Original Article The Eurasian Journal of Medicine Eurasian J Med 2015; 47: 179-83

Systemic Isotretinoin Treatment and Pregnancy: A Longitudinal Cohort Study from Turkey

Sistemik İzotretinoin Tedavisi ve Gebelik: Türkiye'den Bir Retrospektif Çalışma

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Abstract

Objective: Isotretinoin is known to be the most effective treatment of severe and persistent acne. However, one of the most important adverse effects of this drug is known to be teratogenicity. In this regard, tests are administered before initiating the treatment, to assure that an unknown pregnancy is not present and accordingly, patients are advised to take contraceptive precautions during their systemic isotretinoin treatments. On the contrary, many cases of unwanted pregnancies and relevant abortuses have been reported all over the world. In the Turkish literature, only a few reports have been identified about foetal exposure to isotretinoin.

Materials and Methods: In this respect, a study was carried out on fifty-seven female patients, aiming to fulfil the gap of information mentioned above. Female patients, with ages ranging between 14 and 35 years, were recruited to the study and they were administered isotretinoin treatments (cumulative dose of 120 mg/kg) for an average period of 6 months. The patients were followed up during and after the treatment for a total period of 18 months.

Results: As a result, it has been observed that none of the patients got pregnant during the treatment period and relevantly, no abortuses or foetal abnormalities were recorded. Moreover, none of the patients got pregnant 12 months after the termination of the treatment. Additionally, the socio-demographic analysis of the patients indicates that most of the patients were single and 81% of the patients were sexually inactive.

Conclusion: Our findings suggest that the low reportage of teratogenicity due to isotretinoin usage in Turkey could be due to several reasons, such as the sociocultural profile of the female patients undertaking the isotretinoin treatment, and strict adherence to contraceptive methods, and/or underreporting of teratogenic incidents due to lack of studies held in cooperation with obstetricians.

Keywords: Acne, isotretinoin, pregnancy, contraception, teratogenicity

Özet

Amaç: İzotretinoin şiddetli ve inatçı aknenin bilinen en etkili tedavisidir. Ancak bu ilacın en önemli yan etkilerinden biri teratojenik olmasıdır. Bu sebepten tedavi öncesinde bilinmeyen bir gebelik durumu olup olmadığını ortaya çıkarmak için testler yapılmakta ve beraberinde hastaların sistemik izotretinoin tedavileri boyunca kontraseptif önlemler almaları önerilmektedir. Buna rağmen dünyanın pek çok ülkesinden istenmeyen gebelikler ve bununla ilişkili düşükler bildirilmektedir. Ancak Türk literatüründe fetal izotretinoin maruziyeti ile ilgili yalnızca birkaç bildiri tespit edilmiştir.

Gereç ve Yöntem: Yukarıda belirtilen bu veri eksikliğini gidermeye yönelik olarak 57 kadın hasta geriye dönük olarak değerlendirilmiştir. 14-35 yaş arası kadın hastalar ortalama 6 ay boyunca total kümülatif doz olarak 120 mg/kg izotretinoin tedavisi almıştı. Bu hastalar tedavi süresinde ve sonrasında toplam 18 ay boyunca izlenmişti.

Bulgular: Sonuç olarak hiçbir hastanın tedavi sürecinde gebelik yaşamadığı ve dolayısıyla herhangi bir düşük ya da fetal anomali ortaya çıkmadığı gözlendi. Dahası hastaların hiç biri tedaviden 12 ay sonrasında da hamile kalmamıştı. Ek olarak hastaların sosyodemografik incelemesinde hastaların büyük bir kısmının bekar olduğu ve %81 hastanın seksüel olarak aktif olmadığı belirlendi.

Sonuç: Türkiye'de isotretinoin kullanımına bağlı teratojenite bildiriminin düşük olması birkaç sebeple açıklanabilir; örneğin izotretinoin tedavisi alan kadın hastaların sosyokültürel profili, kontraseptif metodlara sıkı uyum ve/veya kadın hastalıkları ve doğum doktorlarıyla koopere çalışmaların yetersizliği dolayısıyla teratojenite olgularının eksik bildirimi.

Anahtar Kelimeler: Akne, izotretinoin, gebelik, kontrasepsiyon, teratojenite

Received: January 18, 2015 / **Accepted:** April 16, 2015
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DOI:10.5152/eurasianjmed.2015.0005

Introduction

Since its introduction in 1982, isotretinoin has been proved effective in the treatment of severe and persistent acne and has a worldwide use [1]. Isotretinoin remains the only effective treatment for this condition, but it has potential adverse effects [2]. The side effects of the drug are generally mild and reversible but there are three specific areas for concern, which are: Mood change, inflammatory bowel disease and risk of teratogenicity [3]. Isotretinoin is highly teratogenic and serious birth defects may occur in the foetuses exposed to isotretinoin during pregnancy. Abroms et al. [4] reported that over 2,000 pregnancies have been exposed to isotretinoin, most resulting in spontaneous or elective abortions since the introduction of the drug in 1982. Although it was released in the Turkish market in 1994, a review of both PubMed and National Turkish Medical Database revealed only a few reports about foetal isotretinoin exposures in Turkey. Considering the young population of Turkey and the presence of thea drug in the market for about 20 years, we thought that sexual attitudes and pregnancy prevention methods of female patients taking isotretinoin treatment should be examined. Thus, a study was conducted, aiming to identify whether the patients were strongly adhering to the contraception methods or if there was underreporting of the unwanted pregnancies.

Materials and Methods

In this retrospective study, we evaluated and observed fifty-seven female patients who were received systematic isotretinoin treatment for acne vulgaris. The participants were given their isotretinoin treatments in a dermatology clinic in İzmir Atatürk Training and Research Hospital, which is a major institution in İzmir, Turkey. The treatments of the participant patients were initiated in January 2012, and they were followed up for a total period of 18 months. The treatment period of each patient was 6 months on average, and it involved a cumulative dose of 120 mg/kg of isotretinoin. Demographic features such as age, education, sexual activity and birth control precautions of the participants were evaluated, and the pregnancies, miscarriages, termination of pregnancy and births given during and after 12 months of the termination of isotretinoin treatment were questioned.

Results

The ages of the participants (female patients receiving isotretinoin treatment) ranged between 14 and 35 years old, with a mean of 21.75 years of age. Most of the patients were educated (university 26.3%; high school59.6%; and elementary 14.3%). Eleven patients (19.3%) were reported to be sexually active, whereas 80.7% reported to be sexually inactive. Most of the sexually active patients (9 of 11) were married. Furthermore, the contraception methods identified were: Protection by male (preservative) (n:5, 45.4%), intrauterine device (n:4, 36.3%) and oral contraceptive pills (n:2, 18.1%) (Table). None of the patients was reported for parallel usage of more than one contraceptive method. The preferred birth control methods among the participants were found to be; preservatives (n:5), intrauterine device (n:4) and oral contraceptives (n:2). Additionally, pregnancy during and 12 months after the treatment period was not observed, hence no abortus or foetal abnormality was observed.

Discussion

Isotretinoin is a known human teratogen. The baby of a mother who has taken isotretinoin for even a few days during pregnancy is under an estimated 20%-35% risk of congenital defects including; craniofacial, cardiovascular, neurologic and thymic malformations. About 30%-60% of children exposed to isotretinoin prenatally have been reported to show neurocognitive impairment, even in the absence of physical defects [5]. However there are a few reports of isotretinoin teratogenicity from Turkey. To the best of our knowledge, there are

Table. Sexual activity, pregnancy prevention methods of the female patients and outcome of isotretinoin treatment in terms of pregnancy

Age	n	Sexually active (n)	Birth control (n)	Pregnancy (n)	Med abortus (n)	Foetal anomaly (n)
14-18	13	0	-	0	0	0
19-22	21	1	1p	0	0	0
23-29	19	7	3p, 2 oc, 2 iud	0	0	0
30-40	4	3	1p, 2 iud	0	0	0

p: preservative; oc: oral contraceptive; iud: intrauterine device

only two case reports of foetal anomaly related with isotretinoin therapy in Turkey [6, 7]. The first case was reported in 2000; with anotia and Taussin-Bing malformation. The other case was reported in 2011; with hydrocephaly, cerebellar vermis hypoplasia, aurica anomalies, micrognatti, patent foramen ovale and ptosis. Few reports found might be reflecting the true low occurrence of teratogenicity, or it might be due to less recognition and underreporting of the cases due to several reasons. It must be bore in mind that when analysing the studies evaluating the side effects of systemic isotretinoin, which were conducted by different groups from Turkey, teratogenicity has never been reported in any of the studies [8-11]. Additionally, studies from Turkey has never revealed isotretinoin as a reason for the termination of pregnancies by the decision of ethic committees [12, 13].

Systemic isotretinoin has been in the Turkish market since 1994 as a patented brand "Roaccutane". Since its introduction in 1994 and the launching of new generic isotretinoin drugs after 2007, isotretinoin can only be prescribed by dermatologist, with an inclusion of a special patient consent form, which is supplied by the manufacturer company. The drug is sold only in the pharmacies with this form and the sale of the drug is controlled by the Ministry of Health. Online selling of isotretinoin is not possible in Turkey. Moreover, all the isotretinoin drugs include warnings both outside and inside of the packages. It must also be noted that other than certain identified drugs, patients do not need to sign a consent form to get a drug from the pharmacies in Turkey. In fact, access to many other teratogenic drugs, such as methotrexate, is not restricted. Therefore, patients who will be undertaking isotretinoin treatment are required to sign official forms to get the drug, and this thought have a striking impact on the patients going under this procedure for the first time in their lives. Thus, the utilization of this simple precaution generally suffices for the patients to be aware of the side effects of the drug during pregnancy. Furthermore, our findings indicate that prescribing systemic isotretinoin treatment to the higher educated people, such as the participants of this study where 85% had high school or university degrees, could have had an impact on the perception of the adverse effects of the drug.

Crijns et al. [14] reviewed the pregnancy prevention programs (PPP) in European countries. Pregnancy incidence was reported as 0.02–0.1 percent in women of childbearing age using isotretinoin. Between 65% and 87% of these pregnancies were terminated. This report indicates that there are failures in the implementation of the PPP in Europe and suggests solutions for improvement of the programs. In North America PPP is called as iPLEDGE, a computer and web system, which tries to ensure that the drug is dispensed only when there is documentary proof that the patient is not pregnant and is using two forms of birth control [15]. Seven years after its introduction, this program significantly reduced the pregnancy rates during isotretinoin treatment. However, the program still does not appear to have solved the issue of foetal exposure to isotretinoin. Shin et al. [16] recently reported 29 foetal exposures out of 9912 courses of treatment with the drug.

In patients with reproductive potential, contraception is recommended one month before initialisation of isotretinoin treatment. The first dose should be initiated after the pregnancy test. Generally, two reliable methods of birth control are recommended [17]. Contraception choices may vary according to the patient's life style, sexual behaviours, as well as cultural, religious and socioeconomic status. Bozkurt et al. [18] reported that the most commonly used method of contraception among women in reproductive age and sexually active women in Turkey was intrauterine devices. In this regard, we also felt the need to consider this issue and evaluated the most common contraception methods preferred by the participant patients of this study. As a result, our study reveals that none of our patients were using two contraception methods together, as recommended in the guidelines of the drug, and the most preferred method of contraception was preservative usage. This finding suggests possible future threats as well as current unrecognized dangers. Moving from this background, we believe that there is still a need for acknowledging patients regarding the significance of the contraception methods and warning them about the relevant dangers.

Furthermore, the data of this study revealed that most of our patients were sexually inactive (81%) and as this patient group was randomly selected as patients starting isotretinoin treatment in January 2012, this may reflect the general profile of the female isotretinoin patients. Additionally, majority of the patients (59.6%) were between 14 and 22 years of age and there was only one sexually active patient among this age group. This finding may be attributed to the fact that age of first coitus in Turkey is higher in comparison to other countries. The mean age of first sexual intercourse is reported as 17.4 in general and 18.4 years of age for girls in Turkey [19, 20]. In accordance with the 2008 Report of the Turkish Ministry of Health, the age of women giving their first birth in Turkey is as 22.3 years [21]. Moreover, the mean age of the participants of this study was 21.27, indicating that participants of this study were younger than the expected age in Turkey to give their first birth. Besides, in comparison to other countries, sexual activity in single women in Turkey is quite low and this may be ascribed due to the conservative structure of the Turkish population. Incidentally, only 3 of our 48 (6.4%) single patients were found to be sexually active, which is also thought to have an impact on the low reportage of reported isotretinoin teratogenicity. Considering the sample of this study, it could be argued that married women do not

generally demand systemic isotretinoin treatment (only 9 out of 57 of the participants were married). Overall, our findings suggest that the age profile, which consists of comparatively younger women undertaking isotretinoin treatment, and age of initiation of sexual activity could be the cause of the low reportage of unwanted pregnancies and relevant foetal exposure to isotretinoin in Turkey.

We would like to acknowledge the limitation of our study due to its small sample size. However, we strongly believe that it may be of population representative quality. Furthermore, we perceive the findings of this study as implications for further study and feel the need for further exploitation with larger samples, which could be more firmly utilized to make generalizations and reach more accurate conclusions. Additionally, we also feel that there may be lack of knowledge about unwanted pregnancies in Turkey due to low reportages from obstetricians. Dissection and curettage (D&C) without presenting a reason is legal under 12 weeks of pregnancy, in Turkey. Therefore, D&C's due to isotretinoin usage during pregnancy may have been underreported. In this regard, we suggest larger studies should be conducted through cooperation with obstetricians so that in utero foetal loses, possible teratogenicity cases due to isotretinoin usages are constantly followed upon and fully reported.

In conclusion, despite the usage of isotretinoin for the treatment of acne vulgaris in thousands of women since its introduction in Turkey in 1994, literature review has revealed that there is a lack of information regarding foetal exposure to isotretinoin. This lack of knowledge has triggered our research and we have conducted a study on fifty-seven female patients, who were administered a cumulative dose of 120 mg/kg isotretinoin for an average period of six months. The patients were followed up and their statuses were recorded during and 12 months after the termination of the treatment, making a total of 18 months. Our findings revealed that there were no unwanted pregnancies and thus no foetal exposure to isotretinoin in Turkey, indicating that this may be due to good patient compliance with therapy and prohibitions. Furthermore, this may be attributed to the young age and marital profile of the patients using isotretinoin, besides late initiation of sexual activity due to the conservative structure of the community. We have reached the conclusion that there is implications for further study comprising larger samples and that these studies may provide stringer evidences if cooperating with obstetricians to keep track of the abortuses due to isotretinoin exposure.

Ethics Committee Approval: Due to the retrospective nature of this study, ethics committee approval was waived.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.O., A.F.K.; Design - S.O., A.F.K.; Supervision - S.O., A.F.K.; Materials - S.O.; Data Collection and/or Processing - S.O., A.F.K.; Analysis and/or Interpretation - S.O., A.F.K.; Literature Search - S.O., A.F.K.; Writing Manuscript - S.O., A.F.K.; Critical Review - S.O., A.F.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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