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Title of article: **Evaluation of hirsutism and hormonal parameters in acne vulgaris patients treated with isotretinoin**

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Running Head: Effect of isotretinoin on hirsutism and hormones

EVALUATION OF HIRSUTISM AND HORMONAL PARAMETERS IN ACNE VULGARIS PATIENTS TREATED WITH ISOTRETINOIN

ABSTRACT

Background: Although the effect of isotretinoin use on hormonal changes in acne pathogenesis is not fully known, there are limited studies on its effects on the development of hirsutism. In this study, it was aimed to evaluate the effect of isotretinoin use on hirsutism and hormonal parameters in patients with acne vulgaris.

Methods: In this study, 30 female acne patients and 30 healthy females were evaluated prospectively. Menstrual irregularity, LH, FSH, Prolactin, Progesterone, 17-OH Progesterone, Estradiol, Total testosterone, DHEA-S, Insulin, Glucose, TSH levels, Ferriman-Gallwey (FG) score and ultrasonography (USG) findings of control group and patient group were recorded.

Results: Pre-treatment progesterone ($p = 0.007$) and estradiol ($p = 0.001$) levels of the patients were statistically lower than the control group. In the patient group, menstrual irregularity ($p <001$) and FG hirsutism score at the 3rd month of treatment were significantly higher than before treatment. In 10% of the patients, there were abnormal findings on pelvic USG in the third month of treatment.

Conclusion: In our study, it could not be revealed that isotretinoin has a significant effect on pituitary, adrenal hormones and insulin resistance. We found that three months of isotretinoin treatment caused an increase in menstrual irregularity and FG hirsutism score.

Keywords: acne vulgaris, hirsutism, isotretinoin, polycystic ovary syndrome

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What' s known: The effect of isotretinoin on hormonal changes has not been fully elucidated, and different results have been observed on hormones in different studies on this subject. It is also thought that isotretinoin may cause menstrual cycle irregularity by affecting many hormones.

What' s new: In our study, it has not been demonstrated that isotretinoin has a significant effect on pituitary, adrenal hormones and insulin resistance. But isotretinoin increased Ferriman Gallwey scores and also caused menstrual irregularity.

EVALUATION OF HIRSUTISM AND HORMONAL PARAMETERS IN ACNE VULGARIS PATIENTS TREATED WITH ISOTRETINOIN

Although acne vulgaris is a disease of adolescence and young adulthood, it is a chronic inflammatory skin disease that can be also observed in the neonatal, infantile, prepubertal period and middle age [1]. The etiology of acne is not known precisely and it is thought to be multifactorial. Apart from androgens, it is known that many hormones such as estrogen, progesterone, prolactin, thyroid hormones, growth hormone, insulin and insulin-like growth factor-1 (IGF-1) also play a role in the development and differentiation of the sebaceous glands. Abnormal expression of one or more of these factors affects acne formation [2]. The role of insulin in the development of acne has been supported by the high prevalence of acne in patients diagnosed with polycystic ovary syndrome (PCOS) [3]. The effect of isotretinoin on hormonal changes has not been fully elucidated, and different results have been observed on hormones in different studies on this subject [4,5]. It is also thought that isotretinoin may cause menstrual cycle irregularity by affecting many hormones. Patients with PCOS often have high levels of IGF-1 and insulin, as well as insulin resistance, high dihydroepiandrostenedione sulphate (DHEA-S) levels, hyperandrogenism, irregular menstrual cycle, acne, and hirsutism. The most common finding of hyperandrogenism in PCOS is hirsutism and it is seen between 60-90% [3,5]. Hirsutism is the presence of excessive terminal hair in androgen sensitive areas. It is seen in 5-15% of women [6].

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Although the amount of hair follicles does not change throughout life, the size and type of hair changes over time. Many factors, mainly androgens, play a role in this changing process [7].

The aim of this study was to evaluate the effects of 3 months of 0.5mg/kg/day isotretinoin treatment on testosterone, progesterone, estradiol, prolactin, glucose, insulin, thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), luteinizing hormone (LH) and Dihydroepiandrostenedionsulphate (DHEA-S) levels and hirsutism in patients with severe or treatment-resistant acne.

MATERIALS AND METHODS

Van Yuzuncu Yil University Faculty of Medicine Medical Ethics Committee approval was obtained for the study (Ethics Committee Decision No: 03, Approval date: 13.02.2019). Informed consent form was obtained from all participants. Thirty female patients aged 18-40 years, who were diagnosed with severe to moderate acne vulgaris and were treated with isotretinoin, were enrolled in this study prospectively. The control group included 30 healthy volunteer women who applied for cosmetic complaints other than hirsutism, did not have acne or any other inflammatory skin disease, did not have a systemic disease, did not use any medication that could affect ovarian hormones or cause hirsutism. Those who were not in the 18-40 age range, who were pregnant, who had additional disease, who made laser-epilation, had known endocrinopathy, who used a drug that could affect ovarian hormones or cause hirsutism, who used previous isotretinoin treatment and who had a systemic disease were not included in the study. Menstrual irregularity, hormone tests, Ferriman-Gallwey score, and USG findings of the patient group before and after 0.5mg / kg / day isotretinoin treatment and of the control group were recorded. Hormonal values (LH, FSH, Prolactin, Progesterone, 17-OH Progesterone, Estradiol, Total testosterone, DHEA-S, Insulin, TSH) were measured from fasting blood samples taken from patients using isotretinoin before treatment and in the third month of treatment. Hormone tests were performed on 2-3rd days of menstruation.

In pelvic ultrasonography, ovarian stromal volume over 10 ml and presence of more than 12 peripheral cysts in each ovary were defined as abnormal findings [8].

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Statistical analysis

The data were evaluated with the SPSS 21.0 (SPSS Inc, Chicago, IL, USA) statistical program. Whether the variables showed normal distribution was evaluated using visual (histogram) and analytical methods (Kolmogorov-Simirnov test). Descriptive statistics for continuous variables are expressed as mean, standard deviation, minimum and maximum values, while categorical variables are expressed as numbers and percentages. The significance of the difference between the groups in terms of means was evaluated with Student T test and the significance of the difference in terms of median values with the Mann-Whitney U test. Nominal variables were evaluated with the Pearson Chi-square or Fisher's exact test. P <0.05 was considered significant in statistical evaluation.

RESULTS

The mean age of the patients included in the study was 22.1 ± 3.4 (18-31 years), while the mean age of the control group was 23.4 ± 3.4 (18-29 years). There was no statistically significant difference in age between the two groups (p = 0.160).

Menstrual irregularity was observed in 10 (33.3%) patients in the third month of isotretinoin treatment. In the patient group, pre-treatment FG score was 1.97 ± 2.47, while it was 2.37 ± 2.73 after treatment. (p<0,05) While there were no cases with an FG score ≥8 at the before treatment, there were five (16.7%) cases with an FG score ≥8 at the 3rd month of isotretinoin treatment. However this cases had higher basal FG scores according to other patients. In addition, 6 (20%) patients had increased hair growth with FG score <8 at the 3rd month of treatment. In the patient group, there were no abnormal findings in pelvic USG before treatment, while there were abnormal findings in three (10%) cases in pelvic USG at the 3rd month after treatment. There were no systemic disease or menstrual irregularity and abnormal USG findings in the control group.

In the patient group, menstrual irregularity (p <001) and FG hirsutism score (p<0,05) at the 3rd month of isotretinoin treatment were statistically significantly higher than before treatment. The demographic and clinical characteristics of the patient group are given in Table 1.

Laboratory parameters of the patient group before and after treatment are given in Table 2. In the patient group, while pre-treatment progesterone level was statistically significantly higher than

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after treatment ($p<0.001$); there was no statistically significant difference between pre-treatment and post-treatment glucose ($p=0.188$), insulin ($p=0.245$), TSH ($p=0.241$), FSH ($p = 0.241$), LH ($p = 0.237$), prolactin ($p=0.241$), estradiol ($p=0.543$), total testosterone ($p=0.311$), DHEA-S ($p=0.237$) and 17-OH progesterone ($p=0.278$) levels (Table 2).

While progesterone ($p = 0.007$) and estradiol ($p = 0.001$) levels were statistically lower in the patient group than in the control group; there was no statistically significant difference between glucose, insulin, TSH, FSH, LH, prolactin, total testosterone, DHEA-S and 17-OH progesterone levels (Table 3).

At the third month of treatment, five patients had an FG score ≥8 and 25 patients with an FG score <8. One of five patients with an FG score ≥8 at the third month of isotretinoin treatment and two of the 25 patients with an FG score of <8 had abnormal findings (increase in ovarian stromal volume and multiple peripheral cysts) on USG at the third month.

There was no statistically significant difference between the patients with or without menstrual irregularity at the 3rd month of their treatment and the patients with high (≥8) or not (<8) FG scores in the 3rd month of their treatment ($p> 0.05$).

DISCUSSION

In women, androgens are mainly synthesized in the ovary and adrenal gland. LH and FSH released from the pituitary gland are gonodotropins that regulate steroid synthesis. DHEA-S, androstenedione and testosterone are serum androgens. DHEA-S is entirely of adrenal origin [9]. The role of androgens in the etiopathogenesis of acne vulgaris is well known. Testosterone, DHEA-S and DHT stimulate sebaceous gland growth and sebum production. Estrogens have the opposite effect; they inhibit the secretion of androgens, modulate genes involved in the growth of the sebaceous gland and inhibit their functions [10]. In the sebaceous gland, the expression of androgen receptor (AR), especially estrogen receptor alpha and progesterone receptors, and progesterone receptor, especially progesterone receptor B, has been shown. Low estrogen levels in acne patients have been found in several studies. It is suggested that exogenous estrogens have a

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beneficial effect on acne. This is also supported by the fact that acne is most common in adolescence due to low estrogen levels during the first few menstrual cycles [11,12].

The action of progesterone appears to be more complex in acne, as premenstrual changes are associated with peak levels of progesterone, but natural and artificial progesterone exhibit both antiandrogenic activity and androgenic activity [12]. In the literature, there are differences between studies showing the relationship between acne vulgaris and serum progesterone levels. Progesterone may increase acne lesions by increasing sebum secretion and keratinocyte proliferation [13,14]. In a study conducted by Bakry et al. with 60 acne patients, total testosterone and progesterone levels were found to be higher in the patient group than the control group [15]. In our study, while progesterone and estrogen levels were significantly lower in patients with acne vulgaris before treatment, no significant difference was found between total testosterone levels.

Isotretinoin is a highly effective treatment for severe nodulocystic acne. Although the mechanism of action is not fully understood, isotretinoin is thought to be isomerized to ATRA, which then interacts with retinoid receptors [16]. There is increasing evidence that the main mode of action of isotretinoin in acne is sebocyte apoptosis resulting in sebum suppression. Isotretinoin is stated to increase the expression of p53 and Forkhead box protein-1 (FoxO-1) and Forkhead box protein-3 (FoxO-3), which are transcription factors that increase apoptosis. Isotretinoin decreases serum IGF-1 levels. IGF-1 controls gonadal and adrenal androgen synthesis and induces 5 alpha reductase, thus stimulating the quantity and quality of androgen receptor (AR) ligands [17].

It has been previously reported that blood glucose levels are higher in patients with acne vulgaris compared to the healthy group. The increase in blood glucose stimulates insulin secretion. This situation decreases the proteins that bind to IGF-1. Thus, the effect of IGF-1 on cell proliferation is facilitated. Insulin also stimulates sebum production by stimulating androgen synthesis, and its release is associated with acne severity [2,18,19]. In a study conducted by Kaymak et al. in which patients with acne at a young age were included, blood glucose and insulin levels did not differ significantly from the healthy group. In the same study, no link was found between insulin level and acne severity [20]. Treatment with 13-cis-retinoic acid may be associated with impaired glucose metabolism, including hyperglycemia. Koistinen et al. reported in their study that 13-cis-retinoic acid decreased whole body insulin sensitivity [21]. In our study, there was no significant

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difference between the patient and control groups in terms of insulin and glucose levels. In addition, no significant effect of isotretinoin on these parameters was detected.

Few clinical studies have investigated the effects of retinoids on pituitary hormone levels. In another study of 47 patients aiming to observe the effect of isotretinoin on the pituitary-adrenal axis, Karadağ et al. found that 3-month isotretinoin treatment significantly reduced cortisol, ACTH, LH, fT3, total testosterone and prolactin levels in acne patients [16]. Çetinözman et al. reported that isotretinoin improves acne in all patients without affecting androgen levels [22]. Feily et al. found that serum testosterone, prolactin, and DHT levels were significantly reduced in patients who received 20 mg of isotretinoin therapy for 3 months. In contrast, the authors reported that serum DHEA-S levels increased significantly after isotretinoin treatment, and that luteinizing hormone, follicle-stimulating hormone, free testosterone, and 17-hydroxyprogesterone did not show any significant changes after treatment [23]. Öztürk et al. found that the mean FSH, LH and estradiol levels were significantly decreased after treatment in 32 patients with acne vulgaris who received cumulative isotretinoin treatment [24]. In a study by Cinar et. al on female fertility of isotretinoin with 79 patients, no significant difference was found in FSH and LH levels at the 6th month of treatment [25]. Saljoughi et al. reported that after treatment with isotretinoin in acne patients, mean serum LH levels increased significantly, but FSH, estradiol, and total and free testosterone serum levels did not change statistically [26]. In another study conducted by Karadağ et al. on 105 patients, LH, prolactin, total testosterone, ACTH, cortisol, IGF-BP3, IGF-1, GH and fT3 levels were shown to be significantly decreased after 3 months of isotretinoin treatment. Authors reported that isotretinoin affects pituitary hormones in all three different doses and that differences in pituitary hormones are more pronounced in high-dose therapy [27]. Acmaz et al. in a study in which all hormonal evaluations were made in the follicular phase of the menstrual cycle, showed that there was a significant decrease in free testosterone level after 6 months of isotretinoin treatment, but there were no significant difference in fT4, fT3, TSH, FSH, LH, Estradiol, insulin, IGF-1, SHBG, DHEA-S and total testosterone levels [17]. In our study, after 3 months of treatment, only the progesterone level among the hormones measured in the follicular phase decreased significantly compared to the pre-treatment. To the best of our knowledge, there are no studies reporting a significant decrease in progesterone level after isotretinoin treatment.

The smooth functioning of the menstrual cycle depends on the normal and balanced functioning of many hormone levels [28]. It has been suggested that retinoids have an important role in

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endometrial growth and secretory differentiation, and serum vitamin A levels were found to be low in patients with menorrhagia. Retinoids have also been shown to inhibit endometrial fibroblast and epithelial cell proliferation. It has also been reported that endometrial adenocarcinoma cells recover with isotretinoin treatment. Several studies investigating the side effects of isotretinoin have reported changes in hormone parameters and menstrual cycle [29]. Therefore, it can raise great concern about the possibility of menstrual irregularities or permanent irregularities during isotretinoin therapy, including amenorrhea. In a study conducted by Kwon et al. on 40 patients, 20% of menstrual irregularities were observed after isotretinoin treatment given for at least 4 months at a dose range of 0.7-1.2 mg / kg / day. It has been reported that the menstrual cycle returns to normal in all patients after isotretinoin discontinuation [30]. Karadağ et al. reported that in 28.8% of the patients using isotretinoin started menstrual irregularity during the treatment [31]. Bruno et al. reported that 15% of female patients taking isotretinoin had menstrual irregularities during the 4-month treatment period. Menstrual irregularity was generally seen as a delay or skipping of the menstrual period [32]. Bener et al. found no statistically significant difference before and during isotretinone treatment in the mean menstrual cycle interval, menstrual bleeding times, and the amount of pad use during a cycle. Authors reported that there was no change in serum FSH, LH, TSH, fT3, fT4, prolactin, 17-OH Progesterone, DHEA-S, free and total testosterone levels in patients with menstrual cycle irregularities [29]. In our study, menstrual irregularity was observed in 10 (33.3%) patients in the third month of isotretinoin treatment.

Hirsutism is excessive terminal hair growth in women. Although hirsutism is often associated with hyperandrogenemia, half of women with mild symptoms have normal androgen levels. The most widely accepted scoring method is the FG scale and values of ≥8 are considered hirsutism. The FG scale is limited by its subjective nature and not disclosing all androgenic areas (eg, sideburns, hips), focal hirsutism, the use of continuous cosmetic measures, or its effect on the patient's well-being [33]. In a study conducted by Demirci et al. on 56 patients, 16 patients had menstrual irregularity and 11 patients had increased hair growth in the 6th month of isotretinoin treatment. According to the hirsutism scoring, it was accepted that only one patient developed hirsutism. Increased hair growth was also observed in five of 16 patients with menstrual irregularities [28]. In a study conducted by Açmaz et al. with 40 female patients diagnosed with PCOS complicated by severe cystic acne, isotretinoin treatment was found to significantly reduce FG score, free testosterone, insulin level, hemoglobin level, acne score and ovarian volume [17] . In the patient

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group in our study, menstrual irregularity and FG score at the 3rd month of treatment were found to be statistically significantly higher than pre-treatment menstrual irregularity and FG score. In addition, hair growth was detected clinically in 11 cases. These results may suggest that although the level of androgen hormones did not change, the sensitivity of androgen receptors to isotretinoin increased peripherally, leading to an increase in FG hirsutism score. Our study supports the study of Demirci et al. which reported that isotretinoin increases the FG hirsutism score. In addition, isotretinoin may cause menstrual disorders by affecting the retinoic acid receptors and estrogen receptors on the endometrium.

Polycystic ovary can be seen in 20% of healthy women ultrasonographically. In addition, PCOS is a disease associated with insulin resistance, obesity, dyslipidemia, hypertension, type 2 diabetes mellitus and glucose intolerance. In ultrasonography, ovarian stromal volume over 10 ml and presence of more than 12 peripheral cysts in each ovary are defined as polycystic ovary [8]. Abali et al. reported that isotretinoin exposure may be responsible for decreased ovarian reserve and toxic effects on rat ovaries [34]. In our study, polycystic ovary finding was detected in three patients.

Progesterone and estrogen levels were found to be lower in our patients. A significant decrease in progesterone level was achieved after isotretinoin treatment. Isotretinoin may have revealed this effect by affecting the binding of progesterone to circulating SHBG. It may also increase the sensitivity of peripheral androgen receptors to androgen, leading to an increase in the FG score. The increase in the FG score contrasts with the properties of isotretinoin such as antiandrogenic and decrease in androgen receptor sensitivity, which has been achieved as a result of research so far. In the literature, there is little data that isotretinoin causes increased hair growth in large patient populations where many side effects are investigated. Further studies in which hormonal tests are also controlled are needed regarding this side effect. Menstrual irregularity may be due to the effect of isotretinoin on estrogen-progesterone receptors on the endometrium.

The low number of cases, the fact that the study was conducted in a single center, the SHBG measurements could not be made and the cumulative isotretinoin dose was not reached are the factors that limit our study.

In conclusion, it has not been demonstrated that isotretinoin has a significant effect on pituitary, adrenal hormones and insulin resistance. Isotretinoin increased FG scores and caused menstrual

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irregularity. However, further studies are required regarding the permanence of these effects after treatment.

Conflicts of interest: None

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Data availability

The datasets generated and/or analyzed during this study are available from the corresponding author on reasonable request.

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Table Legends:

Table 1: Demographic and clinical characteristics of the patient group.

Table 2: Comparison of the laboratory parameters of the patients before and 3 months after isotretinoin treatment.

Table 3: Comparison of basal laboratory parameters of the patient and control groups.

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Table 1

		Patient group (n=30)	
Demographic and clinical characteristics		(n) (%) Mean±SD –	**p**
Age		22,1±3,4	
Family history		9 (30)	
Menstrual irregularity	Basal	0 (0)	
			< 0.001
	3rd month	10 (33.3)	
Acne severity	Moderate	21 (70)	
	Severe	9 (30)	
Ferriman-Gallwey hirsutism score ≥8	Basal	0 (0)	
			< 0.023
	3rd month	5 (16.7)	
Abnormal findings on pelvic USG	Basal	0 (0)	
			0.083
	3rd month	3 (10)	

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Table 2

Parameters	Basal Mean±SD	3rd month of treatment Mean±SD	*p*
Glucose (mg/dL)	86.3±10.1	87.4±8.0	0.188
TSH (mIU/mL)	1.4±0.7	1.4±0.9	0.241
Insulin (µIU/mL)	13.9±11.3	13.0±9.6	0.245
FSH (mIU/mL)	4.8±1.4	5.1±1.4	0.241
LH (mIU/mL)	4.1±2.0	6.1±5.8	0.237
Prolactin (ng/mL)	16.3±5.3	16.9±8.0	0.241
Progesterone (ng/mL)	0.5±1.2	0.3±0.5	**< 0.001**
Estradiol (pg/mL)	39.9±32.5	47.6±44.8	0.543
Total testosterone (nmol/L)	1.0±0.3	1.0±0.3	0.311
DHEA-S (µg/dL)	344.6±135.1	360.1±115.6	0.237
17-OH progesterone (ng/mL)	1.7±0.9	1.7±0.7	0.278

TSH: Thyroid stimulating hormone,

FSH: Follicle stimulating hormone **LH:** Luteinizing hormone

DHEA-S: Dihydroepiandrostenedione sulphate.

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Table 3

Parameters	**Patient group** Mean±SD –	**Control group** Mean±SD –	***p***
Glucose (mg/dL)	86.3±10.1	91.0±9.8	0.075
TSH (mIU/mL)	1.4±0.7	1.4±0.8	0.870
Insulin (µIU/mL)	13.9±11.3	11.8±8.5	0.420
FSH (mIU/mL)	4.8±1.4	4.3±1.8	0.253
LH (mIU/mL)	4.1±2.0	5.5±4.0	0.111
Prolactin (ng/mL)	16.3±5.3	15.8±7.9	0.752
Progesterone (ng/mL)	0.5±1.2	2.7±4.1	**0.007**
Estradiol (pg/mL)	39.9±32.5	88.3±65.0	**0.001**
Total testosterone (nmol/L)	1.0±0.3	1.2±0.4	0.095
DHEA-S (µg/dL)	344.6±135.1	369.0±150.8	0.512
17-OH progesterone (ng/mL)	1.7±0.9	2.2±0.8	0.071

TSH: Thyroid stimulating hormone,

FSH: Follicle stimulating hormone

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DHEA-S: Dihydroepiandrostenedione sulphate.

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