Original paper

The clinical predictors of biochemical hyperandrogenemia and its relation to treatment resistance in women with acne

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Abstract

Introduction: The prevalence of biochemical hyperandrogenemia (BHA) in female acne varies across studies. While certain phenotypic features may suggest hormonal evaluation, clinical predictors of BHA are unclear. Furthermore, the predictors of treatment outcome remain inconclusive, and despite common belief, no strong evidence links BHA to treatment resistance.

Aim: To identify determinants of BHA and treatment response in female acne.

Material and methods: Female acne patients who underwent hormonal tests (androstenedione, DHEAS04, E2, FSH, LH, free testosterone, prolactin, SHBG, TSH, total testosterone, and 17-OHP) from January 2020 to September 2022 were analysed for associations of clinical parameters with BHA, PCOS, and treatment resistance.

Results: Among 86 females (mean age: 24, range: 14–41), acne categories were as follows: persistent (46.5%), adult-onset (26.7%), recurrent (19.8%), and adolescent (7%). Clinical and BHA rates were 65.1% and 70.9%, respectively. The most common elevated hormones were 17-OHP (65%) and androstenedione (40%). Hirsutism and truncal acne were associated with BHA. High DHEAS04 and menstrual irregularity were linked to the persistent category, and 17-OHP elevation was related to a chronic course. PCOS prevalence (17.4%) was associated with high DHEAS04, Free Androgen Index, TT, low E2, and hirsutism. Persistent/recurrent acne and hirsutism were associated with treatment failure.

Conclusions: The persistent course and prolonged duration of acne in females, combined with hirsutism and truncal location, are associated with BHA. Patients without androgenic signs may have BHA, and PCOS diagnosis can be established through appropriate referral. Treatment response does not correlate with hormone levels; however, prolonged duration/persistent course and hirsutism predict poorer outcomes.

Key words: acne, androgens, hormones, polycystic ovary syndrome, treatment.

Introduction

The association between androgens and acne is well-known [1–5]. Routine hormonal evaluations are not typically performed for all acne patients; however, underlying androgen excess is suspected when symptoms such as hirsutism and menstrual irregularity are present. However, serum androgen elevation can occur without clinical hyperandrogenemia [6–8], and conversely, clinical hyperandrogenemia can be present without biochemical hyperandrogenemia (BHA) [1].

Likewise, hyperandrogenemia cannot be predicted based on the severity of acne as serum androgen levels do not correlate with acne scores [1, 2, 6]. Therefore, it remains unclear which clinical features indicate serum hyperandrogenemia.

Moreover, evidence suggests that the course of acne may be associated with BHA. Adult female acne has two main subtypes according to its progress. "Persistent acne" is the continuation of acne from adolescence to adulthood, whereas "adult-onset acne" is the occurrence of acne for the first time after the age of 25 years [9]. A third type, "recurrent acne", is less well-characterized and refers to acne that disappears after adolescence but recurs after several years [9–12]. The relationship between acne categories and hyperandrogenemia remains unclear. Some authors associate hyperandrogenemia to persistent acne [9], while others suggest a correlation with adult-onset acne [13]. One of the reasons for the unclear relationship between acne category and BHA is the lack of routine hormonal evaluations in women under

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25 [1, 10, 14], and limited number of studies comparing them with other age groups [7].

Furthermore, despite common belief, the association between chin acne and BHA has not been proven [15]. In contrast, a relationship between hyperandrogenemia and truncal acne has been suggested, though serum androgens were not compared according to location [4, 6].

As evidenced above, there is a need to clarify the clinical predictors of underlying hyperandrogenism in women with acne, including clinical hyperandrogenism, the course of acne, age, and location.

In addition, there is uncertainty on the risk factors for treatment resistance in female acne. While some reports suggest that female adults are more resistant to therapy than adolescents [12, 16], others indicate that adult females may respond well to conventional treatment [15]. The treatment response is unlikely to depend on the acne severity since mild acne may be resistant to treatment [13]. On the other hand, although treatment resistance is often thought to be due to underlying hormonal problems [14, 17–20], the accuracy of this assumption has not been thoroughly investigated.

Aim

In the present study, we aimed to determine the clinical predictors of underlying BHA in female acne patients and to investigate whether serum hyperandrogenemia and other clinical parameters are related to treatment resistance. Additionally, we evaluated the clinical and laboratory parameters associated with polycystic ovary syndrome (PCOS).

Material and methods

This retrospective study included female acne patients admitted to our dermatology outpatient clinic between January 2020 and September 2022 who had undergone laboratory tests for hormones after clinical suspicion of hyperandrogenemia. This study was approved by the Institutional Ethics Review Board (Project no. KA22/440) and performed in accordance with the principles of the Declaration of Helsinki.

The indications for ordering hormone tests were as follows: 1) signs of hyperandrogenemia in the patient's clinical examination or medical history (menstrual irregularity/hirsutism, previous hormonal disorder such as PCOS), 2) lack of/partial response to previous acne treatments/resistance to treatment, 3) frequent flare-ups after previous treatments, 4) acne that began or continues in adulthood. If serum hyperandrogenemia was detected, the patient was referred to the gynaecology/endocrinology department, and the result of the assessment was recorded. Data obtained from patients' medical records are presented in Tables 1 and 2. The laboratory results were collected from the hospital records. The exclusion criteria included pregnant women, patients receiving hormonal treatment for at least 3 months prior to recruitment, postmenopausal women and patients with chronic systemic diseases.

Assays

Blood samples were obtained in the follicular phase (on the days 2–3rd) of the menstrual cycle at 8:30 a.m. after overnight fasting. The hormone tests included thyroid-stimulating hormone (TSH), prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), total testosterone (TT), free testosterone (fT), sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS04), 17-hydroxyprogesterone (17-OHP), and androstenedione (AND). TSH, PRL, FSH, LH, E2, TT, SHBG, and DHEAS04 levels were determined by the chemiluminescent microparticle immunoassay method (Abbott Diagnostics, IL, USD). fT, 17-OHP and AND tests were measured by the radioimmunoassay method using DIAsource ImmunoAssays (Louvain-la-Neuve, Belgium) reagents. The free androgen index (FAI = [total testosterone/SHBG] × 100) and LH/FSH ratio were calculated for eligible patients. The conversion factor of TT from conventional units (ng/dl) to international units (nmol/l) was 0.0347. The presence of BHA was defined as having TT, DHEAS04, fT, 17-OHP or AND higher than normal, SHBG lower than normal, FAI > 5 [9] and LH/FSH ratio ≥ 2 [6]. The presence of biochemical hormone derangement was defined as having a low or high level of any hormones.

Statistical analysis

Descriptive statistics were calculated for all study parameters. The Mann-Whitney *U* test was used when comparing non-normally distributed groups. When more than two variables were compared, the Kruskal-Wallis test was used. For comparison of categorical variables, the χ^2 test was used. The correlation analyses were performed using the Spearman method. "Statistical Package for Social Sciences" SPSS v25 (IBM Corp., Armonk, NY, USA) software was used for data analysis. $P < 0.05$ was considered significant.

Results

The demographic and clinical characteristics of patients (n = 86, mean age: 24, range: 14–41), and the course and classification of acne are given in Tables 1 and 2, respectively. The treatment responses and the results of gynaecology/endocrinology referrals are provided in Table 3. The results of hormone tests and the status of hormone levels are given in Tables 4 and 5, respectively. Detailed analyses revealed notable results as outlined below.

Table 1. Demographic and clinical characteristics of female acne patients (n = 86)

Parameter			*n* (%)	Mean ± SD
Age				23.74 ±5.58
The presence of adolescent acne		Yes	62 (72.9)	
		No	23 (27.1)	
The age when adolescent acne began				14.2 ±42.05
Adolescent acne on	Forehead	Yes	44 (69.8)	
		No	19 (30.2)	
	Cheeks	Yes	21 (33.3)	
		No	42 (66.7)	
	Chin	Yes	17 (27)	
		No	46 (73)	
	Trunk	Yes	10 (15.9)	
		No	53 (84.1)	
The location of current acne compared to adolescent acne		Same	19 (30.6)	
		Different	43 (69.4)	
The location of current acne		Face	60 (69.8)	
		Face and trunk	24 (27.9)	
		Trunk	2 (2.3)	
The location of current acne on cheeks		Yes	70 (84.3)	
		No	13 (15.7)	
The location of current acne on the forehead		Yes	30 (36.1)	
		No	53 (63.9)	
The location of current acne on the chin and neck		Yes	42 (50.6)	
		No	41 (49.4)	
The presence of previous PCOS diagnosis		Yes	8 (9.3)	
		No	78 (90.7)	
The presence of menstrual irregularity		Yes	15 (17.4)	
		No	71 (82.6)	
The presence of hirsutism		Yes	25 (29.1)	
		No	61 (70.9)	
Premenstrual aggravation of acne		Yes	68 (81)	
		No	16 (19)	
The presence of clinical hyperandrogenism		Yes	30 (34.9)	
		No	56 (65.1)	

The DHEAS04 levels were higher (p = 0.019), and DHEAS04 elevation was more common (p = 0.023) in persistent acne patients than in adult-onset and recurrent acne. The presence of BHA was not different among adult acne categories. Finding FAI > 5 (p = 0.019) and LH/FSH ≥ 2 (p = 0.012) was significantly more common in adolescents compared with adults.

DHEAS04, fT, 17-OHP, and AND levels were higher in patients with hirsutism (p = 0.004, p = 0.011, p = 0.002, and p = 0.019, respectively). Elevated TT, DHEAS04, 17-OHP, and AND levels were significantly associated with hirsutism (p = 0.022, p = 0.009, p = 0.019, and p = 0.003, respectively). Similarly, elevated FAI levels (p = 0.038) and BHA (p = 0.026) were more common in patients with hirsutism. The 17-OHP level (p = 0.021) and LH/FSH ratio were higher in those with menstrual irregularity (p = 0.025).

The 17-OHP level (p = 0.028) was higher in patients with a relatively stable/chronic course than in patients with an unstable course. The "current acne age" was lower in patients with BHA (p = 0.01) and biochemical hormone derangement (p = 0.008).

The DHEAS04 (p = 0.032) and FAI levels (p = 0.035) were significantly higher in patients with previous PCOS diagnoses. Additionally, the high levels of TT (p = 0.022) and FAI (p = 0.019) were more common in patients with previous PCOS diagnoses. A low E2 level was associated with overall PCOS diagnosis (p = 0.021).

Menstrual irregularity was more common in persistent acne than in adult-onset and recurrent acne patients (p = 0.049). Hirsutism did not differ among adult

Table 2. The course and classification of acne in female patients (n = 86)

Parameter	*n* (%)	Mean ± SD
The course of acne		
Continues with the same intensity	13 (15.1)	
The severity has decreased	5 (5.8)	
The severity has increased	23 (26.7)	
Not present at adolescent but appeared after	23 (26.7)	
Present in adolescence, absent for many years thereafter, and reappeared	17 (19.8)	
Resolves with treatment but reoccurs	5 (5.8)	
The course of acne severity		
Relatively stable/chronic course	23 (26.7)	
Severity increased/became apparent after absence	63 (73.3)	
The classification of acne according to the traditional definition		
Persistent acne (continues from adolescence to the age of 25)	13 (15.1)	
Adult onset acne (starts over the age of 25)	3 (3.5)	
Other (does not fall into either category)	70 (81.4)	
The distribution of patients according to the proposed category		
Persistent (continues from adolescence)	40 (46.5)	
Adult onset (acne for the first time after adolescence)	23 (26.7)	
Recurrent (recurs years after adolescent acne is over)	17 (19.8)	
Adolescent acne (acne ≤ 18 years)	6 (7)	
The age at onset of current acne (for adult-onset and recurrent acne)		23.12 ±4.56
The age at which acne occurred for the first time (for all patients)		16.21 ±4.11
The total duration of acne [years] (for all except recurrent acne)		6.20 ±5.20
The study follow-up period [weeks]		36.17 ±28.99

acne categories. Having menstrual irregularity was significantly associated with hirsutism (p = 0.001).

Hirsutism was more common in patients with previous PCOS diagnoses than patients without (p = 0.043). While previous PCOS diagnosis was present in 33.3% of those with menstrual irregularity, it was present in 4.2% of those without (p = 0.003). The acne age, duration, and categories were not associated with PCOS diagnosis.

Serum hormone results were comparable between patients with good and poor treatment responses. Adolescent acne and hirsutism were significantly more common, and the "first acne age" was significantly lower in patients with poor treatment response (p = 0.006, p = 0.012, and p = 0.001, respectively). Treatment failure was more common in persistent and recurrent acne patients than adult-onset patients (p = 0.026).

There was no difference in serum hormone results according to the different facial locations. Patients with truncal acne had significantly higher PRL, AND, and FAI levels (p = 0.001, p = 0.055, and p = 0.016, respectively). Elevation of PRL (p = 0.012) and the presence of hormone derangement (p = 0.032) were higher in patients with truncal acne than in patients without. Hormone levels were similar between patients experiencing premenstrual flare and those who did not.

The location of acne was not different according to PCOS diagnosis or clinical hyperandrogenemia and did not differ among acne categories.

Discussion

The present study describes the factors associated with BHA and the treatment response in women with acne. Additionally, it provides detailed insights into the course of acne, highlighting the shortcomings in its classification.

Our finding that 87% of adult patients developed acne before the age of 25 reinforces the opinion that the term 'adult-onset acne' should not be restricted to those aged 25 and older [10]. Persistent acne has been reported to be more common than adult-onset acne in previous studies [12], which is in line with our results. Although a recent contradictory report demonstrated adult-onset acne predominance, 28% of adult-onset acne patients had adolescent acne in the latter study [9].

Table 3. The treatment responses and results of gynaecology/endocrinology referral of female acne patients (n = 86)

Parameter	*n* (%)
The previous acne treatment	
Not received	30 (35.7)
Topical agents	31 (36.9)
Topical agents with oral antibiotics	10 (11.9)
Oral isotretinoin	13 (15.5)
The response to previous treatment	
Did not receive any/did not use regularly	12 (18.5)
Complete response	0 (0)
Partial response	19 (29.2)
Poor response	7 (10.8)
Responded but reoccurred	27 (41.5)
The response to previous treatment	
Responded but reoccurred	27 (31.4)
Partial/no response	26 (30.2)
Not known	33 (38.4)
First acne treatment	
Topical agents	23 (26.7)
Topical agents with oral antibiotics	56 (65.1)
Oral isotretinoin	7 (8.1)
The course of the treatment response	
Cured and does not use treatment anymore	8 (9.5)
Under control, and uses drugs when acne occurs	27 (32.1)
Partial response, continues the treatment	7 (8.3)
Partial response, the treatment was rearranged	5 (6)
Poor response despite multiple rearrangements	2 (2.4)
Under treatment with oral isotretinoin	21 (25)
Under treatment with oral contraceptives	5 (6)
Discontinued treatment despite having acne	4 (4.8)
Partial response to treatments but having frequent attacks	5 (6)
The overall treatment response	
Good response	35 (40.7)
Poor response	35 (40.7)
Other	15 (17.4)
The result of gynaecology/endocrinology assessment	
Patient was not referred	28 (32.5)
Patient was referred, PCOS present	9 (10.5)
Patient was referred, PCOS not present	38 (44.2)
Patient was referred, but did not go	11 (12.8)
The presence of PCOS diagnosis (previous and new diagnoses)	
Not present	35 (40.7)
Present	15 (17.4)
Not known	36 (41.9)

Table 4. The results of hormone tests in female patients with acne (n = 86)

Parameter	Normal values	Mean ± SD
TSH [mU/l]	0.35–4.94	1.69 ±1.03
PRL [µg/l]	5.18–26.53	19.41 ± 9.58
FSH [U/l]	3.03–8.08	5.2 ±2.9
LH [U/l]	2.39–6.6	4.26 ±2.23
Estradiol [ng/l]	21–251	31.16 ±11.65
TT [ng/dl]	10–57	33.43 ±12.05
TT [nmol/l]	0.347–1.97	1.16 ±0.42
DHEAS04 [µg/dl]	95.8–511.7	291.7 ±128.19
fT [ng/l]	0.29–3.18	1.4 ±0.65
17-OHP [µg/l]	0.11–1.08	1.28 ±0.39
Androstenedione [µg/l]	0.9–3	2.97 ±1.43
SHBG [nmol/l]	11.7–137.2	58.06 ±26.97
LH/FSH	< 2	0.87 ±0.45
FAI	≤ 5	2.55 ±1.68

AND – androstenedione, DHEAS04 – dehydroepiandrosterone sulfate, E2 – estradiol, FSH – follicle-stimulating hormone, LH – luteinizing hormone, fT – free testosterone, PRL – prolactin, SHBG – sex hormone-binding globulin, TSH – thyroid-stimulating hormone, TT – total testosterone, 17-OHP – 17-hydroxyprogesterone.

For recurrent acne, the available data on its characteristics are limited [9], and categorizing recurrent acne within the persistent acne group complicates the acquisition of comprehensive information about this subtype [10, 15]. "Recurrent acne" accounted for 21% of adult acne in our cohort, while persistent and adult-onset frequencies were 50% and 29%, respectively.

While BHA has been found to be 55% [5] and 63% [7] in adult female acne, a subsequent study suggested that endocrine abnormalities were not common in these patients based on the patients' history [14]. A recent study revealed an intriguing discrepancy: while serum hyperandrogenemia was reported in 18% of adult female acne, 67% of the patients had high 17-OHP levels [6]. On the other hand, little evidence exists on the hormone levels in females younger than 25 [10]. Biochemical hyperandrogenemia was reported between 50% and 81% in studies including adolescent and adult women [1, 2, 5, 14].

We observed BHA in 71% of the cohort, with 17-OHP being the most commonly elevated hormone. This finding supports studies reporting elevated 17-OHP levels ranging from 54% [21] to 67.6% [6], although there are studies that find 17-OHP levels similar to the controls [8, 22]. While 21-hydroxylase enzyme deficiency may be a contributing factor to the aetiology of acne [17, 23–25], moderate elevations in 17-OHP can also be observed in the absence of non-classical congenital adrenal hyperplasia (NCCAH) [9]. Stress [3] and the abnormal secretory response [8] have been suggested to increase 17-OHP in women with acne. Previous studies have demonstrated elevated levels of AND in female acne patients [2, 5, 22]. Consistent with these findings, our study identified AND as the second

Table 5. The status of hormone levels in female patients with acne (*n* = 86)

Parameter	Hormonal derangement	*n* (%)
TSH	Low	0 (0)
	Normal range	82 (96.5)
	High	3 (3.5)
PRL	Low	0 (0)
	Normal range	70 (82.4)
	High	15 (17.6)
E2	Low	23 (26.7)
	Normal range	63 (73.3)
	High	0 (0)
TT	Low	0 (0)
	Normal range	83 (96.5)
	High	3 (3.5)
DHES04	Low	2 (2.3)
	Normal range	79 (91.9)
	High	5 (5.8)
fT	Low	2 (2.3)
	Normal range	83 (96.5)
	High	1 (1.2)
17-OHP	Low	0 (0)
	Normal range	30 (34.9)
	High	56 (65.1)
AND	Low	1 (1.2)
	Normal range	51 (59.3)
	High	34 (39.5)
SHBG	Low	0 (0)
	Normal range	69 (98.6)
	High	1 (1.4)
LH/FSH	Normal (< 2)	84 (97.7)
	High (≥ 2)	2 (2.3)
	Normal (< 5)	62 (89.9)
	High (≥ 5)	7 (10.1)
The presence of biochemical hyperandrogenemia	Not present	25 (29.1)
	Present	61 (70.9)
The presence of any biochemical hormone derangement	Not present	16 (18.6)
	Present	70 (81.4)

AND – androstenedione, DHEAS04 – dehydroepiandrosterone sulfate, E2 – estradiol, FSH – follicle-stimulating hormone, LH – luteinizing hormone, fT – free testosterone, PRL – prolactin, SHBG – sex hormone-binding globulin, TSH – thyroid-stimulating hormone, TT – total testosterone, 17-OHP – 17-hydroxyprogesterone.

most frequently elevated hormone. The origin of 17-OHP and AND, which can be secreted from both the adrenal and ovarian glands in females with acne, warrants further investigation. E2 was low in 23% of the cohort, which has been suggested to have a protective role against acne [14, 22]. The low E2 in PCOS patients may be related to an intensified androgen milieu without the counterbalancing effect of E2.

Evidence on the differences in BHA by age is limited [1, 14]. Slayden *et al.* demonstrated high serum androgens in adolescents compared to adults; however, the results were not significant, and the author attributed this to the low number of patients [7]. In the present study, FAI levels and the LH/FSH elevation rate were significantly higher in adolescents than adults. Since laboratory investigation was performed based on specific indications and not for all adolescent female acne patients, future studies should be conducted to determine the prevalence of BHA in adolescents with acne.

Controversy exists regarding the differences in serum hormone levels across different acne categories. While previous studies have associated hyperandrogenism with adult-onset acne [11, 13], Sardana *et al.* linked persistent acne to BHA. However, 48% of the patients classified as having persistent acne in the latter study did not have adolescent acne, indicating an inconsistency in acne categorization [9]. DHEAS04 was higher in persistent acne patients in our cohort than in adult-onset and recurrent acne. Additionally, a high level of 17-OHP in patients with relatively stable/chronic course supports the association of the persistent course with serum hyperandrogenemia. Similarly, the finding of a younger age at acne onset (for adult-onset and recurrent acne) in patients with BHA suggests a relation between hormonal disturbance and the duration of acne in adult females.

The rate of clinical hyperandrogenemia has been reported at about 72% in two previous studies [1, 6], whereas it was 35% in our cohort. It was 11% in a study where menstrual irregularity was not included as an androgenic sign [15]. The prevalence of hirsutism was 29% in our research, which has been reported as 20–30% in female adult acne [10]. The rate of menstrual irregularity varies between 19% [15] and 48% [2] in the literature, and was 17% in the present study.

Serum androgens may be elevated in patients without concomitant clinical hyperandrogenemia [6–8]. Consistent with this, 62.5% of our patients without hyperandrogenic signs had elevated serum androgens. On the other hand, patients may have normal serum androgens despite having hirsutism [1]. Hirsutism was associated with BHA and elevation in multiple androgens in the current study, which supports a previous report demonstrating a closer association of hirsutism with BHA

than alopecia and acne [23–25]. Our study confirms that hirsutism is more common in patients with menstrual irregularity [14]. Menstrual irregularity was more common in persistent acne patients than in adult-onset and recurrent acne patients, which is in line with Sardana *et al.* study [9].

17–27% of adult females with acne have been found to have PCOS [10]. Higher rates of up to 40–50% have also been reported [1, 2]. PCOS was diagnosed in 17.4% of our cohort, but this probably does not represent the prevalence in the whole cohort since not all patients were referred to the gynaecology/endocrinology department/clinic. Menstrual irregularity and hirsutism were more common in patients with PCOS diagnosis, which is compatible with previous results [4]. However, about 24% of the patients without menstrual irregularity and 12.5% without androgenic signs were diagnosed with PCOS. This finding suggests that it is essential not to rely only on clinical manifestations to search for PCOS. High DHEAS04, TT, and FAI levels were associated with PCOS, in line with the literature [4]. The fact that nearly half of the PCOS patients were diagnosed under our guidance emphasizes the importance of hormonal investigation in acne patients. Of interest, not all patients we referred due to BHA exhibited PCOS, which aligns with the literature demonstrating elevated serum androgens independent of the presence of PCOS [1]. The prevalence of premenstrual acne flare was 81% in our cohort, which has previously been reported as 30% [3] and 85% [13]. Our results contradict the prevailing notion [14] that premenstrual acne flare is associated with BHA.

The relocation of acne by age has been well-known. Acne on the forehead is more common in adolescents [12, 15]. Similarly, the location of adult acne differed from that in adolescence in 69% of the patients. Although Sardana *et al.* associated truncal location with persistent acne; we could not find any association between acne location and acne categories. This discrepancy might stem from a potential issue in their acne categorization as some patients classified as having persistent acne did not have adolescent acne [9].

The classical assumption that hormonal acne appears on the chin has yet to be confirmed by extensive studies. A previous report associated chin acne with endocrinological abnormalities based on the patients' history [15]. However, we did not find any association between the location of acne on the chin and BHA. On the other hand, there is evidence that truncal acne may be a marker of hyperandrogenemia [4, 6]. The present study strengthens earlier findings by revealing a significant association between truncal acne and high levels of PRL, AND, and FAI.

The literature on treatment responses in female acne patients is inconsistent [13, 15], and evidence regarding the determinants of treatment failure is limited. Our study provides important insights into this issue.

Contrary to the widespread belief that treatment-resistant acne is related to endocrinopathies in female acne patients [14, 17–20], our study showed that serum hormone results did not differ between patients with good or poor responses. However, adolescent acne was more common, and the "first acne age" was lower in our patients with poor response. Additionally, persistent and recurrent acne patients were significantly less likely to respond to treatment than adult-onset patients. These findings suggest that the duration of acne influences the treatment response.

Hormonal therapy has been recommended for all acne patients with serum hyperandrogenism and patients who do not respond to traditional treatment [10]. Given the positive outcomes observed with conventional therapy in many patients with BHA, a stepwise approach may offer a rationale even for females with androgen excess. However, the significant association between hirsutism and treatment failure suggests that hormonal agents may be added to conventional therapy earlier in patients with hirsutism.

Additionally, the present study raises questions that could be the subject of further research. Considering the high prevalence of BHA in the study and the reluctance many patients have towards systemic hormone therapy, the investigation of the additive effect of early-stage topical antiandrogens on conventional treatments in women with acne would provide valuable insights into the role of hormones in acne pathogenesis.

Our study has several limitations. Due to its retrospective design, not all parameters could be obtained for the whole cohort. Additionally, since this cohort comprises patients undergoing hormonal assessments for specific indications, future studies investigating hormones in all acne patients presenting to the outpatient clinic will better elucidate differences between groups. Finally, the number of adolescents was quite small because hormonal evaluation is not routinely performed in this age group. Therefore, the results regarding adolescents cannot be extrapolated to all adolescents with acne.

Conclusions

BHA is common in adult and adolescent women with acne, with the most frequently elevated hormones being 17-OHP and AND. Truncal acne and hirsutism serve as predictive markers for underlying hyperandrogenemia, although androgen excess may be observed without clinical signs. The results also suggest that the persistent course and duration of acne in adult females are related to serum androgen elevation. Although patients without clinical hyperandrogenism may have PCOS, hirsutism is strongly associated with PCOS. Biochemically, high levels of DHEAS04, FAI, and TT and low E2 levels should raise suspicion of a PCOS diagnosis. The establishment of PCOS diagnosis in a considerable proportion of patients follow-

ing our referral underscores the importance of conducting hormonal analyses in females with acne. While the response to treatment does not correlate with hormone levels, persistent and recurrent acne patients, and those with longer duration of disease carry a higher risk of treatment failure. The favourable results in females with high androgen levels indicate that conventional treatment can be initiated first, even for these patients. However, the association of treatment resistance with hirsutism suggests that hormonal therapies should be considered earlier for female acne patients with hirsutism.

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Conflict of interest

The authors declare no conflict of interest.

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