Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2019;44(3):705-711
DOI: 10.17826/cumj.490997

ARAŞTIRMA / RESEARCH

Reliability of cardiovascular drug use in pregnancy with clinical pharmacology teratology risk analysis

Klinik farmakoloji teratoloji risk analizi ile gebelikte kardiyovasküler ilaç kullanımının güvenilirliği

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Cukurova Medical Journal 2019;44(3):705-711.

Abstract

Purpose: Maternal cardiac disease is one of the major causes of non-obstetric maternal morbidity and mortality. In the treatment of cardiovascular diseases during pregnancy, it is important to prescribe the drugs that control maternal disease and to minimize potential drug-related risk to the fetus. The aim of this study is to evaluate the teratogenic safety of cardiovascular drugs in pregnancy.

Materials and Methods: We collected data of pregnant women who used drugs for cardiovascular disorders and admitted to our unit for drug analysis between 2014 and 2018. Teratology Information Service assessed the teratogenic risk of drugs. After delivery, a follow-up was conducted with families to obtain the presence of any congenital malformations or adverse neurodevelopmental effects in the infant.

Results: Use of ramipril in the first six weeks of pregnancy resulted in spontaneous abortus at the 10th week. Use of warfarin in the first 12 weeks resulted in exitus at the postnatal fourth day. Telmisartan exposure in the first six weeks resulted in intrauterine death in the 18th gestational week.

Conclusion: Drugs acting on renin-angiotensin system should be discontinued when pregnancy is detected. Warfarin is contraindicated for use in pregnancy except mechanical heart valve pregnancies with high risk of thromboembolism, as it leads to coumarin embryopathy and nervous system anomalies in the first trimester exposures. Pregnant women should be directed to the teratogenic drug analysis and evaluated for possible increase in drug-related congenital malformation risks at early gestational period. Teratogenic risk counselling and follow-up ensures reliable data on drug safety during pregnancy.

Anahtar kelimeler: Teratology; cardiovascular agents; pregnancy; pharmacology

Öz

Amaç: Maternal kardiyak hastalık, non-obstetrik maternal morbidite ve mortalitenin ana nedenlerinden biridir. Hamilelik sırasında kardiyovasküler hastalıkların tedavisinde, maternal hastalığı kontrol eden ilaçların reçetelenmesi ve fetusa karşı potansiyel ilaca bağlı risklerin en aza indirilmesi önemlidir. Bu çalışmanın amacı gebelikte kardiyovasküler ilaçların teratojenik açıdan güvenilirliğini değerlendirmektir.

Gereç ve Yöntem: 2014-2018 yılları arasında kardiyovasküler hastalıklar sebebiyle ilaç kullanan ve ilaç analizi için birimimize başvuran gebelerin verilerini topladık. Teratoloji Bilgi Servisi ilaçların teratojenik riskini değerlendirdi. Doğumdan sonra, infantta olası konjenital malformasyon veya nörogelişimsel bozuklukları saptamak için ailelerle irtibata geçildi.

Bulgular: Hamileliğin ilk altı haftasında ramipril kullanımı 10. haftada spontan abortus ile sonuçlandı. İlk 12 haftada warfarin kullanımı postnatal dördüncü günde eksitusa neden oldu. İlk altı haftada telmisartan maruziyeti 18. gebelik haftasında intrauterin ölümle sonuçlandı.

Sonuç: Gebelik tespit edildiğinde renin-anjiyotensin sistemi üzerine etki eden ilaçlar kesilmelidir. Varfarin, birinci trimester maruziyetinde kumarin embriyopatisi ve sinir sistemi anomalilerine yol açtığı için, yüksek tromboembolizm riski taşıyan mekanik kalp kapakçığı olan gebeler dışında gebelikte kullanım için kontrendikedir. Gebe kadınlar teratojenik ilaç analizine yönlendirilmeli ve erken gebelik döneminde ilaçla ilişkili konjenital malformasyon risklerindeki olası artış için değerlendirilmelidir. Teratojenik risk danışmanlığı ve takibi, hamilelik sırasında ilaç güvenliği konusunda güvenilir veriler sağlar.

Keywords: Teratoloji; kardiyovasküler ajanlar; gebelik; farmakoloji

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Geliş tarihi/Received: 30.11.2018 Kabul tarihi/Accepted: 26.12.2018 Çevrimiçi yayın/Published online: 28.05.2019

INTRODUCTION

Maternal heart disease complicates 1 to 4 % of all pregnancies in developed countries. However, cardiac disorders are major causes of non-obstetric maternal morbidity and mortality[1]. Drug use is frequently seen in pregnant women due to chronic diseases or complaints related to cardiovascular system (CVS). In treatment of cardiovascular diseases during pregnancy, it is important to prescribe the drugs that control the maternal disease and to minimize the potential drug-related risk to the fetus.

Rheumatic heart disease is the most common heart disease in pregnant women in developing countries. However, in developed countries the most common heart disease in pregnant women is congenital heart diseases, since progress in medical and surgical treatment has resulted in large numbers of women with congenital heart disease surviving to child-bearing ages and proceeding with pregnancy. In addition, the age of pregnancy is postponed to older ages. Advanced maternal age brings various systemic diseases, and this result in an incresase in the incidence of hypertension, hypercholesterolemia and coronary artery disease during pregnancy course[2].

Drug use during pregnancy is a worrying issue for the patients and the health professionals. Drug exposure may lead to concerns about the continuation of the pregnancy if the safety of the drug is not known[3]. There is uncertainty in the available data of many drugs, and also clinical experience is still insufficient for the majority of drugs to verify their safety in pregnancy. When performing teratogenic risk analysis, the maternal disease should also be taken into consideration as well as the exposed drugs. The functional class of the mother with cardiac disease may threaten normal intrauterine growth and development of the fetus. A registry study including 1321 pregnant women with structural or ischemic heart disease found strong associations between modified World Health Organization (WHO) class and offspring outcome, especially preterm birth and birth weight[4]. A prospective study of 213 pregnancies in 203 women with congenital heart disease found that risk assessment using modified WHO classification, Zwangerschap bij Aangeboren HARtAfwijkingen (ZAHARA) offspring risk score, CARdiac disease in PREGnancy (CARPREG) offspring risk score, and number of offspring predictors showed increases in class or risk score with increased offspring risk[5].

To expand the human data and advance the discussion relating to the CVS drugs, we aimed to evaluate the safety of their use in pregnancy. In this study, pregnant women who admitted to the Teratology Information Service of Pharmacology for CVS drug exposure were analysed.

MATERIALS AND METHODS

This study was conducted in the hospital of Kahramanmaras Sutcu Imam University Medical Faculty, Kahramanmaras, Turkey. Ethics committee approval was obtained for this study from Medical Faculty Ethics Committee for Clinical Investigations of Kahramanmaras Sutcu Imam University (Approval Date: 26.09.2018; Approval No: 2018/17/15).

A number of twelve pregnant women with cardiac disorders, who admitted to the Teratology Information Service (TIS) between the years 2014 and 2018, were included in the study. Pregnant women were protocoled through individual drug-related teratogenic risk analysis. Using a structured questionnaire at the first contact with TIS, all relevant data including medications, exposure to other agents and co-morbidities were documented by face to face interview with the women. The following information was obtained: obstetric and medical histories, education, treatment indications and details of drug or other exposures, timing in pregnancy, duration, dose and concomitant medications, inadvertent exposure to contraceptives during pregnancy, social or illicit drug use, smoking, ionized radiation exposure, herbal consumption, and symptoms of maternal toxicity related to the agents exposed. 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. After the expected date of delivery, a follow-up was conducted with a structured telephone interview with the women. Details on prenatal diagnostics, course and complications of pregnancy and delivery, gestational age at delivery and neonatal outcome parameters such as birth weight, minor and/or major congenital anomalies and postnatal disorders were obtained.

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 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)[6]. 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

Maternal characteristics and background of participants

Between 2014 and 2018, twelve pregnant women with exposure to CVS drugs during pregnancy were identified. The medications were renin-angiotensin system (RAAS) related drugs: ramipril (2.5 mg/day), trandolapril (2 mg/day), losartan (50 mg/day), telmisartan (80 mg/day) and olmesartan (20 mg/day); antiagregant agents: warfarin (2.5-5 mg/day), acetylsalicylic acid (100 mg/day) and ticagrelor (180 mg/day); beta blocker agents: metoprolol (25-100 mg/day), propranolol (20 mg/day) and bisoprolol (5 mg/day); anti-lipidemic agents: atorvastatin (40 mg/day). RAAS inhibitor drugs were started before conception and discontinued in the first six weeks of gestation, except olmesartan was used till 17th week. The antiagregant agents, warfarin, acetylsalicylic acid and ticagrelor were used before conception during the first trimester. Beta blocker agents, metoprolol, propranolol and bisoprolol were used starting before conception, metoprolol thoughout pregnancy, and propranolol till the 20th week. Acetazolamide was used in the first trimester. Anti-lipidemic agent, atorvastatin was used starting before conception till the second gestational week.

All pregnancies were treated at therapeutic and standard doses, taken orally, 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 concommitant drugs involved in other systemic groups. Detailed maternal characteristics are presented in Table 1.

Table 1. Maternal characteristics of pregnant women

Maternal indication	Gestational age (week)	Drugs	Gestational period (week)	Dose (mg/day)
Chronic renal failure	6	Ramipril	0-6	1x2.5 mg
Mitral valve replacement	11	Warfarin Trandolapril Metoprolol	0-6 0-6 Throughout pregnancy	1x2.5 mg 1x2 mg 1x50 mg
Dysrhythmia	9	Propranolol	0-7	1x20 mg
Peripheral artery disease	14	Warfarin	0-12	1x2.5-5 mg
Hypertension	11	Losartan+ HCT	7-11	1x50/12.5 mg
Hypertension	7	Telmisartan+ HCT	0-6	1x80/12.5 mg
Dysrhythmia	8	Metoprolol Bisoprolol	0-8 0-8	2x50 mg 1x5 mg
Dysrhythmia	6	Metoprolol	0-6	1x25 mg
Coronary artery disease	8	Atorvastatin Ticagrelor Metoprolol Acetylsalicylic acid	0-2 0-2 0-2 0-2	1x40 mg 2x90 mg 1x50 mg 1x100 mg
Hypertension	18	Olmesartan+ HCT	0-17	1x20/12.5 mg
Peripheral artery disease	5	Warfarin	0-5	1X5 mg
Dysrhythmia	21	Propranolol	0-20	1x40 mg

Pregnancy outcomes and the abnormal fetal results after drug exposure

The median gestational age at admission was 8.5 weeks (range: 5 - 21). The median start time of exposures was before conception, and median duration of drug exposure was 42 days (range: 7 day- throughout pregnancy). Patterns of exposure and exposed co-medications are presented in Table 2. The use of ramipril in the first six weeks of pregnancy resulted in spontaneous abortus in the 10th week, the use of warfarin in the first 12 weeks resulted in exitus on the postnatal fourth day and the use of telmisartan in the first six weeks resulted in intrauterine death in the 18th gestational week (Table 3). One infant whose mother was exposed to warfarin and trandolapril for the first six gestational weeks and metoprolol for the whole pregnancy period, was born preterm (34 weeks) and was defined small for gestational age (1750 g).

Table 2. Patterns of maternal exposure and co-medications

Exposed drugs	Start time (week)	Duration (day)	Administration routine	Co-medications
Ramipril	Before conception	42	p.o	Mycophenolate mofetil
Trandolapril	Before conception	42	p.o	Warfarin Metoprolol
Losartan+HCT	7	28	p.o	-
Telmisartan+HCT	Before conception	42	p.o	Citalopram
Olmesartan+HCT	Before conception	119	p.o	-
Warfarin	Before conception	42	p.o	Trandolapril Metoprolol
Warfarin	Before conception	84	p.o	-
Warfarin	Before conception	35	p.o	-
Acetylsalicylic acid	Before conception	14	p.o	Ticagrelor Metoprolol Atorvastatin
Ticagrelor	Before conception	14	p.o	Atorvastatin Metoprolol Acetylsalicylic acid
Metoprolol	Before conception	Throughout pregnancy	p.o	Trandolapril Warfarin
Metoprolol	Before conception	56	p.o	Bisoprolol Olanzapine Levothyroxine
Metoprolol	Before conception	42	p.o	Citalopram Trazodone
Metoprolol	Before conception	14	p.o	Ticagrelor Atorvastatin Acetylsalicylic acid
Propranolol	Before conception	49	p.o	Methimazole Medroxyprogesterone Progestin
Propranolol	Before conception	140	p.o	Methimazole
Bisoprolol	Before conception	56	p.o	Metoprolol Olanzapine Levothyroxine
Atorvastatin	Before conception	14	p.o	Ticagrelor Metoprolol Acetylsalicylic acid

p.o: per oral; HCT: hydrochlorothiazide

Table 3. The abnormal fetal results of the pregnant women after drug exposure

Drugs (daily dose)	Start time (week)	Drug exposure (week)	Co-medication (daily dose)	Co-medication exposure (week)	Results
Ramipril (1x2.5 mg)	Before conception	0-6	Mycophenolate mofetil (2x500 mg)	0-6	Spontaneous abortus on 10.week
Telmisartan +HCT (1x80/12.5mg)	Before conception	0-6	Citalopram (1x20 mg)	0-6	İntrauterin exitus on 18.week
Warfarin (1x5 mg)	Before conception	0-12	-	-	Postnatal exitus on 4.day

HCT: hydrochlorothiazide

DISCUSSION

In this study, we evaluated the safety of CVS system-related drugs to expand human data about their use during pregnancy.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II-receptor blockers (ARBs) are well known to cause fetotoxic defects when used during the second or third trimester due to impaired perfusion of fetal organs, including the kidneys. Typical features include oligohydramnios / anhydramnios, postnatal anuria, hypoplastic skull bones, limb contractions and lung hypoplasia which may lead to fetal or neonatal loss[7,8]. Inadvertent exposure to RAAS inhibitors during the first trimester also may lead to teratogenic effects, altough it may be confounded by maternal disease[9]. In a systematic review, 48 % of 118 fetuses exposed to ACE inhibitors and 87 % of fetuses exposed to ARBs had complications related to the use of these medications [10]. These data also apply to Angiotensin Receptor- Neprilysin Inhibitors (ARNIs) (sacubitril/valsartan), since they contain ARBs[11].

We found that ramipril in the first six weeks of pregnancy resulted in spontaneous abortus in the 10th week and the use of telmisartan in the first six weeks resulted in intrauterine death in the 18th gestational week. Both drugs were used for hypertension and started to be used before conception. After counsilling TIS, pregnant women discontinued the RAAS medications and replaced the drugs with reliable antihypertensive medications as their physicians suggested. Another point is that ramipril was taken concomitantly with mycophenolate mofetil, which is a well-known teratogenic agent during pregnancy. Mycophenolate is associated with an increased risk of congenital malformations such as external ear abnormalities, cleft lip and palate, anomalies of the distal limbs, heart, esophagus, kidney, and nervous system, and first trimester pregnancy loss when used by pregnant women[12]. Hence concurrent drug exposure should be taken into account because it folds teratogenic potential. Telmisartan was taken concomitantly with citalopram. From previous studies, therapeutic use of citalopram is not associated with major birth defects[13].

Hypertension with or without antihypertensive drug treatment is also associated with adverse pregnancy outcome such as poor fetal growth, stillbirth, preterm birth and accounts for a substantial fraction of maternal morbidity compared with normotensive pregnancies [14]. In the case of inadvertent exposure, RAAS inhibitors should be replaced by the agents with proven reliability such as alpha methyldopa and metoprolol[11]. Oral anticoagulant agents cross the placenta and their use in the first trimester were reported to cause embryopathy (limb defects and nasal hypoplasia) in 0.6–10 % of cases[15,16]. Substitution of vitamin K antagonists (VKAs) with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) in the first trimester may eliminate the risk of embryopathy[11]. There is evidence that the embryopathy risk with VKAs is also dose-dependent. The risk was 0.45–0.9 % in pregnancies with low-dose warfarin according to two recent systematic reviews[15,16]. The malformation risk is expressed as 0.7–2 % (ocular and central nervous system abnormalities and intracranial haemorrhage) when VKAs are used in the second and third trimesters. Fetopathy has also been described with UFH but not with LMWH throughout pregnancy[17].

We found that warfarin used in the first twelve weeks of pregnancy without any additional drugs, and resulted in postnatal exitus on the fourth day.

Warfarin was started to be used before conception. After counsilling TIS on the 12th week, pregnant women discontinued the VKA and replaced the drug with reliable LMWH, enoxaparin. LMWH does not cross the placenta; increased risks of fetal bleeding or teratogenic effects have not been reported [18]. LMWH is recommended over UFH for the treatment of acute venous thromboembolism (VTE) and VTE prophylaxis in pregnant women. LMWH may also be indicated in mechanical heart valves [18,19]. Women who require long-term anticoagulation with warfarin and who are considering pregnancy, LMWH substitution should be done prior to conception when possible[18].

It is important to note the limitations of our study. Although we have done interviews face to face with the women at the first contact, we performed telephone interview after delivery. This is the way that all TISs worldwide currently implement. However, pregnant women may not have detailed medical information about their infants as we could not provide the protochol files of the gravida. Physical examination and genetic analysis could not be performed on the living babies. An infant's follow-up should cover the age of 1 or 2 years, since a substantial proportion of congenital anomalies can be missed during the early stage. Postnatally or intrauterine exitus would be examined by autopsy or genetic evalutions in order to investigate the causes of death due to possible malformed patterns. Lastly, we have a limited sample size and lack comparison cohorts. However, this study may be considered as a small contribution to the available data of CVS drugs until epidemiological studies during pregnancy are further completed.

Risk estimation should be individualized depending on the underlying cardiac diagnosis and the medications. Information about medicines and teratogenicity is changing very quickly, and it is misleading only if it is decided according to drug classification systems. In women with moderate or high risk of complications during pregnancy, pre-pregnancy counselling and management during pregnancy should be performed in an expert centre by a multidisciplinary team. TISs are available to provide counseling services to pregnant women about drug exposures.

Yazar Katkıları: Çalışma konsepti/Tasarımı: DAA; Veri toplama: DAA, YE; Veri analizi ve yorumlama: DAA; Yazı taslağı: DAA; İçeriğin eleştirel incelenmesi: DAA, YE; Son onay ve sorumluluk: DAA, YE; Teknik ve malzeme desteği: DAA, YE; Süpervizyon: DAA, YE; Fon sağlama (mevcut ise): yok.
Hakem Değerlendirmesi: Dış bağımsız.

Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

Author Contributions: Concept/Design : DAA; Data acquisition: DAA, YE; Data analysis and interpretation: DAA; Drafting manuscript: DAA; Critical revision of manuscript: DAA, YE; Final approval and accountability: DAA, YE; Technical or material support: DAA, YE; Supervision: DAA, YE; Securing funding (if available): n/a.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

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