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FUNCTIONAL ASSESSMENT OF FUNCTIONAL HYPOGONADOTROPIC HYPOGONADISM W.S.R. MALNUTRITION AND IT'S POSSIBLE CURE BY SAHASRAVEERYADI GRANULES

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ABSTRACT

Puberty is beginning of adolescence. Puberty can be a stressful and concerning time for adolescents and their families, as it represents a period of significant emotional and physical changes to the body. Pubertal timing is strongly determined by genetics but it also depends on environmental factors such as body mass, nutrition, psychological factors. The onset of puberty brings a number of changes including development of primary and secondary sexual characters,growth spurts, an increase in body fat, increase in bone and muscle development. All of these changes must be supported with adequate intake of nutrition and healthy food choices and hence maintaining the healthy BMI. Typically, girls enter puberty between the age of 8 and 14 years. Delayed puberty in females means that breast development hasn't occurred by 13 or menstruation hasn't begun by 16. One of the commonest cause for delayed puberty isFunctional Hypogonadotropic Hypogonadism seen in poor nutrition intake by girls. Nutrition in childhood and early adolescence affects the timing and form of puberty with consequences of linear growth, body composition and maturation of other physiological systems. Under nutrition and low body fat or an altered ratio of lean mass to body fat seem to delay the adolescent spurt and to retard the onset of menarche. This is review article to see the effect of Sahasraveeryadi Granules in Functional Hypogonadotropic Hypogonadism. Sahasraveeryadi Granules are showing promising effect in increasing BMI, balancing hormones, working both on primary and secondary sexual characters in females simultaneously, maintaining healthy HPO axis and hence attaining healthy and on time

puberty.

KEYWORDS: Delayed puberty, Functional Hypogonadotropic Hypogonadism, Sahasraveeryadi Granules.

INTRODUCTION

Puberty is beginning of adolescence. The onset of puberty brings a number of changes including development of primary and secondary sex characteristics, growth spurts, an increase in body fat, increase in bone and muscle development. All of these changes must be supported with adequate intake of nutrition and healthy food choices. Puberty starts when the pituitary glands begin to produce two hormones LH and FSH which cause the ovaries to enlarge and begin producing oestrogens, The growth spurt starts shortly after breast begin to develop and the first menstruation cycle begins about 2-3 years later.

Puberty is when your body starts to produce sex hormones and undergoes a number of related changes. Typically, girls enter puberty between the ages of 8 and 14 years. Sex hormones are responsible for the physical manifestations of puberty. These include thelarche, the onset of breast development; pubarche, the appearance of pubic hair; gonadarche, the onset of sex hormone production by the gonads; menarche, the initiation of menses. Delayed puberty in females means that breast development hasn't occurred by 13 or menstruation hasn't begunby 16. If and when these processes do start, delayed puberty might prevent them from progressing normally. According to Steinberg (2017), puberty has three main physical manifestations: rapid growth that results in increasing body height and weight, the development of primary sex characteristics, gonads (sex hormones) and development of secondary sex characteristics (changes in breast and genitals, growth of pubic, facial and body hairs).

Adolescence is a time of transformative growth when both under nutrition and obesity affect the maturation of multiple physiological systems. Adolescent malnutrition is multiplicative in that, if any one physiological system is affected, the development of other systems will also be compromised. Nutrition in childhood and early adolescence affects the timing and form of puberty with consequences on linear growth, body composition and maturation of other physiological systems.

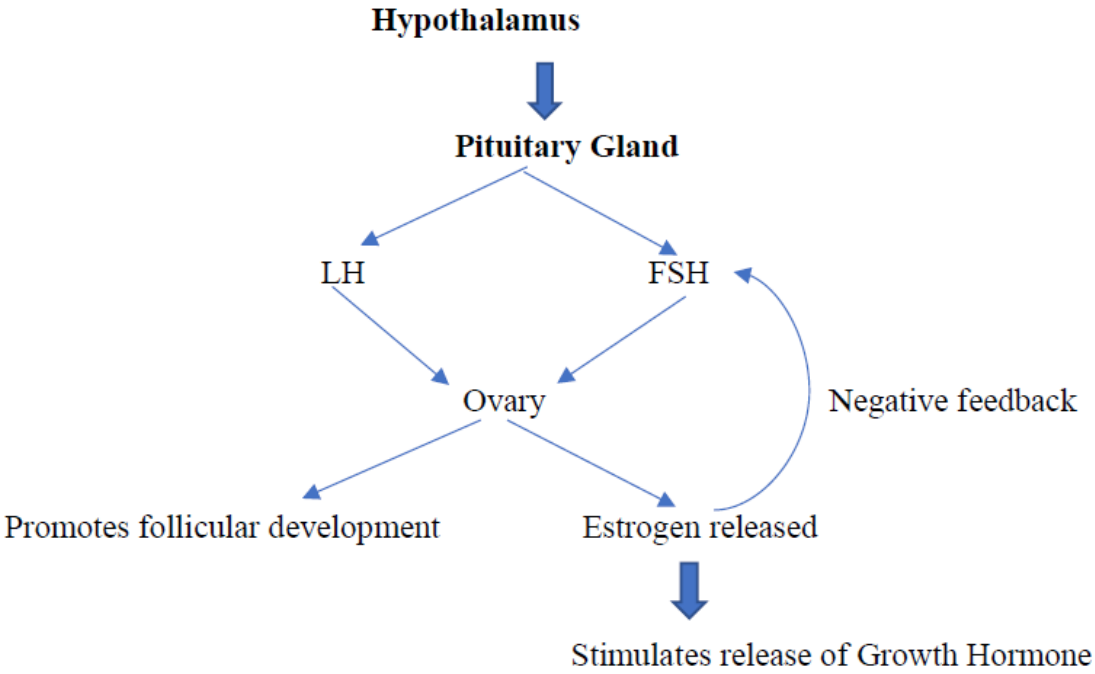

Figure 1: Initiation of normal physiological puberty: Menarche.

Puberty entails a progressive non-linear process starting from pre-pubescent to full sexual maturity through interaction and co-operation of biological, physical and psychological changes. Consuming an adequate and balanced diet during all phases of growth (infancy, childhood, puberty) appears necessary both for proper growth and normal pubertal development. The most common cause of delayed puberty is a functional delay in production of Gonadotropin-Releasing Hormone (GnRH) from the hypothalamic neuronal networks that synergize to initiate the episodic or pulsatile release of the GnRH. GnRH then stimulates pituitary production of the gonadotropins: luteinizing hormone (LH), which stimulates steroidogenesis in the gonads, and follicle-stimulating hormone (FSH), which stimulates gametogenesis. This delay may be due to individual genetic variations, known as Constitutional Delay of Growth and Puberty (CDGP) or other functional defects, such as under nutrition or chronic illness. The resulting GnRH deficiency leads to delays in the secretion of LH and FSH and the subsequent gonadal secretion of sex steroids and in gametogenesis.

AIMS AND OBJECTIVES

1. To understand the epidemiological burden on pubertal female with special reference to delayed puberty.
2. To understand the role of nutrition in pubertal period.
3. To assess Functional Hypogonadotropic Hypogonadism (nutritional deficiency) as a

cause of delayed puberty and review the effect of Sahasraveeryadi Granules on it.

4. To find the easy, early, cost effective and non-hormonal way to deal with nutritional deprived delayed puberty.

MATERIAL AND METHOD

- Collection of material: Required data was obtained from various research papers, PubMed, Scopus, Google scholar, Science direct, Web of knowledge, Web of series and manual search of grey literature, reference clicking and expert contact.
- **Methods**: Study design and search strategy: The study was done after observing the increasing rate of epidemiological burden because of delayed puberty due to poor nutritional values in females. This systematic review study was designed in 2022. The present study was aimed systematically reviewing therapeutic effect of Sahasraveeryadi Granules on delayed menses. To increase scope of research manual search in some of valid journal database were performed.
- Out of various causes of delayed puberty Functional Hypogonadotropic Hypogonadism being commonest caused by poor nutrition is selected and how SahasraveeryadiGranules could help in breaking the pathogenesis of disease is reviewed.

The global nutritional crisis, which forms the backdrop for lives of 1.8 billion adolescents in low-middle income countries has made stunted growth and delayed onset of puberty common in many regions. The onset and progression through various stages of puberty are influenced by number of factors. In humans the age of puberty appears to be related more to body weight than to chronological age. Under nutrition and low body fat or an altered ratio of lean mass to body fat or an altered ratio of lean mass to body fat seem to delay the adolescent spurt and to retard the onset of menarche. According to Frisch, a minimum level of fatness {17% of body fat} is associated with menarche; however heavier minimum weight for height representing an increase amount of body fat (22%) appears necessary for onset and maintenance of regular menstrual cycle in girls over 16 years of age. This critical amount of body fat implies that a particular body composition in addition to other environmental and psychological factors is important in triggering and maintaining pubertal process. Apparently, hypothalamic sensitivity to oestrogens is decreased when the critical ratio of lean mass to body fat is reached and changes in hypothalamic and pituitary hormones promote pubertal progression and establishment of reproductive functions. Poor nutrition alters the ratio of lean mass to body fat and delays onset of menarche. Underweight females generally experience menarche at later

ages than normal weight females. Body's fat content along with a variety of environmental and psychological factors are responsible for development and maintenance of female reproductive system.

Puberty results in very rapid somatic growth, brain development, sexual maturation, and attainment of reproductive capacity. It is accompanied by final maturation of multiple organ systems and major changes in the central nervous system and in psychosocial behaviour (Patton and Viner 2007).

Normally there is negative feedback on hypothalamus in childhood. With the onset of puberty, this negative feedback is removed and there is significant increase in amplitude of pulsatile release of GnRH by the hypothalamus leading to puberty.

Age of puberty in girls – 8 to 12 years
Mean age of puberty in girls- 10.5 years.

On an average the entire time taken for all events to occur in puberty is 4.6 years.
Menarche occurs 2.6 years after onset of puberty.

✦ PROPERTIES AND MODE OF ACTION OF THE DRUG ON THE BASIS OF THEIRCHEMICAL COUNSTITUENTS

1. **ASHWAGANDHA-** The active constituent withaferin A, withanolides, several steroidal lactones & saponins makes ashwagandha as best adaptogenic drug and is known to increase body weight, mean corpuscular haemoglobin concentration and total protein in body.

✦**EFFECT ON FEMALE REPRODUCTIVE SYSTEM-**By having the phytochemicals like steroidal lactones, sitoindosides, beta sitasterol, ergostanes etc this herb work to normalise physiological functional work on H-P-O Axis, neuro-endocrine system, increase the ovarian weight and folliculogenesis with increase in gonadal weight. It is found to compensate LH, FSH decrease or increase.

2. **SHATAVARI –** Presence of various saponins like shatavarins show best adaptogenic effect. It can be given in general debility, chronic infection, inflammatory conditions & helps to gainweight. Amylase and Lipase activities of root have digestive properties.

✦ **EFFECT ON FEMALE REPRODUCTIVE SYSTEM –** Crude extract of plant increases uterine weight. Glycoside, diosgenin, cytosterol present in plant have an estrogenic influence. Italso reduces the risk of postmenopausal osteoporosis. It also improves hormonal imbalance and reduce the symptoms of menopause. It increases the weight of ovaries and improves folliculogenesis, root extract is helpful in serum FSH stimulation.

3. **BALA**-Methanol and aqueous extract of plant helps in reduction of serum glucose level withconcomitant improvement in lipid profile, glycogen content and gain in body weight also theseextract acts as anti-inflammatory & analgesic and have anti-osteoarthritis and anti-stress activity.

✦ **Effect on Female Reproductive System** -It contains phytosterol, sitosterol, sidasterone A, Sidasterone B, rutin, hypaphorine etc which helps in strengthening the urogenital systems of females.

4. **LODHRA**-Hypolipidemic activity in ethanolic extracts of Symplocos racemosa show significant reduction in elevated serum lipids(TC,TG,VLDL,LDL) and restored the decreasedHDL.

✦ **Effect on Female Reproductive System** -Aqueous extract of bark containing Loturine, Colloturine etc. on oral administration show significantly stimulated FSH & LH level and normalise their level in blood. It shows anti-androgenic effect, decrease testosterone level, restores oestrogen, progesterone & cholesterol level hence restores ovarian tissue & improves both ovarian and uterine weight hence strengthen the female reproductive organs. Additionally it also encourages easy flow during menstrual cycle, helps in purifying blood and restores uterus health leading to regular healthy menses.

BMAs these drugs had been used as a great nutritional source as well as has a great impact on our reproductive system (as mentioned in text), so it is expected that their synergism will equally be beneficial in attaining healthy puberty and menarche.

✦**ANUPANA OF DRUG**

GAUKSHEER- Due to its properties like Jeevaniya, Madhura, Bhrumana, Vrishya, Balya, Deepaniya etc.

✦ POSOLOGY: -
Drug Name: Sahasraveeryadi Granules
Constituents: Ashwagandha, Shatavari, Bala, Lodhra
Dosage: 6 gm - 12 gm depending on: Bala, desh, kala, prakriti, agni of patient
Aushadh Sewana Kala: Antrabhakta and Nishakala.
Anupana of drug: Gau dugdh
Route of administration: Orally
Duration of trial: 3 months
Follow up: 15 days

 # WHY POLY-HERBAL FORMULATION (PHF) OF DRUG IS SELECTED

Drug formulation in Ayurveda is based on two principles-

First as a single drug and second use of more than one drug called PHF. This PHF strategy exploits combining several drugs to achieve extra therapeutic effectiveness known as poly-herbalism. For this time-tested drugs – Ashwagandha, Bala, Shatavari, Lodhra are clubbed together to see their synergistic effect as **Sahasraveeryadi Granules.**

Scientific studies have revealed that plants of varying potency when combined theoretically produces greater result as compare to individual use of plant. Combination of herbs may act on multiple targets at same time to provide relief. A lower dose of preparation would be needed to achieve desirable pharmacological action.

Malnutrition

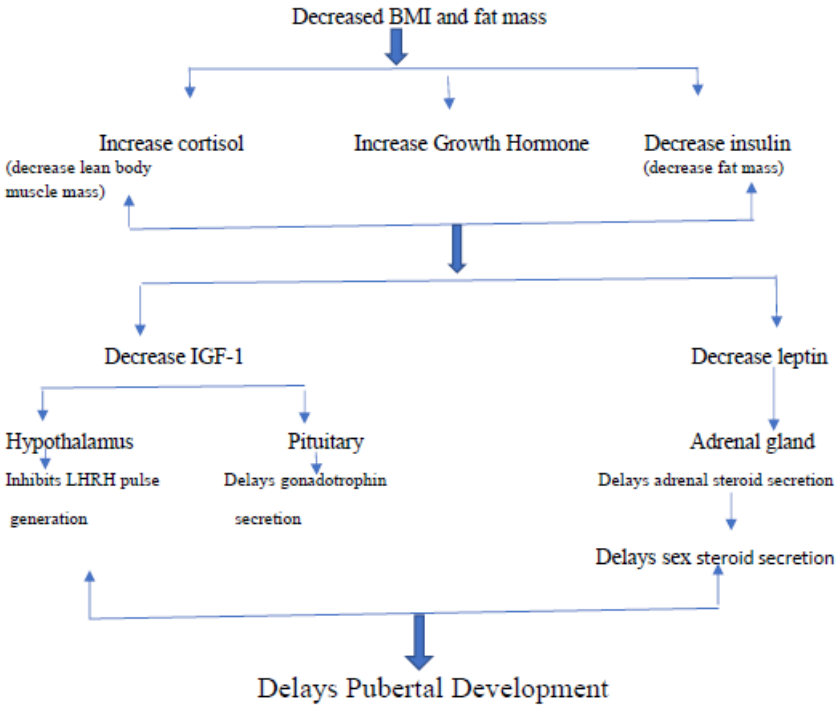

Figure 2: How Malnutrition leads to delayed puberty in younggirls.

The process of puberty begins earlier than most recognize, that is, between the ages of six and eight years with the early phase of adrenarche, the turning on of the adrenal glands. Adrenarche has few phenotypic signs in most children, but increasing evidence indicates that adrenal androgens may contribute to the structural and functional development of the brain and associated behaviours in adolescence (Whittle and others 2015). Body Mass Index (BMI) is associated with adrenal androgens (Corvalan, Uauy, and Mericq 2013). The second phase of puberty is gonadarche, the process of sexual maturation and achievement of reproductive capacity (Marshall and Tanner 1968). The production of gonadal steroids stimulates the growth and development of secondary sexual characteristics; it also kindles development across all organ systems, including the central nervous system. Other endocrine systems mature during puberty, including the growth hormone/insulin-like growth factor and thyroid axes.

Marshall and Tanner (1968) developed a system for identifying stages in the external signs of puberty. The earliest external changes—breast buds in girls and testicular enlargement in boys—typically appear about age 11 years, but vary among individuals. Despite a similar age of gonadarche in boys, these early changes are more visible in girls. Menarche, the onset of menstrual periods (menses), typically occurs in late puberty, approximately two years after breast budding. While menses appears to signal reproductive maturity for girls, it largely signals maturity of the uterus because early menstrual periods are irregular and girls are rarely fertile immediately after menarche (Hochberg and Belsky 2013).

Puberty is generally complete within two to four years following gonadarche, but other changes including fat and muscle patterning continue through adolescence. The timing of puberty is partly genetic (Day and others 2016), but intrauterine events, nutrition, family factors, stress, and socioeconomic conditions also play roles (Hochberg and Belsky 2013).

The bone, renal, immune, and cardiovascular systems are also developing, and liver enzymes and blood lipids are maturing. Bone mineral accretion accelerates during puberty under the influence of gonadal steroids, with peak bone mass achieved by the early 20s (Loud and Gordon 2006). Cardiovascular and renal development means that blood pressure and heart rate make a transition to adult values, in parallel with growth in height and mass. The cardiovascular risk profile differs between the genders, with more adverse lipid patterns among boys than girls. Other blood markers, such as haemoglobin levels, similarly change to a sexually dimorphic pattern.

OBSERVATION AND DISCUSSION

Adolescent malnutrition is multiplicative in that, if any one physiological system is affected, the development of other systems will also be compromised. Nutrition in childhood and early adolescence affects the timing and form of puberty with consequences on linear growth, body composition and maturation of other physiological systems. Puberty entails a progressive non-linear process starting from pre-pubescent to full sexual maturity through interaction and co-operation of biological, physical and psychological changes. Pubertal growth acceleration is largely due to synergistic effects of increased secretion of gonadal sex steroids, Growth Hormone (GH) and IGF-1 and I insulin. During puberty free insulin, IgF-1 and IGF binding protein 3(IGFBP -3) concentration correlate positively with leucine retention (protein accretion). IGF-1 and Growth Hormone decrease leucine oxidation and regulate the efficiency of protein utilisation during puberty. There is significantly increase in DHEA-S during the year when girl had highest rise in BMI compared with the year when BMI rise is lower. This suggest that an increase in body fat may play a critical role in turning on of adrenal androgen secretion and adrenarche. Leptin is reduced and can mediate an inhibitory effect on Hypothalmic Pituitary Gonadal axis and pubertal development. Basal levels of LH(Leutinising Hormone) and FSH (Follicle Stimulating Hormone) are significantly lower and their response of LH to GnRH are diminished. This activity of the GH /IGF -1 and HPG axis is generally restored by nutritional rehabilitation and stable weight gain. Consuming an adequate and balanced diet during all phases of growth (infancy, childhood, puberty) appears necessary both for proper growth and normal pubertal development. Delayed puberty is defined clinically as absence of first signs of pubertal development beyond the normal range. Delayed puberty may also negatively affect adult psychosocial functioning and educational achievement and individuals with history of delayed puberty carry a higher risk for metabolic and cardiovascular disorders.1 Functional Hypogonadotropic Hypogonadism is much more common in females. It occurs secondary to conditions that reduce total body fat which involves significant reduction in calories that decreases leptin concentration in body resulting in deficiency of gonadotropin releasing hormone. GnRH from hypothalamic neuronal network synergise to initiate the episodic or pulsatile release of GnRH. It then stimulates pituitary production of gonadotropin LH which stimulates steroidogenesis in gonads and FSH which stimulates gametogenesis. Reduced LH and FSH secretion combined with lower body fat depress oestrogen production thus delaying puberty. Sahasraveeryadi Granules containing four drugs with Madhur, tikta rasa, laghu, snigdha gunna, madhur vipaka and sheeta veerya have properties of veerya Vardhan, oja vrdhan, balya, brihaniya, rasayana and various phytochemicals works synergistically as

good adaptogen combination which helps in increasing BMI of underweight females by improving their lipid profile. Granules also helps in stimulating LH and FSH and normalizing their level in blood, maintains sex hormone balance and thus improves ovarian and uterine weight which works to normalise the physiological work of HPO axis, hence strengthening the whole female reproductive system.

Causes of delayed puberty

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Functional hypogonadotropic hypogonadism

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- Delays but spontaneous puberty develops.
- Seen in systemic illness and poor nutrition etc.

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Sahasraveeryadi Granules (Ashwagandha, bala, shatavari, lodhra)

- Having qualities – Madhur tikta rasa
  - Tridosha shamak
  - Sheeta veerya, Madhur vipaka
  - Laghu, sigdha guna
- Having properties-
- Veeryavardhan Oja vardhak
- Rasayana Deepana
- Balya Pachana
- Pushtiprada Brihaniya

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Works both on general and reproductive health-

- Good adaptogenic drug.
- Helps in purifying blood.
- Increase body weight, mean corpuscular haemoglobin, total protein and have good anti-oxidant properties.
- Restores cholesterol levels.
- Improvement in lipid profile and glycogen content.

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- Improves hormonal balance.
- Improves folliculogenesis, increase weight of ovaries.
- Stimulates FSH and LH levels.
- Restores oestrogen and progesterone.

Normalise HPO axis and hence balances oestrogens and progesterone levels. Helps in maintaining general and reproductive health among females by acting as a health promoter drink.

Figure 3: Breaking Pathogenesis of Delayed Puberty by Sahasraveeryadi Granules.

CONCLUSION

Puberty is the maturational process of the reproductive endocrine system that results in achievement of adult height and body proportion, in addition to development of the genital organs and the capacity to reproduce. The most common cause of delayed puberty is functional delay in production of GnRH(specially due to under Nutrition) from the hypothalamic neuronal networks that synergise to initiate the episodic or pulsatile release of GnRH. Malnutrition during childhood is associated with delayed puberty and compromised pubertal growth spGnRH Nutritional status during infancy, childhood and peri pubertal period has a significant effect on pubertal development. A strong association is found between onset of puberty and BMI. Sahasraveeryadi Granules by increasing body weight and normalising HPO axis helps in balancing female sex hormones thus improves and maintain general and reproductive health. The Granules will overall results in healthy puberty onset in females.

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