

ORIGINAL ARTICLE

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Effects of isotretinoin treatment on menstrual cycle in acne patients

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Abstract

Isotretinoin is a vitamin A derivative frequently employed in the treatment of acne. Although it is highly effective in acne treatment, menstrual irregularities are a frequently reported as a side effect. This study retrospectively analyzed the data of 122 female patients undergoing systemic isotretinoin therapy for the treatment of acne. Demographic and clinical information of the patients were recorded. The mean age was 20.2 years and the mean age of onset for menstruation was 13.3 years. Menstrual irregularities were observed during treatment in 65 patients (68.4%), whose menstruation was regular before treatment. Among them, 45.3% (43 patients) started to have less frequent menses, 18.9% (18 patients) started to have more frequent menses, 2.1% (2 patients) started to have prolonged menstrual bleeding, and 2.1% (2 patients) started to have shorter menstrual bleeding during treatment. Hirsutism during treatment was statistically more prevalent in those with menstrual irregularities during treatment ($p=0.02$). In conclusion, our study indicates that patients with regular menstrual cycles prior to isotretinoin treatment developed irregular menstrual cycles after initiation of the medication with a higher prevalence of hirsutism. Further clinical research is necessary to elucidate the mechanism by which isotretinoin affects hormonal imbalances, thereby leading to menstrual irregularities.

Keywords: Isotretinoin, menstrual irregularities, menstrual cycle, acne

Introduction

Isotretinoin is a vitamin A derivative that has been used as the primary treatment for moderate to severe nodulocystic acne. Beyond this, isotretinoin has been used in the treatment of many other conditions like mild acne, acne inversa, inflammatory skin conditions, genodermatoses, and even skin cancers [1]. Isotretinoin is frequently preferred in acne treatment due to its direct impact on factors involved in acne pathogenesis, including the normalization of follicular desquamation, diminishment of sebaceous gland activity, inhibition of Cutibacterium acnes proliferation and anti-inflammatory effects. Notably, isotretinoin significantly reduces comedogenesis by suppressing hyperkeratinization [2-4].

In addition to its potent therapeutic effects and mostly successful treatment outcomes, isotretinoin also carries potential side effects.

The primary caution in isotretinoin use is its teratogenicity, necessitating the use of effective contraceptives during and for three months after therapy. Therefore, managing women of childbearing age requires heightened attention to prevent birth defects [5]. In this group of patients, another important and understudied impact of isotretinoin is on the ovarian reserve, sex hormones, and the menstrual cycle irregularities, which cause severe anxiety in this population undergoing isotretinoin treatment [6]. It is observed that women of childbearing age are experiencing changes in their menstrual periods during the isotretinoin treatment. It has been predominantly reported as oligomenorrhea or amenorrhea in the literature [7-9]. However, further evaluation is needed regarding its effect on the menstrual cycle. In this context, we conducted a retrospective study to investigate changes in women's menstrual periods undergoing isotretinoin treatment.

CITATION

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Material and Methods

The patients who presented to Niğde Training and Research Hospital Dermatology Clinic for acne vulgaris were evaluated from June 2022 to June 2023. Niğde Ömer Halisdemir University Faculty of Medicine Medical Ethics Committee approval was obtained and informed consent forms were waived due to the retrospective nature of the study. Patients who used hormonal contraceptive methods during or within 6 months before the start of treatment and patients with a body mass index (BMI) greater than 30 were excluded from the study. Additionally, patients who reported recent stressful life events, strict diet control, and/or strenuous physical activity, those who had less than a year of menarche, and those with comorbidities were not included in the study. In the group with regular menses, patients with abnormal levels of thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, prolactin, estrogen, and abnormal sonographic findings were excluded. A total of 122 female patients with acne receiving isotretinoin treatment were enrolled in the study. Menstrual irregularities are defined as per the Federation of Gynecology and Obstetrics (FIGO) classification system [10,11]. In the Modified Ferriman-Gallwey (mFG) score, a total score of more

than 7 was used for the diagnosis of hirsutism. The initial dose of isotretinoin was 0.2-0.3 mg/kg/day and was gradually increased according to the patient's tolerance. All patients were examined in person monthly for at least 6 months. Patients who had or developed irregular menses were evaluated with ultrasonography and blood hormone levels for the diagnosis of polycystic ovary syndrome (PCOS), following the diagnostic criteria defined by the PCOS Consensus Workshop Group [12].

Results

Patient characteristics are summarized in Table 1. A total of 119 patients were included in the study, with a mean age of 20.2 (±3.97) years (minimum 15, maximum 37, median 19). The mean age of onset for menstruation was 13.3 (±1.97) years. The mean age of onset for the initiation of isotretinoin was 20 (±3.96) years. Before treatment, 95 patients (79.8%) had regular menses, while 24 patients (20.2%) had irregular menses. Among those with regular menses before treatment, 68.4% (65 patients) started experiencing irregular menses during treatment, whereas 41.7% (10 patients) of those with irregular menses before treatment started to have regular menses during treatment, but there was no statistical difference (p=0.465). Menstrual irregularities after isotretinoin treatment are shown in Table 2.

Table 1. Patient characteristics

Mean age (years)	20.2 (±3.97)
Mean age of onset for menstruation (years)	13.3 (±1.97)
Mean age of onset for the initiation of isotretinoin (years)	20 (±3.96)
Menstruation	
Regular	95 patients (79.8%)
Not regular	24 patients (20.2%)
Number of days between each menstrual cycle	
<28 days	20 patients (16.8%)
28 days	78 patients (65.5%)
>28 days	21 patients (17.7%)
Menstruation duration (days)	5.8 (±1.5)
Marital status	
Married	4 patients (3.7%)
Single	115 patients (96.3%)

Table 2. Menstrual irregularities after isotretinoin treatment

Menstrual cycle (with regular menses before treatment n=95)	
Regular	30 patients (31.6%)
Not regular	65 patients (68.4%)
Menstruation changes	
Less frequent menses	43 patients (45.3%)
More frequent menses	18 patients (18.9%)
Prolonged menstrual bleeding	2 patients (2.1%)
Shorter menstrual bleeding	2 patients (2.1%)
Mean isotretinoin dosage with menstrual irregularity (mg)	18.5 mg
Mean month menstrual irregularity occurred	2 months

The group of patients whose menses were regular (without hormonal and sonographic abnormalities) before treatment (95 patients) were evaluated. Among them, 31.6% (30 patients) remained to have regular menses, 45.3% (43 patients) started to have less frequent menses, 18.9% (18 patients) started to have more frequent menses, 2.1% (2 patients) started to have prolonged menstrual bleeding, and 2.1% (2 patients) started to have shorter menstrual bleeding during treatment.

Only the group of patients whose menses were regular before treatment (95 patients) was evaluated and then divided into two groups: group A (patients who remained to have regular menses during treatment) and group B (patients who developed

any type of menstrual irregularity during treatment). There was no statistical difference between the mean age ($p=0.43$), mean age of onset of isotretinoin ($p=0.46$), mean age of onset for menstruation ($p=0.82$), or mean duration of menstrual bleeding before treatment ($p=0.16$). Hirsutism during treatment was statistically more prevalent in group B ($p=0.02$) (Table 3). When only group B was evaluated, the mean month of the onset of menstrual irregularity after treatment started was $2.2 (\pm 1.45)$ months, and the mean dose by weight per day when the menstrual irregularity started after treatment was 0.324 mg/kg/day . In 83.1% (54 patients) of group B, the menstrual irregularities resolved spontaneously.

Table 3. Relationship of parameters with menstrual change

	Patients with regular menses during treatment	Patients with irregular menses during treatment	p
Mean age (years)	20.77	20.08	0.432
Menarch age (years)	13.37	13.26	0.822
Duration of menstrual bleeding before treatment (days)	5.57	5.98	0.168
Mean age of onset of isotretinoin	20.53	19.91	0.468
Hirsutism			
No	27	45	0.028*
Yes	3	20	

* $p<0.05$ significant difference, $p>0.05$ no significant difference; t (t) test

Discussion

There have been several reports that evaluated the effect of isotretinoin on the endocrine system. Isotretinoin treatment can adversely affect the pituitary-ovarian axis. In the study conducted by Feily et al., hormone levels before and after isotretinoin were compared and a significant decrease in FSH, LH and estradiol levels were detected after treatment [13,14]. Accordingly, amenorrhea and oligomenorrhea have been frequently reported in the literature in menstrual irregularities due to isotretinoin treatment. In our study, irregular menstruation was detected with isotretinoin treatment in 66.3% of patients who had regular menstrual cycles before treatment. This rate was higher than similar studies in the literature [6,15,16]. This difference may result from variations in study structures, including more frequent follow-up examinations and a longer follow-up period in our study. Additionally, the fact that the isotretinoin treatment dose ($0.2\text{-}0.3 \text{ mg/kg/day}$) in our study was lower than in other studies may be also contributory in these different results. Although the development of menstrual irregularity with treatment is a worrying situation for patients, this side effect resolved spontaneously in 83.1% of the patients. This finding is also supported by the study conducted by Kwon et al., in which all menstrual irregularities resolved spontaneously [6].

In the study conducted by Alhetheli et al., it was reported that individuals using isotretinoin for more than ten months and

those treated with doses ranging $0.7\text{-}1.2 \text{ mg/kg/day}$ experienced menstrual irregularities more frequently [15]. In our study, it was observed that the average isotretinoin dose associated with patients experiencing menstrual irregularities was 18.5 mg and on average menstrual irregularities started in the second month of treatment. The reason for this difference may be due to the frequency of follow-up of the patients, marital status or different age groups.

While our study did not find a statistically significant result, we observed that 41.7% of individuals with irregular menstrual periods experienced a regular menstrual cycle after receiving isotretinoin medication. This effect of isotretinoin which is a vitamin A derivative, can be supported by the study of Politzer et al. showing the effect of vitamin A in the treatment of menorrhagia [17].

The development of hirsutism was found to be significantly higher in patients with menstrual irregularities due to the use of isotretinoin. This finding is correlated with the data in the study of Tükenmez et al. and Aktar et al. [16,18]. However, in the study conducted by Acmaz et al. with PCOS patients, a decrease was found in the FG scores of the patients after isotretinoin treatment [19]. Additionally, isotretinoin has intricate effects on androgenic hormone levels and can increase dehydroepiandrosterone sulfate (DHEAS) levels, which can explain the development or worsening of hirsutism [14]. Comprehensive studies involving more patients are needed to clarify this issue.

Our research has some limitations. First of all, the retrospective design of our study can be considered a limitation because it may cause bias in patient selection. Second, as a single-center study, the sample size was relatively limited. Lastly, we did not assess the severity of acne experienced by participants.

Conclusion

In conclusion, while menstrual irregularity is a common side effect of isotretinoin that usually resolves spontaneously, further research is warranted to clarify this association and the effect of isotretinoin treatment on hirsutism.

Conflict of Interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical Approval

IRB approval status: Reviewed and approved by Niğde Ömer Halisdemir University Faculty of Medicine IRB; approval #2023/79.

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