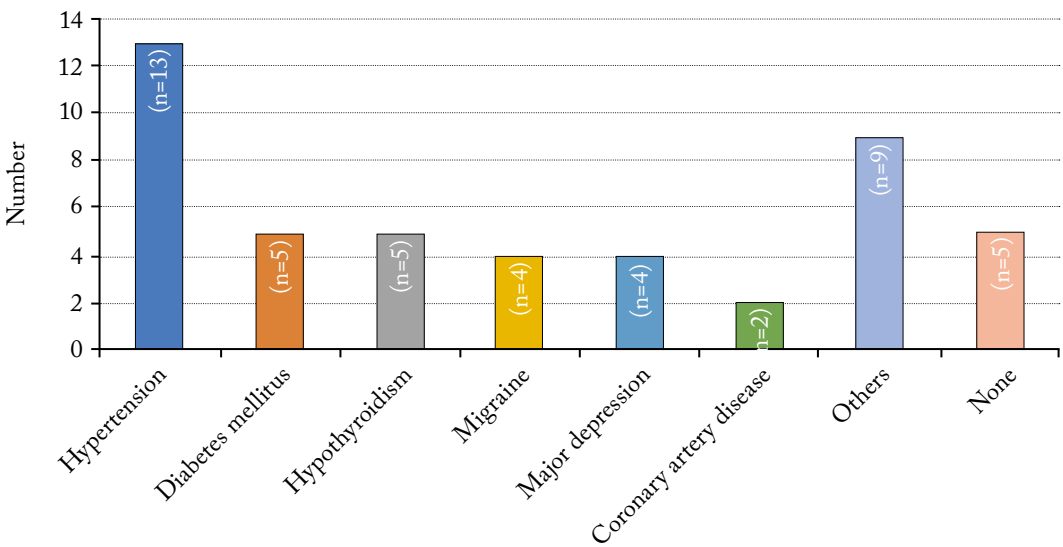

Figure 1. Chronic diseases of the pregnants.

Table 3
Distribution of the medication exposures

Groups of the medicines	n	%
Cardiovascular system medicines (CVSMs)*	55	100.0
Beta blockers	24	43.6
Diuretics	7	12.7
Angiotensin converting enzyme (ACE) inhibitors	6	10.9
Calcium channel blockers	5	9.0
Angiotensin receptor blockers (ARBs)	4	7.3
Antiarrhythmic	3	5.5
Antiaggregants	3	5.5
Hypolipidemics	3	5.5
Only one group CVSM exposure**	36	76.6
More than one group CVSM exposure**	11	23.4
Concomitant medicines***	33	100.0
Central nervous system medicines	10	30.3
Analgesics	6	18.2
Antidiabetics	5	15.2
Antibiotics	3	9.1
Others	9	27.2

CVMs: Cardiovascular medications; * Percentages are based on the total number (55) of CVMs; ** Percentages are based on the total number (47) of pregnants; *** Percentages are based on the total number (33) of concomitant medicines.

Table 4
Properties of the cases ended in miscarriage or elective termination

	Case 11	Case 17	Case 24	Case 36	Case 41
Age (year)	39	36	40	36	31
Gestational week	7	8	6	5	8
Chronic disease	Yes (Hypothyroidism)	Yes (DM)	None	Yes (Hyperthyroidism)	None
Presence of birth defect in recent pregnancies	None	None	None	None	Yes
Consanguineous marriage	None	Yes (3rd degree)	None	None	None
Substance/illicit drug use	None	None	None	None	None
Radiation exposure	None	None	None	None	None
Miscarriage or elective termination	Miscarriage	Elective termination	Elective termination	Elective termination	Miscarriage
Used CVSMs	Metoprolol, spironolakton, amiodarone	Fosinopril sodium	Metoprolol	Metoprolol, diltiazem	Nebivolol
Concomitant medications	None	Metformin hydrochloride, noretisterone	Hydroxyzine hydrochloride	Benzathine benzylpenicillin, acetylsalicylic acid	Duloxetine hydrochloride

DM: Diabetes mellitus; CVSMs: Cardiovascular system medicines.

DISCUSSION

In this study, the demographic characteristics of the pregnant women and pregnancy outcomes who exposed to CVMs during their pregnancies were examined. Although most of the pregnancies resulted healthy live births, two (4.3%) pregnancies ended in miscarriage and three (6.4%) pregnancies were terminated electively. The rates of miscarriage and elective termination in this study are similar to the general population.[7,8]

Cardiac diseases are complicated by approximately 1% of all pregnancies.[9] Pregnant women with or without underlying cardiovascular disease may need to use CVMs due to the physiological changes during pregnancy. This need may be caused by worsening of an existing disease or by a newly developing condition. In general, medications used to treat cardiovascular conditions are antihypertensives, diuretics, antiarrhythmics, anticoagulants and antilipidemics. Moreover, CVMs are preferred in other indications such as migraine, tremor, hyperthyroidism, and anxiety disorders.[9] However, the effects of CVMs on the developing fetus have not been fully understood, yet. Pregnant women need a careful assessment and counselling for CVMs use and their maternal/fetal effects, as well as expert cardiac care in pregnancy. Teratogenicity Information Services are specialized units providing information on the use of medication/substance during pregnancy and lactation period. The TIS of Dokuz Eylul University is a regional unit dedicated to provide information about medication/substance use during pregnancy and/or lactation period since 2011.

Epidemiological data on CVMs exposures during pregnancy are limited. In a study carried out in Germany on drug prescriptions in pregnancy, CVMs accounted for 17% of the medicines prescribed during pregnancy.[10] In another study conducted by Demir et al.,[11] CVMs were responsible for 9.5% of all exposures among the pregnant women admitted to TIS. Göker et al.[12] also reported that the use of CVM ratios were 1.14% and 8.17% in a study evaluating pregnants admitted to two reference hospital in our country. In this study, this rate was 12.6% of the patients applied to the TIS of our institution.

The increasing prevalence of women with adverse pregnancy outcomes (stillbirth, fetal malformations or abortus) due to the increasing maternal age of first pregnancy remains as a challenging issue. Advanced maternal age, particularly over 35 years of age, poses a greater risk of pregnancy complications.[13] Almost 7% of stillbirths are attributed to advanced maternal age (>35 years) worldwide. Also, adolescent pregnancy (<16 years) is associated with an increased risk of adverse pregnancy outcomes.[1,14] In this study, the mean age of pregnant women was 34.0±5.5 years. Additionally, it is noteworthy that four (80%) of five pregnancies ended in miscarriage or elective termination were older than 35 years old (31 to 40 years).

The pregnancy termination rates in consanguineous marriages may be higher due to the increased risk for recessively inherited congenital diseases.[14] In a study carried out in our country, the rate of consanguineous marriage was found to be 12.7%.[11] In this study, the rate of consanguineous marriage was found as 6.4% and all pregnancies with consanguineous marriages resulted in a healthy infant.

On the other hand, the presence of chronic diseases during pregnancy also poses a risk for adverse pregnancy outcomes. The most common chronic diseases in pregnant women are epilepsy, hypertension, diabetes mellitus, psychiatric diseases, and thyroid dysfunctions.[15] In this study, approximately 90% of the mothers had a chronic disease, consistent with the previous reports, and hypertension, diabetes mellitus, and hypothyroidism were the most common diseases. Furthermore, 60% of the mothers whose pregnancies ended in miscarriage or terminated electively had an underlying maternal chronic disease such as hypothyroidism, hypertension, or diabetes mellitus.

Beta-blockers are the most commonly used drugs in the treatment of hypertension in pregnancy and are also frequently used in the management of conditions, such as thyrotoxicosis, hypertrophic cardiomyopathy, and mitral stenosis.[16-19] In this study, in line with the previous reports, the most commonly used CVMs during pregnancy were beta-blockers, diuretics, angiotensin-converting enzyme inhibitors, calcium channel blockers, and angiotensin receptor blockers, respectively. In addition, 80% of the mothers whose pregnancies ended in miscarriage or elective termination used beta-blockers. Beta-blockers can cross the placenta and may cause potential physiological changes in the fetus.[20] Although there are inconsistent data about the relationship between

the use of beta-blockers in pregnancy and the risk of fetal growth restriction, preterm birth, cardiac malformations, and perinatal mortality, there are some reports indicating that direct relationship could not be established due to methodological limitations in the interpretation of available data and presence of confounding factors. However, it is also reported that uncontrolled hypertension during pregnancy may increase the risk of maternal and fetal adverse events such as preeclampsia, premature birth, gestational diabetes, fetal growth restriction, and intrauterine demise.[21-25]

In the current study, amiodarone with concomitant medications was used in a pregnancy ended in miscarriage. Amiodarone and desethylamiodarone, its major metabolite, can cross the placenta and reach 9 to 14% of maternal serum concentrations in fetus.[25] The available data are limited to identify the fetal risk related to amiodarone use in pregnancy. Amiodarone use during pregnancy may also increase the risk of neonatal hypothyroidism with or without goiter and predisposes to neonatal hyperthyroxinemia. It may be also associated with fetal bradycardia, long QT syndrome, ventricular septal defect, prematurity, and death. Amiodarone can be used during pregnancy, if the potential benefit to the mother justifies the possible risk to the fetus. Neonatal electrocardiogram and thyroid functions monitoring are also recommended.[25]

To the best of our knowledge, previous reports are usually limited to the use of CVMs alone during pregnancy, and are lacking the information regarding pregnancy outcomes related to their use with concomitant medications. Furthermore, other confounding factors that may affect pregnancy outcomes such as maternal age, smoking or alcohol use, radiation exposure, and chronic disease should be considered. Our relatively low sample size is the main limitation of this study. Although the number of the cases in this study is limited, our results may contribute to the literature. To achieve more accurate results, further large-scale, prospective studies are needed investigating specific CVMs groups.

In conclusion, based on our study results, it is not possible to establish a definite causality relationship between pregnancy outcomes and CVMs exposure. Nevertheless, we believe that the results of this study can contribute to the existing body of knowledge in this field and provide additional information to the physicians regarding the teratogenic risks of CVMs exposures during pregnancy.

Declaration of conflicting interests

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