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HYPERANDROGENISM IN FEMALE: A CRITICAL VIEW

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ABSTRACT

Androgen is male sex hormone secreted by adrenal cortex and ovaries in female. Androgenic disorders are the most common endocrinopathy of women of reproductive age, with prevalence of 10% - 20%. In this majority of patients with Androgen excess will have Polycystic ovary syndrome. The most common clinical manifestation of hyperandrogenism in women is persistent acne, hirsutism, androgenic alopecia. These causes physical & mental disturbance and loss of confidence which make women to hide from the world. Hyperandroginism is the gift of modern era, the exact disease related to Hyperandroginism was not mentioned in *Ayurvedic* literature. In this paper the attempt had been made to discuss causes, *dosha- dushya* involvement and pathogenesis of hyperandrogenism in female with respect to *Ayurveda* and according to that develop a treatment protocol to treat it.

Keywords: Hyperandrogenism, Hirsutism, Androgenic alopecia.

INTRODUCTION

Hyperandrogenism is the condition developed due to modernisation in day today life which may involve improper *Dinacharya (*Daily routine*)*, *Ritucharya* also *Rajaswalaparicharya (*routine or do's during menstruation and whole menstrual cycle), *Garbhiniparicharya* (antenatal care or routine should be followed during pregnancy) etc. It is lifestyle disorder having hormonal imbalance. In comtemptory medicine Hyperandrogenism does not have exact treatment to treat and side-effect of that medicine are much more. So to treat this endocrinopathy of woman of reproductive age through *Ayurveda* one must know the exact causes, pathogenesis, and treatment of this disease given in modern science.

Aacharya Charak has quoted that the physician should not worry about naming of particular disorders if it is not known to him. He should initiate treatment after assessing pathogenesis, location and etiological factors of the disorders.[1]

Androgen[2]-

An androgen is a substance having the capacity to produce masculinity. There are many of these, some occurring naturally and some produced artificially. All tend to be anabolics as well as sex determinants and there is a tendency to group them according to the dominant action. Testosteron is one of the most important androgen metabolised in the liver extremely rapidly and excreted from urine after degradation.

Androgen conserves nitrogen and assist in the build up of protein. They also favour potassium, phosphorus and sulphur retention and for these reason important of muscle

and the growth of bone. They therefore bring about an increase in weight, promote muscular strength and energy, and give a sensation of well being. Androgen accelerates epiphyseal closure and ultimately limits stature; they also cause retention of sodium, chloride and fluid.

Action of androgen in female-

Atrophy of the tubes, vagina, vulva and breast- Androgens directly depresses the activity of all the tissues of the female genital tract and induce atrophy and secretary quiescence of the lining epithelia. The breast shrinks, cervical secretion dries up and menstruation ceases.

Suppression of uterine and tubal contractions- These decrease both in frequency and in amplitude.

Ovaries –The ovarian cycle is arrested and ovulation and menstruation cease. This is a direct effect rather than one exerted through the hypothalamic-pituitary system.

Secondary sexual characters- Androgens are normally responsible for certain female sex characters as the axillary and pubic hairs, axillary sweating and activity of apocrine glands.

Evaluation of Hyperandrogenism :

Physical Examination

Manifestations of androgen excess are typically evident with a detailed history and physical examination. The history should emphasize age of onset, timing of onset (gradual or rapid), and duration of symptoms, and menstrual history should be elicited to determine irregularities. Physical examination should include inspection of the skin, breasts, pelvis, and abdomen.

Common Symptoms

Hirsutism, excessive terminal (coarse) hair growth in androgen-dependent areas of the body, is the most common sign of hyperandrogenism, occurring in 60%to 80% of patients.[3]Hirsutism should not be confused with hypertrichosis, which is defined as a diffuse increase in vellus (fine) hair growth.

Virilization, defined as the development of male characteristics in women, that is of rapid onset is generally a more ominous sign, suggesting the presence of an androgen-secreting ovarian or adrenal tumor. An estimated 5% to 10% of women in the general population are hirsute.[4,5] However, prevalence rates of hirsutism depend somewhat on the scoring method used to determine its presence. Hatch and colleagues 7 modified this scoring system to include 9 androgen-sensitive areas of the body. Each area is scored from 0 to 4 depending on the amount of terminal hair growth. A score of 8 or greater indicates the presence of hirsutism, although some experts recommend a score of 6 or greater.[1,6]

Acne is a common manifestation of hyperandrogenism.[7] Acne is characterized by increased sebum production, follicular epidermal hyperproliferation, proliferation of *Propionibacterium acnes*, and inflammation and occurs predominantly on the face and to a lesser extent on the back and chest. Androgens play a key role in the development of adult onset acne. Measurement of circulating androgens in patients presenting with adult onset acne and hirsutism is helpful for finding the underlying cause.[8,9]

Acanthosis nigricans is characterized by areas of hyperpigmented, velvety plaques typically found in the axilla, neck, and groin areas and is found in patients with PCOS or type 2 diabetes mellitus.[10]1 Its presence should prompt an evaluation for impaired glucose tolerance.[5]

LABORATORY EVALUATION

Testosterone is the key circulating androgen; it is secreted directly from the adrenal glands and ovaries or produced through metabolism of androstenedione or **DHEA-S** in peripheral tissues.[10]

The normal testosterone level in women is less than 100 ng/dL. Free testosterone binds to tissue receptors, and measurement of free testosterone is 50% more sensitive for detecting androgen excess than total testosterone.[10] The calculated free androgen index (FAI; total testosterone level divided by sex hormone–binding globulin [SHBG] level) can be used to estimate free testosterone and is a sensitive marker for detecting androgen excess.[11] A ratio of less than 7 on the FAI is considered normal in women. Very high levels of total testosterone (> 200 ng/dL) or DHEA-S (> 700 µg/dL) can suggest an underlying neoplasm, but not all patients with these values will have a tumour.

CAUSES OF HYPERANDROGENISM

• Polycystic ovary syndrome
• Idiopathic hirsutism
• Hyperandrogenic insulin-resistant acanthosis nigricans
(HAIRAN) syndrome
• Congenital adrenal hyperplasia (classic and non classic)
• Cushing's syndrome
• Androgen-secreting tumors (ovarian, adrenal)
• Hyperprolactinemia
• Hypothyroidism
• Androgenic medications (eg, danazol)

Polycystic Ovary Syndrome

First described in 1935 by Stein and Leventhal,[12]PCOS is the most common endocrine disorder in women of childbearing age, affecting 5% to 10% of women in this age-group. PCOS usually begins atpuberty,[4] and manifestations of PCOS include hirsutism, obesity, insulin resistance, acanthosis nigricans, and menstrual irregularities PCOS is commonly associated with insulin resistance and hyperinsulinemia. Insulin stimulates secretion of androgens by ovarian theca cells and also inhibits SHBG production, which increases free androgens.[13, 14] similarly, excess luteinizing hormone (LH) increases ovarian androgen secretion. An LH/follicle-stimulating hormone (FSH) ratio of greater than 2.5:1 is the classic pattern associated with PCOS. Because of decreased levels of FSH relative to LH, the ovarian granulosa cells cannot aromatize the androgens into estrogens. Although a finding of polycystic (multifollicular) ovaries on ultrasound is not solely diagnostic of PCOS, the presence of polycystic ovaries can strengthen the diagnosis. PCOS is, in fact, a syndrome—a collection of signs and features in which no single test is diagnostic.[15] Diagnostic criteria for PCOS were established by the 2003 Rotterdam Consensus Workshop. PCOS can be diagnosed when 2 of the following3 features are present:

(1) oligo- or anovulation,
(2) Clinical and/or biochemical signs of hyperandrogenism (i.e, hirsutism, acne, male pattern balding, elevated
Serum androgens), and
(3) Polycystic ovaries.

It is important to exclude other disorders with a similar clinical presentation before a diagnosis of PCOS is made.[16]

Hyperandrogenic Insulin-Resistant Acanthosis Nigricans (HAIRAN) Syndrome

The HAIRAN syndrome is an acronym for a disorder in women that consists of hyperandrogenism (HA), insulin resistance (IR), and acanthosis nigricans (AN).Women with HAIRAN syndrome also tended to have a greater body mass and waist-to-hip ratio as

compared with all other diagnostic groups.[4] As compared with women with PCOS, women with HAIRAN syndrome have a much greater degree of insulin resistance and hyperinsulinemia and a higher association with type 2 diabetes.[17]

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is the result of 21-hydroxylase deficiency. This enzyme defect leads to the accumulation of steroid precursors, which are subsequently converted to androgen (**Figure 2**). Classic CAH presents at birth with virilization of the female external genitalia, whereas late-onset (non classic) CAHis milder and typically does not present until early puberty. The symptoms of non classic CAH include premature pubarche, primary amenorrhea, menstrual dysfunction, hirsutism, acne, and infertility.[18] This disease closely mimics PCOS; therefore, in a patient presenting with phenotypic features of PCOS, it is important to consider late-onset CAH in the differential diagnosis. Laboratory assessment is critical for the diagnosis of CAH. In adults, a 17-hydroxyprogesterone level greater than200 ng/dL may be due to non classic CAH.

Cushing's syndrome

Menstrual irregularities and hirsutism are common symptoms in women with Cushing's syndrome, collectively occurring in 80% to 90% of patients.[19] These symptoms are hallmark findings of PCOS and are not specific to Cushing's syndrome. In the absence of multifollicular ovaries, PCOS may be differentiated from Cushing's syndrome by the presence of central obesity, facial plethora, moon facies, and violaceous abdominal stria greater than 1 cm.

Androgen-Secreting Tumors

Although androgen-secreting tumors are rare (< 1%of patients), they must be excluded in women who develop hirsutism or signs of virilization, including increased muscle mass, breast atrophy, clitoromegaly, and deepening of the voice, over a short period oftime.33 Elevated DHEA-S is seen in androgen-secreting adrenal tumors, while elevated testosterone is seen in both androgen-secreting adrenal and ovarian tumors.[20]

Table.1 Differential Diagnosis of Hyperandrogenism[4]

Diagnosis Additional	Incidence	Findings	Testing
Polycystic ovary syndrome	82%	Irregular menses, glucose intolerance, elevated blood pressure	Elevated insulin levels, multiple ovarian cysts on ultrasound
Hyperandrogenism with normal ovulation	7%	Regular menses	Elevated androgen levels
Idiopathic hirsutism	5%	Regular menses	Normal androgen levels
Hyperandrogenic insulin-resistant acanthosis nigricans (HAIRAN)	3%	Acanthosis nigricans	Elevated fasting glucose and insulin levels
Late-onset congenital adrenal hyperplasia (nonclassic)	2%	Short stature	Elevated 17-OH-progesterone

Congenital adrenal hyperplasia (21-hydroxylase deficiency)	1%	Possible virilisation	Elevated 17-OH-progesterone
Hypothyroidism	<1%	Fatigue, weight gain, amenorrhea	Elevated thyroid-stimulating hormone, low free thyroxine
Cushing's syndrome	<1%	Abdominal striae, central obesity	Elevated cortisol levels

So the above data suggest the pathology regarding androgen start from its origin of secretion that is from ovaries and adrenal gland but for maintenance of its proper level in blood, Liver (Cholestrole), pancreas (insulin) plays an important role. So the drugs have to be selected which normalise the function of above organs.

Ayurveda and Hyperandrogenism

Hyperandroginism is the gift of modern era, so the exact disease related to Hyperandroginism was not mentioned in *Ayurvedic* literature. It does not correlate the condition to a single disease but the symptoms bear a resemblance to the different terminologies in *Ayurvedic* classics. The symptoms of Hyperandrogenism may be correlated with *Pushpaghni Revati* having symptoms as *Vritha pushpa* (Anovulation), *Sthula ganda* (indirectly denotes obesity), *Lomasha ganda* (Hirsutism).Also as described above main cause of hyperandrogenism is PCOD (82%) may be correlated with '*Anartava*' (Amenorrhoea), '*Yonivyapad*' (anatomical and physiological disorders of the reproductive system) like –*Arajaska* (Oligomenorrhoea due to vitiation of *Vata-dosha*), *Lohitakshaya* (Oligomenorrhoea due to vitiation of *Vata-Pitta doshas*), *Shushka* (dryness of vagina), *Shandhi* (reproductive disorder of genetic origin), *Vandhya* (infertile), *Pushpaghni Revati* (Idiosyncratic anovulatory menstruation), *Abeejata* (anovulation), *Rajo dushti* and *Ashtartava dushti* (menstrual flow disorder due to vitiation of *Doshas*) etc. The terms *Raja* and *Artava* have been used synonymously or otherwise in the classics. Usually *Raja* is considered as the *upadhatu* of *Raktadhatu*[21]whereas *Artava* as the *saptam dhatu itself.21* Similarly their *srotasa*(channels) are also two entirely different entities. In the present paper, *Raja* has been considered as the menstrual flow while *Artava* is indicative of the ovum.

Table: 2

Vyadhi	***Hetu***	***Lakshana***	**Contemporary symptom**
Pushpaghni Revati[22]	Improper lifestyle during pregnancy	*Vritha pushpaSthula gandaLomasha ganda*	Anovulation, obesity, Hirsutism
Arajaska Yonivyapad[23]	*Pittaprakopakaaaharvihar*	*Shushkata*of the *Raja*	1. An increased interval between two cycles. 2.scanty menstrual flow
Lohitakshyaya	*Vata-Pittapradhanaahar-vihar*	*Rajaksheenata*	scanty menstrua-

Yonivyapad[24]			tion
Shushka Yonivyapad[25]	*Vataprakopakahetusevan*	*Yonirukshata*	dryness of genital tract
Shandhi Yonivyapad[26]	*Vata* vitiationdue to genetic factors		uterus, ovaries or the genital system itself is undeveloped.
Vandhya Yonivyapad[27]	*Dhatukshaya*	*Nashtartava*	loss of menstruation
Abeejata[28,29]	frequent or untimely coitus, over-exercise, *ruksha*(dry),*tikta*(bitter), *kashaya*(astringent), *atilavana*(excessively salty),*amla*(sour)and *ushna*(hot)*aahar*, as also *chinta*/*shoka* (stress-related tension), *bhaya*(fear), *krodha*(anger) and *aghata*i.e.injuries due to *shastra*(weapon)or*kshara*(alkali)	*Artavaabeejata*	Anovulation
Ashtartava Dushti[30]	*Artava* vitiated by the *Doshas*	*Abeejata*	anovulatory menstruation only
Rajodushti[31]	vitiation of *Raja* by the *Doshas*, primarily *Vata* and *Pitta*	*Ksheenata*	Oligomenorrhoea

Considering all the above mentioned types of conditions/diseases quoted in the classics it can be noted that neither of them bears a complete resemblance to the current features of hyperandrogenism.

For the treatment of any disease through *ayurveda* one should know the *Hetu* (Cause)for *Parivarjan (*abstinence*)*, *Samprapti* (Pathogenesis) for *Samprapti vighatana (*break down), and *Chikitsasiddhanta* (treatment principle).

***Hetu* (Cause)-**

Considering above mentioned condition it can state that it is a disease caused by vitiation of *dosha* during embryonic life or after birth by improper life style.

Beejadosha (Genetic) may occurred due to improper *Garbhini Paricharya* (antenatal care) as *Acharya Kashapa* mentioned causes of *Jatharini Revati* as improper *Ahar-Vihar* (life style) during pregnancy. *Pushaghni Revati* has some symptoms related to Hyperandrogenism.

Vitiation of of *Dosha* after birth is due to improper life style means due to breaking rules told by *Acharyas* regarding *Dinacharya*, *Ritucharya* and most important for women i.e. *Rajasvalaparicharya*. In day today life there is increase burden of work

causing stress which contributes to vitiation of *ManasDosha* (psychological factors*)* and ultimately leads to hormonal changes.

***Samprapti* (Pathogenesis)-**

By seeing above table, it is clear that this is the disease belongs to the category of *Santorpannatha vikar* (disease caused by overweight / nutrition).As an androgen is a substance having the capacity to produce masculinity so weight gain is mainly observed in patients of PCOD and other causes of Hyperandrogenism given above.

Vitiation of above factors occurs due to:

- *Agnimandya- Jatharagni & Dhatvagni*

Agnimandya (decrese digestive power) is the key factor for production of any disease. *Pitta* is consider as *Agni* by *Acharya Sushruta* and *Pitta* is nothing but Bile from liver and Pancreatic secretions,. Formation and metabolism of hormones are at the level of Liver as Cholestrol is formed there which is responsible for production of androgen, regarding pancreatic secretion insulin alters the androgen secretion.

The above stated aetiological factors give rise to *Jatharagni* (digestive power at stomach level) and *Dhatvagnimandya* (digestive power at cellular leval) along with *Aamotpatti* (end product fromed due to improper digestion) resulting in *Medoroga* viz. *Sthaulya* (obesity). *Aamotpatti* and *Agnimandya* cause an improper nourishment of the consecutive *dhatus*. *Artava*, being the *saptamdhatu* thus becomes *ksheen* (undernourished). The bulky appearance of the *antaphala* (ovaries) can be attributed to their vitiation by *Kapha* and *Meda* thus leading to an increase in the ovarian volume, which increases the secretion of the androgens and worsened the condition. Possible pathogenesis of *ksheen artava* is related with the vitiation of all the three *dosha*, but time period varies according to different phases of menstrual cycles. The vitiation of *vata* and *pitta* in first phase, affects the formation of endometrial thickness, where as the vitiation of *kapha* in second phase is responsible for the *srotorodha (*obstruction in channels). Thus the combined effect of all the three *dosha* creates the symptom of *kheenartava.*

It can be stated that *Kapha* predominance manifests as obesity, subfertility, hirsutism, diabetic tendencies and hypothermia. *Pitta* predominance manifests as alopecia, acne, dysmenorrhoea with clots and where as *Vata* predominance manifests with dysmenorrhoea, oligomenorrhoea and severe menstrual irregularity.

Hyperandrogenism, the main pathogenesis occurs due to vitiation of

Dosha

- *Vata (Apana,)*
- *Pitta (Pachaka,Sadhaka)*
- *Kapha (Kledaka)*

Dushya

- *Dhatu-Rasa, Rakta, Shukra*
- *Upadhatu-Raja*

Strotas- Rasavaha, Raktavaha, medovaha & Manovaha Strotas

***Ayurvedic* management of Hyperandrogenism-**

1. *NidanParivarjan* (Abstinence of causative factors)- It is first line of treatment in all types of diseases through *Ayurveda.* So the etiological factors responsible for pathogenesis of the disease should be excluded firstly.

Etiological factors:

-1. Beejadoshaj *(*Genetic*)*

-2.Apathyanimitaj (Acquired due to improper life style)

For the prevention of *Beejadosha*, *Ayurveda* mentioned the *Shodhan* therapy, which includes *Panchakarma* (helps in whole body detoxification, including *Raja)* before conception, whereas *Garbhini-paricharya* must be followed by female after conception.

Apathyanimitaj – Hyperandrogenism is life style disorder, so adaptation of proper life style through *ayurveda* i.e. *Dinacharya, Ritucharya,& Rajaswala paricharya* is mandatory.

2. *Samprapti Vighatana* (Break down of pathogenesis)-

As Hyperandrogenism comes under the category of *Santarpanotha Vikar* as mentioned above, so the prime line of treatment is *Apatarpana* which includes *Shodhana* and *ShamanaChikitsa.*

***Shodhana* (cleaning the body of abnormalities especially the *doshas*)-**

1. ***Vamana* (Emesis)-** In Hyperandrogenism, the type of *Strotodushti* is of *Sanga* type, which is due to predominance of *Kapha*. And *Vamana* (emesis) is mainly prescribed for vitiated *Kapha*.

2. ***Virechana* (Purgation)-** *Pitta* is responsible for all the hormonal activities/secretion which maintains equilibrium of body. So, due to vitiated *Pitta*, excessive secretion of Androgen may occur. *Virechana* therapy is the prime treatment of *Pitta dosha*.

Also according to *Ashraya-ashrayi Sidhanta*, *Pitta* is *ashrayi* of *Rakta*, so vitiation of *Pitta* leads to vitiation of *Rakta*. And *Rakta* is transport medium of nutrition as well as hormone, enzymes etc. Acne, Acanthosisnigricans which are symptoms of Hyperandrogenism is nothing but due to *Pitta-Rakta* vitiation also menstrual irregularities are also due to these *dosha*. Thats why *Virechana* along with *Raktamokshana* (expulsion of blood) may play principal role for normalisation of hormonal equilibrium.

3. ***Basti* (Enema)-**Excess Androgen secretion is from Ovaries and adrenal gland and these could be considered under *Pakvashaya* , which is seat of *Vata Dosha* and specially *Apana Vata*. Also *Apana Vayu* is the controller of all activities related to *Dharan* (hold) and *Nishkramana* (expelled) of *Shukra-Artava.*

The classics too quote *Basti* to be the modality of choice in this context due to its utility in conditions of vitiated *Vata*.[32]

Especially *Anuvasan* (enema with medicated oil), *Niruha* (enema with medicated decoction) and *Uttarbasti* (enema in the genital tract) which are more beneficial in this condition. The classics too quote *Basti* to be the modality of choice in this context due to its utility in conditions of vitiated*Vata*.[32]

***Shaman chikitsa* (Suppression of abnormality at its place only)**

In the menstrual disorders caused by *Vatadi dosha*, drugs suppressing that particular *dosha* should be used. *Kashyapacharya* quotes the use of *Rasona*[33] (*Allium cepa*), *Shatapushpa* (*Anethum graveolens*) and *Shatavari* (*Asparagus racemosus*) to be beneficial in all disorders of *Artava*. He advocates the utility of *Shatapushpakalpa* (a formulation of *Shatapushpa*) [34]in the infertile woman to gain pregnancy.

Also it belongs to *Santorpannotha vikar* so *Apatartan* (decresing the strength and weight) by Shaman should practice which may include *Lekhaniya Mahakashaya, Mustadi Kwatha, Chikitsa siddhanta* of *Staulya, Prameha* etc.

DISCURSION &CONCLUSION-

Hyperandrogenism is a common endocrinopathy of women of reproductive age

which is life style disorder. It is not directly mentioned in *Ayurvedic* classics but from the pathogenesis and clinical manifestations of the hyperandrogenism, it is evident that it is *Tridoshaja vyadhi* in which *Rasavaha*, *Raktavaha, Medovaha & Manovaha strotasa* are involved. Also it belongs to *Santorpannothavikar* so *Apatarpan* by *Shodhana* and *Shaman* & life style modification by practicing *Dinacharya*, *Ritucharya*, *Rajasvala paricharya* etc. should be done.

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