

Exploring the Clinical and Investigational Profile of Females with Hirsutism at a Tertiary Care Center

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Abstract

Introduction: Hirsutism is a common clinical condition with multifactorial etiology, ranging from endocrinological abnormalities to benign idiopathic causes to, rarely, severe malignant disorders. It negatively impacts the quality of life and self-esteem of affected women, necessitating proper etiological diagnosis and management.

Aims and objectives: To evaluate etiology of hirsutism and study clinical manifestations and biochemical characteristics associated with it.

Materials and Methods: After obtaining approval from Institutional Ethics Committee, a cross-sectional observational study was conducted at the tertiary care hospital for 2 years. Detailed history, clinical examination, assessment of hirsutism as per modified Ferriman Gallwey score, investigations including hormonal assays and radiological examination were done for all patients. Data were analyzed using appropriate statistical tests.

Results: Among 43 women, 65.11 % had mild hirsutism, 25.58% had moderate and 9.30 % had severe hirsutism. Menstrual irregularities were noted in 58.14%, and 13.95% had a family history of hirsutism. Acne (65.11%) and seborrhea (51.16%) were the most common cutaneous findings. 16.28 % and 27.91% women were overweight and obese respectively. Insulin resistance (Homeostasis Model Assessment of Insulin Resistance i.e., HOMA IR index >2) was present in 46.51% patients, with PCOS (Polycystic Ovary Syndrome) being the leading cause, and showed significant correlation with BMI ($p = 0.001$). LH/FSH ratio >2 (i.e. ratio of Luteinizing Hormone to Follicle-Stimulating Hormone) was present in 39.53 % and 46.51 % recorded positive findings of polycystic ovarian morphology by radiological examination.

Conclusion: The most common cause of hirsutism in our study was found to be PCOS followed by idiopathic hirsutism. Diligent assessment of hirsute women with particular attention to metabolic components such as insulin resistance, as indicated by the HOMA-IR index must be undertaken to identify the root cause and tailor appropriate interventions

Keywords: Etiology; Hirsutism; HOMA-IR index; Insulin resistance; Polycystic ovary syndrome

Introduction

Hirsutism is defined as excessive terminal hair growth in women at androgen dependent sites i.e. in male distribution pattern. It results from an increase in circulating androgens, either exogenous or endogenous (whose source is primarily ovary or adrenal gland) or from increased sensitivity of the hair follicle to the normal serum androgen levels (end organ dysfunction). It affects approximately 5 to 10% of women of reproductive age and has an adverse effect on quality of life.¹ It should be differentiated from hypertrichosis which is independent of age, sex and is

characterized by an increase in the amount of lanugo, vellus or terminal hair anywhere on the body.²

Both severity of hirsutism and degree of its acceptance depends on racial, cultural and social factors.³ The modified Ferriman Gallwey (mFG) score is commonly used for grading the presence and severity of hirsutism in clinical practice.⁴

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The term “SAHA syndrome” (also known as dermatologic androgenization syndrome) was coined by Orfanos to encompass presence of seborrhea, acne, hirsutism, alopecia in females as a result of peripheral hyperandrogenism.² Other signs and symptoms which gives clues towards hyperandrogenism are acanthosis nigricans (AN), obesity, virilization (wherein women develop masculine features like male pattern hair loss, increase in muscle mass, clitoromegaly, deepening of voice) and features of Cushing syndrome.

Hence it becomes imperative to evaluate every female patient thoroughly who is coming with complaints of unwanted body hair. In the present study we have evaluated the etiology of hirsutism and studied clinical manifestations and biochemical characteristics associated with hirsutism.

Materials and methods

A cross-sectional observational study was conducted at a tertiary care hospital in Western India for 2 years after obtaining approval from Institutional Ethics Committee. 43 patients were enrolled in the study based on inclusion and exclusion criteria. Inclusion criteria were patients of all age groups presenting with clinical hirsutism. Those not willing to participate and pregnant or lactating females were excluded from the study. Patient's clinical history was recorded using a case record form which included socio-demographic data, the age of onset and duration of hirsutism, whether the onset was sudden or gradually progressive, history of weight gain/loss, marital status, method of contraception (if any) with duration, history of infertility, easy fatigability, malodorous perspiration and change in libido. Detailed menstrual history was recorded in accordance with standard guidelines. Patients were asked regarding complaints of galactorrhea, visual field disturbances, easy bruising, striae, centripetal weight gain, polyuria, polydipsia and polyphagia for any underlying endocrinological or metabolic disorders. Family or past history of similar complaints, any history of gynecological surgeries or drug intake were also noted.

Patients were examined for presence of hirsutism, its distribution and scoring was done as per modified Ferriman Gallwey (mFG) score and severity grading as per Abraham classification.² The mFG score includes nine body areas—upper lip, chin, chest, arm, upper abdomen, lower abdomen, upper back, lower back, and thighs. Each area was graded from a score of 0 to 4.⁵ They were also examined for presence of acanthosis nigricans, acne, androgenetic alopecia, seborrhea, signs of virilization (like increase in muscle mass, deepening of voice, male pattern hair loss, clitoromegaly, breast atrophy and loss of female body contours) hypertension and visual field defects. Features of Cushing syndrome or any other endocrinopathy, if present were noted. Patients' height and weight were recorded and body mass index (BMI) was calculated to classify them as

per WHO Asian BMI standards.⁶ Hormonal evaluation using blood samples was done in the follicular phase between the 3rd and 5th days of the menstrual cycle at 8 am after overnight fasting. Serum total testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), LH: FSH ratio, dehydroepiandrosterone sulfate (DHEAS), thyroid stimulating hormone (TSH), prolactin, fasting blood sugar (FBS), fasting insulin and fasting lipid profile were performed for all patients. Abdomino-pelvic ultrasound was also done during the same period for all the patients to look for polycystic ovaries and intra-abdominal mass.

To diagnose Polycystic ovary syndrome (PCOS), Rotterdam criteria 2003 were adopted which required the presence of at least two out of three of: - i. Oligo or anovulation ii. Biochemical and/or clinical signs of hyperandrogenism (hirsutism/acne/androgenetic alopecia) iii. Presence of polycystic ovaries (PCO) or polycystic ovarian morphology (PCOM) [Ovarian volume >10cm³ and/or 12 or more follicles between 2- and 9-mm size in at least one ovary].⁷ Additional laboratory investigations were carried out in selected patients as per requirement like serum 17 hydroxyprogesterone (17-OHP), serum cortisol level, 24-hour free urinary cortisol, S. ACTH (adrenocorticotrophic hormone) and MRI brain (to look for pituitary adenoma). Endocrinologist opinion was obtained for all patients who had deranged parameters for further appropriate management.

Data were entered twice in MS Excel 2019 and analysed using SPSS (Statistical Package for the Social Sciences; IBM Corp; version 25) and Epi Info 7.1 software. Qualitative variables were summarised in terms of proportions and percentages. The normality of quantitative data was initially assessed using a histogram and the D'Agostino-Pearson test. Quantitative variables were presented as mean (SD). Results were illustrated with relevant charts and tables. Outcomes were compared using a t-test for quantitative variables and a chi-squared test for qualitative variables. A p-value of less than 0.05 was deemed statistically significant.

Results

A total of 43 patients were included in the study and their baseline characteristics have been summarized in table 1.

Age of these patients ranged between 16 to 48 years with the mean age of the study group being 25.63 years. Maximum members of the study population belonged to the 15–25-year age group (n=28, 65.11%), followed by the 26–35-year group (n=9, 20.93%). 6.98% each belonged to 36–45 year and above 46-year age group. The age of onset of hirsutism ranged between 11 to 46 years with mean age of onset being 21.46 years. Mean duration of hirsutism was 4.13 years. The average latent period between onset of hirsutism and seeking treatment was 4.16 years. Age of onset of menarche

Table 1:- Baseline characteristics of study population

Characteristics	Categories	Frequency	Percentage (%)
Age of onset of hirsutism (in years)	10-20	24	55.81
	21-30	15	34.89
	31-40	2	4.65
	41-50	2	4.65
Marital status	Married	19	44.19
	Unmarried	24	55.81
Menstrual irregularities	Oligomenorrhea	23	53.49
	Amenorrhea	2	4.65
	No	18	41.86
mFG score (Severity)	Mild (8 - 16)	28	65.11
	Moderate (17 - 25)	11	25.58
	Severe (> 25)	4	9.30
BMI (Kg/m ²)	Normal	24	55.81
	Overweight	7	16.28
	Obese	12	27.91
Comorbidities	Dyslipidemia	10	23.26
	Hypertension	1	2.33
	Hypertension + Diabetes mellitus	1	2.33

Table 2:- Associated clinical manifestations seen in patients

Clinical findings	Number of patients	Percentage %
Acne	28	65.11
Seborrhea	22	51.16
Androgenetic alopecia	11	25.58
Malodorous perspiration	9	20.93
Acanthosis nigricans	8	18.60
Easy fatigability	8	18.60
Galactorrhea	4	9.30
Infertility	3	6.98
Features of Cushing syndrome	1	2.33

ranged between 9-16 years with mean age being 13.44 years. 58.14 % gave a history of irregular menstruation. PCOS was diagnosed in 68 % of the patients with irregular menstrual cycle. Positive family history of hirsutism was seen in six patients (13.95 %). Out of these six, four were diagnosed with PCOS (66.67%), one each had adrenal SAHA and ovarian SAHA + HAIR-

AN syndrome. (Hyperandrogenism, Insulin resistance and Acanthosis Nigricans) History of weight gain was present in 18 patients (41.86 %) and 44.19 % of patients (n = 19) had BMI above normal. The minimum and maximum mFG score of our study group was 8 and 28 respectively, while the average was 14.95. Table 2 depicts the various clinical manifestations seen in our patients, wherein the most common was acne in 65.11% followed by seborrhea in 51.16 %.

Out of eight patients who reported easy fatigability four had PCOS (50%) (Out of these, three had hypothyroidism along with PCOS), two (25%) had Idiopathic hirsutism (IH), one had isolated hypothyroidism and one had NCAH (Nonclassical congenital adrenal hyperplasia). Out of nine patients who complained of malodorous perspiration, six had PCOS (66.67%). (Out of these, three of them had hypothyroidism along with PCOS), one each were diagnosed with IH, NCAH, Cushing syndrome. One of our patients had a history of intake of cimetidine following which she had developed galactorrhea. None of our patients had breast atrophy, clitoromegaly, increased muscle mass or complaints of change in libido and deepening of voice.

Table 3:- Investigative profile of study population

Investigations	Findings	Frequency	Percentage (%)
S.Total testosterone	Raised	6	13.95
S. DHEAS	Raised	5	11.63
LH:FSH ratio	> 2	17	39.53
S.TSH	Raised	8	18.60
S. Prolactin	Raised	8	18.60
S. Fasting insulin	Raised	10	23.26
HOMA-IR	> 2	20	46.51
S.17-hydroxy progesterone	Raised	1	2.33
S. ACTH, 24- hour urinary cortisol	Raised	1	2.33
USG Pelvis	PCOM/PCO	20	46.51
MRI Brain	Pituitary adenoma	1	2.33

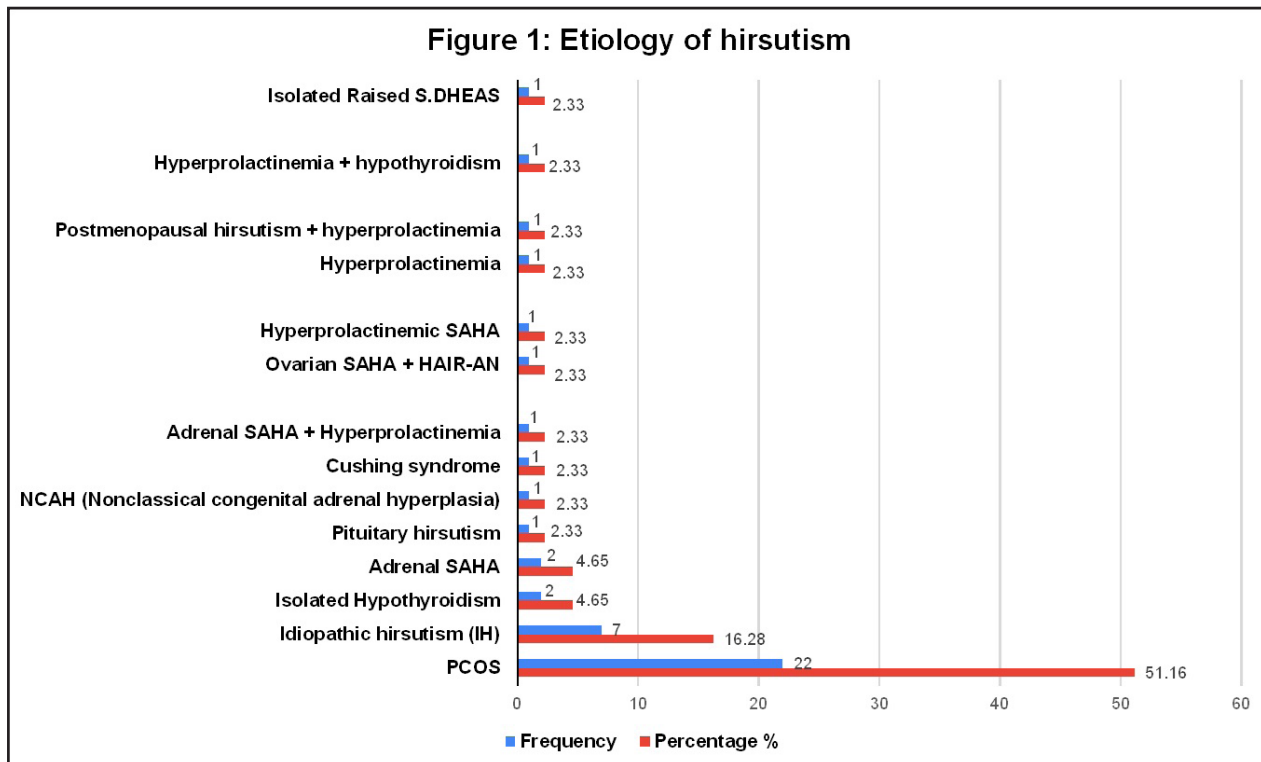


Figure 1: - Etiology of hirsutism

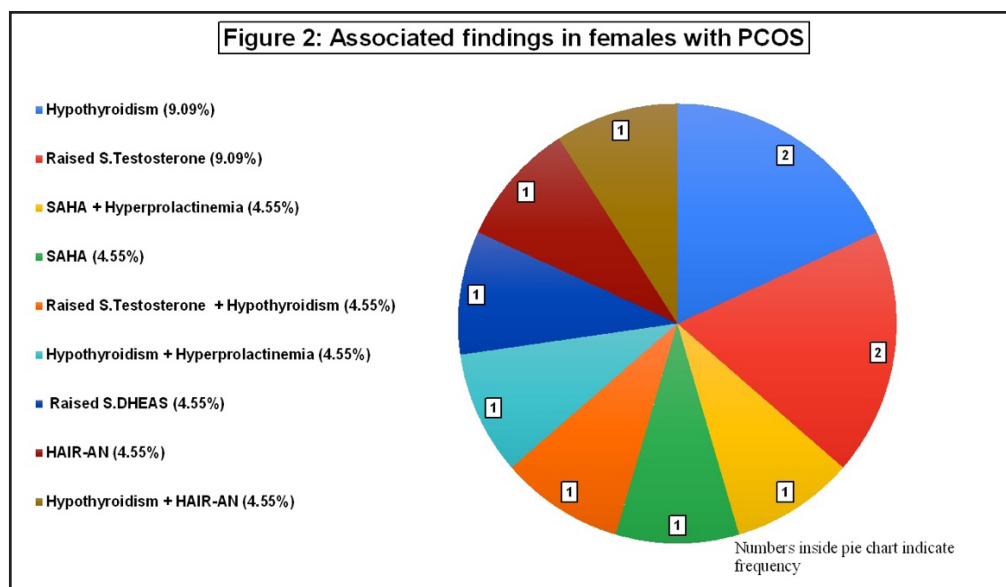


Figure 2: - Associated findings in females with PCOS

The investigative profile of our patients has been summarized in table 3.

Out of six females with raised total testosterone, 3 were diagnosed with PCOS, 2 with adrenal SAHA, one had ovarian SAHA + HAIR-AN syndrome. Of the five patients with elevated DHEAS levels, 3 had adrenal SAHA, one had PCOS and one had isolated raised levels of DHEAS with insulin resistance (IR). Amongst 17 patients with LH/FSH ratio >2, 16 were diagnosed with PCOS and one had ovarian SAHA + HAIR-AN syndrome. Out of eight females with raised serum prolactin levels, one each had isolated raised serum

prolactin, pituitary hirsutism, hyperprolactinemic SAHA, adrenal SAHA, PCOS, PCOS + hypothyroidism, hypothyroidism. One female was postmenopausal with raised prolactin levels. Interestingly, prolactin levels were significantly higher in non-PCOS patients (19.80 ± 16.49 vs 11.37 ± 8.16 ng/mL, $p = 0.038$), suggesting that hyperprolactinemia may contribute to hirsutism through mechanisms independent of classic PCOS pathways.

Insulin resistance was estimated using HOMA-IR index (homeostasis model assessment of insulin resistance) which was calculated using the formula: fasting insulin

x fasting glucose/405. HOMA-IR >2 was used as the cut-off value.⁸ PCOS was the leading diagnosis amongst 11 out of 20 patients with IR (HOMA-IR >2) and seven out of 10 females with raised S.fasting insulin levels. HAIR-AN syndrome was diagnosed when a patient had clinical or biochemical hyperandrogenism, insulin resistance (HOMA-IR index >2) and clinically evident AN.⁸ In this study 3 patients had HAIR-AN syndrome, not as an isolated diagnosis but rather in association with PCOS, PCOS + hypothyroidism & ovarian SAHA (one case of each). The MRI brain of one patient showed pituitary adenoma who had galactorrhea, hyperprolactinemia, androgenetic alopecia. In our study the most common cause of hirsutism was found to be PCOS in 51.16 % followed by idiopathic hirsutism in 16.28 %. Various other etiologies found are shown in Figure 1, Figure 2 highlights the accompanying findings seen in females with PCOS.

Discussion

Hirsutism is a widely observed condition that typically follows a benign course. Rarely, though, it might be the initial sign of serious underlying illness that necessitates accurate diagnosis and targeted treatment.

The majority of our study population fell within the 15–25-year age group, with a mean age of 25.63 years, consistent with findings from other studies (Table 4). The mean duration of hirsutism in our cohort was 4.13 years, suggesting a more indolent course, often characteristic of benign etiologies such as PCOS or idiopathic hirsutism. The absence of cases with rapid progression reinforces the lack of androgen-secreting adrenal or ovarian tumors in our cohort. Similar trends were noted by Dhanotia et al., who reported a mean duration of 3.29 years in a population with primarily benign causes.¹¹

Regarding severity of hirsutism, 65.11% of patients exhibited mild hirsutism (mFG 8–16), 25.58% moderate (mFG 17–25), and only 9.30% had severe hirsutism (mFG >25). Although various authors have encountered non-coherent results in the distribution of severity, there seems to be convergence upon the rarity of severe hirsutism (Table 4). In our study, mFG score did not show a statistically significant correlation with serum testosterone or DHEAS levels, a finding consistent with prior research by Chhabra et al., Ruutiainen et al., and Souter et al.^{10,15,16}

The average mFG score in our study was 14.95, similar to Sharma et al. (12.44 ± 3.64) and Zargar et al. (13.5 ± 4.6).^{12,17} Menstrual irregularities were seen in 58.14% of patients, slightly higher than Zargar et al.'s 50.8%.¹⁷ Of those with irregular cycles, 68% were diagnosed with PCOS, higher than Sharma et al.'s 64.2%, but lower than Wankhade et al.'s 88.2%, who also found a significant link between PCOS and menstrual irregularities.^{12,14} In our study, significant associations were found between irregular cycles and both an LH/FSH ratio >2 (56% vs. 16.67%, $p = 0.01$) and polycystic ovaries on ultrasound

(60% vs. 27.78%, $p = 0.038$), when comparing patients with irregular cycles to those with regular cycles.

Among signs of hyperandrogenism, acne was the most frequent (65.11%), followed by seborrhea (51.16%), which is similar to the findings of Sharma et al. and Chhabra et al. who also reported acne in 60% and 55% respectively.^{10,12} Androgenetic alopecia and AN were observed in 25.58% and 18.60%, respectively, consistent with Wankhade et al. (26% and 20%).¹⁴ In our study, 50% of patients with AN and 45.45% with androgenetic alopecia had PCOS. Sharma et al. also reported a higher prevalence of these features in PCOS patients (AN in 73.68% and female pattern hair loss in 47.36%).¹²

Higher mFG scores and increasing severity of hirsutism (Chi-square trend) showed significant positive association with acne, androgenetic alopecia, seborrhea (all $p < 0.0001$), reinforcing their association with more severe hyperandrogenism. Those with AN had significantly higher HOMA-IR scores (5.55 ± 2.05 vs 3.37 ± 1.69, $p = 0.003$), and elevated TSH ($p = 0.006$). Malodorous perspiration was reported by 20.93% of patients, and those with this symptom had a longer duration of hirsutism (8.83 ± 7.01 vs 2.88 ± 1.57 years, $p < 0.0001$) and higher mFG scores (19.56 ± 5.25 vs 13.56 ± 5.47, $p = 0.005$). Predominant presence of type I isozyme of 5 alpha reductase in apocrine sweat gland which converts testosterone to dihydrotestosterone may account for the presence of this symptom. Such uncommonly asked complaint can serve as an important clue in diagnosis of hyperandrogenic disorders.

In our study, 17.86% of patients with mild hirsutism (5/28), 45.45% with moderate hirsutism (5/11), and 50% with severe hirsutism (2/4) were obese (BMI >25). Chhabra et al. also found a significant association between hirsutism severity and BMI. Among overweight patients in our study, 28.57% (2/7) had PCOS, and 75% (9/12) of obese patients had PCOS, similar to Chhabra et al.'s finding where 84.21% of patients (16/19) with a BMI >25 had PCOS.¹⁰ While BMI did not show a statistically significant association with hirsutism severity ($p = 0.075$), it was positively correlated with serum testosterone ($r = 0.3589$, $p = 0.0181$), TSH ($r = 0.3965$, $p = 0.0085$), and fasting insulin ($r = 0.3591$, $p = 0.0180$), suggesting metabolic involvement even in the absence of overt clinical correlation.

In our study 46.51 % (n=20) patients had insulin resistance (IR) with PCOS being the leading cause seen in 11 females followed by idiopathic hirsutism. HOMA-IR index >2 was seen in 50% females with PCOS and all three HAIR-AN syndrome patient. 52.63% females with BMI of 23 and above (i.e. overweight and obese) had IR out of which two of them were diagnosed with diabetes mellitus and hypertension. BMI correlated significantly with HOMA-IR ($r = 0.48$, $p = 0.001$). IR has been associated with PCOS, metabolic syndrome, type 2 diabetes mellitus and cardiovascular diseases. Regular follow up of these young patients must be done for prevention of metabolic and other cardiovascular complications.

Table 4: - Comparison of our study with various other studies

Variables		Our study	Sharma NL, et al ⁹	Chhabra S, et al ¹⁰	Dhanotia PG, et al ¹¹	Sharma D, et al ¹²	Ansarin H, et al ¹³	Wankhade VH, et al ¹⁴	Zargar AH, et al ¹⁷	Subha R et al ²⁰	Ansari RT, et al ²¹
Mean age of study group (in years)		25.63	25.84	24.18	25.45	23.8	20.9	29.42	26.1	29.19	15.50
Age group having maximum members in study		15-25	20-30	16-30	20-29	21-25	21-25	NA (not available)	NA	15-25	22-31
Severity of hirsutism (% of patients)	Mild (%)	65.11	98	32.5	95.45	80	65	82	NA	72.6	NA
	Moderate (%)	25.58	2	52.5	4.55	20	32.5	14	NA	27.4	89.3
	Severe (%)	9.30	0	15	0	0	2.5	4	NA	0	NA
Most common etiology of hirsutism	1 st most common cause (%)	PCOS (51.16%)	NA	PCOS (70%)	IH (43.18%)	IH (50%)	PCOS (62.5%)	IH (40%)	IH (38.7%)	IH (52%)	PCOS (65%)
	2 nd most common cause (%)	IH (16.28%)	NA	IH (15%)	PCOS (38.64%)	PCOS (38%)	IH (35.2%)	PCOS (32%)	PCOS (37.3%)	PCOS (31.5%)	IH (16%)

The pathogenesis of HAIR-AN syndrome is thought to involve an insulin receptor and/or post-receptor defect, leading to compensatory increased circulating insulin and LH, which subsequently results in excess ovarian androgen secretion. Hence assessment of IR using index like HOMA-IR should be an integral part of evaluation of females with hirsutism. Although various reference ranges for HOMA-IR have been proposed for different populations, its clinical application is limited due to the absence of standardized reference ranges for the Indian population. This study aims to highlight the importance of HOMA-IR in hirsutism evaluation and contribute to the growing body of evidence that could pave the way for developing standardized reference ranges for the Indian population in future studies.

Literature suggests PCOS to be the leading root cause of hirsutism.^{18,19} Idiopathic hirsutism also appears to be one of the important causes. In our study most common cause of hirsutism was found to be PCOS (n=22, 51.16 %) followed by idiopathic hirsutism (n=7, 16.28 %) which was similar to study by Chhabra et al; who reported PCOS in 70 % patients and IH in 15% cases.¹⁰ Another study by Ansarin H et al., in Iranian females had found PCOS (62.5%) as the leading cause followed by IH (35.2%).¹³ There are also other Indian studies which report idiopathic hirsutism (IH) as the most common cause followed by PCOS; the findings of these various studies have been shown in table 4.

The term “idiopathic hirsutism” is often overused in diagnosing hirsutism, and it should be reserved for cases where thorough investigations yield no conclusive findings. Women with hirsutism should undergo a

detailed evaluation to determine the underlying cause. We believe that, in most cases if not all, this thorough assessment will reveal the cause of the condition, enhance our understanding of hirsutism and allow for a more targeted approach to treatment.

A major strength of our study lies in the use of multiple correlational analyses to explore the interrelationship between clinical features, hormonal abnormalities, and metabolic indices such as HOMA-IR and BMI. This allows a more nuanced understanding of phenotypic patterns in Indian hirsute women. However, the study's limitations include its modest sample size and single-center design, which may affect generalizability.

Conclusion

Our findings emphasize the critical importance of a comprehensive diagnostic evaluation of hirsutism, extending beyond cosmetic concerns to uncover potential underlying endocrine and metabolic disorders, which necessitate a careful differential diagnosis and tailored treatment. The prevalence of IR, as assessed by the HOMA-IR index, underscores the metabolic component of hyperandrogenism and we advocate to incorporate IR assessment (HOMA-IR index) in routine evaluations for hirsute women. Additionally, there is limited research on the relationship between HOMA-IR and endocrinological or metabolic abnormalities in Indian hirsute women, and our study aims to encourage further exploration in this area to improve early detection and intervention to mitigate long-term health risks.

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