INTRODUCTION

Hypogonadotropic hypogonadism (HH) is defined as a clinical syndrome that results from gonadal failure due to abnormal pituitary gonadotropin levels. HH may result from either absent or inadequate hypothalamic GnRH secretion or failure of pituitary gonadotropin secretion. Low circulating sex steroids associated with low or inappropriately normal gonadotropin levels typically characterize HH. The precise and early diagnosis of HH can prevent negative physical and psychological sequelae, preserve normal peak bone mass, and restore the fertility in affected patients ***(Silveira and Latronico, 2013).***

HH can be congenital or acquired. Congenital HH is divided into anosmic HH (Kallmann syndrome) and congenital normosmic idiopathic HH. Acquired HH can be caused by drugs, infiltrative or infectious pituitary lesions, hyperprolactinemia, encephalic trauma, pituitary/brain radiation, exhausting exercise, abusive alcohol or illicit drug intake, and systemic diseases such as hemochromatosis, sarcoidosis and histiocytosis X. Diagnosis requires the determination of serum follicle-stimulating hormone levels (FSH), luteinizing hormone (LH) levels and testosterone levels as well as MRI scans of the brain and sella ***(Fraietta et al., 2013).***

Inhibin B is produced exclusively by the testis, predominantly by the Sertoli cells in the prepubertal testis. Inhibin B controls FSH secretion via a negative feedback mechanism. During puberty, the main control of inhibin B secretion switches from FSH to spermatogenesis. Basal inhibin B increases under FSH stimulation in the first pubertal stages when the last wave of Sertoli cell proliferation occurs. At puberty, when Sertoli cell proliferation ceases and spermatogenesis starts, the basal, adult inhibin B level is set and can be considered to be an index of Sertoli cell density ***(Meachem et al., 2001).***

AIM OF THE WORK

To measure serum levels of inhibin B in male patients with hypogonadotropic hypogonadism.

REVIEW OF LITERATURE

Physiology of puberty

Puberty is the progression from childhood to the achievement of mature adult secondary sexual characteristics and final adult stature. The hypothalamic–pituitary–gonadal (HPG) axis is active in-utero and for the first 6 months in boys and 2 years in girls (mini puberty). This activity then decreases in childhood due to an inhibitory 'brake' until the onset of puberty ***(Kuiri-Hänninen et al., 2014)***. There is evidence that this 'brake' is more intense and lasts longer in boys, consistent with clinical observations of earlier puberty and greater prevalence of precocious puberty in girls. This 'brake' was originally believed to be centrally controlled and independent of ovarian or testicular action. However, recent studies have shown U-shaped gonadotrophin levels in normal males from birth to puberty, and the same pattern with considerably greater levels in anorchid boys, indicating some contribution of gonads to negative feedback of gonadotrophins in childhood. At puberty, the 'brake' restraining the HPG axis is released, and the hypothalamic generation of gonadotrophin-releasing hormone (GnRH) pulses is stimulated to activate the HPG axis ***(Wei and Crowne, 2016).***

Male puberty:

The hypothalamus, the pituitary gland, and the testes form a system that is responsible for the adequate secretion of

male hormones and normal spermatogenesis; this system is integrated in a classic endocrine feedback loop (Figure 1). The testes require stimulation by the pituitary gonadotropins, i.e., luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are secreted in response to hypothalamic GnRH ***(Layman, 2007)***.

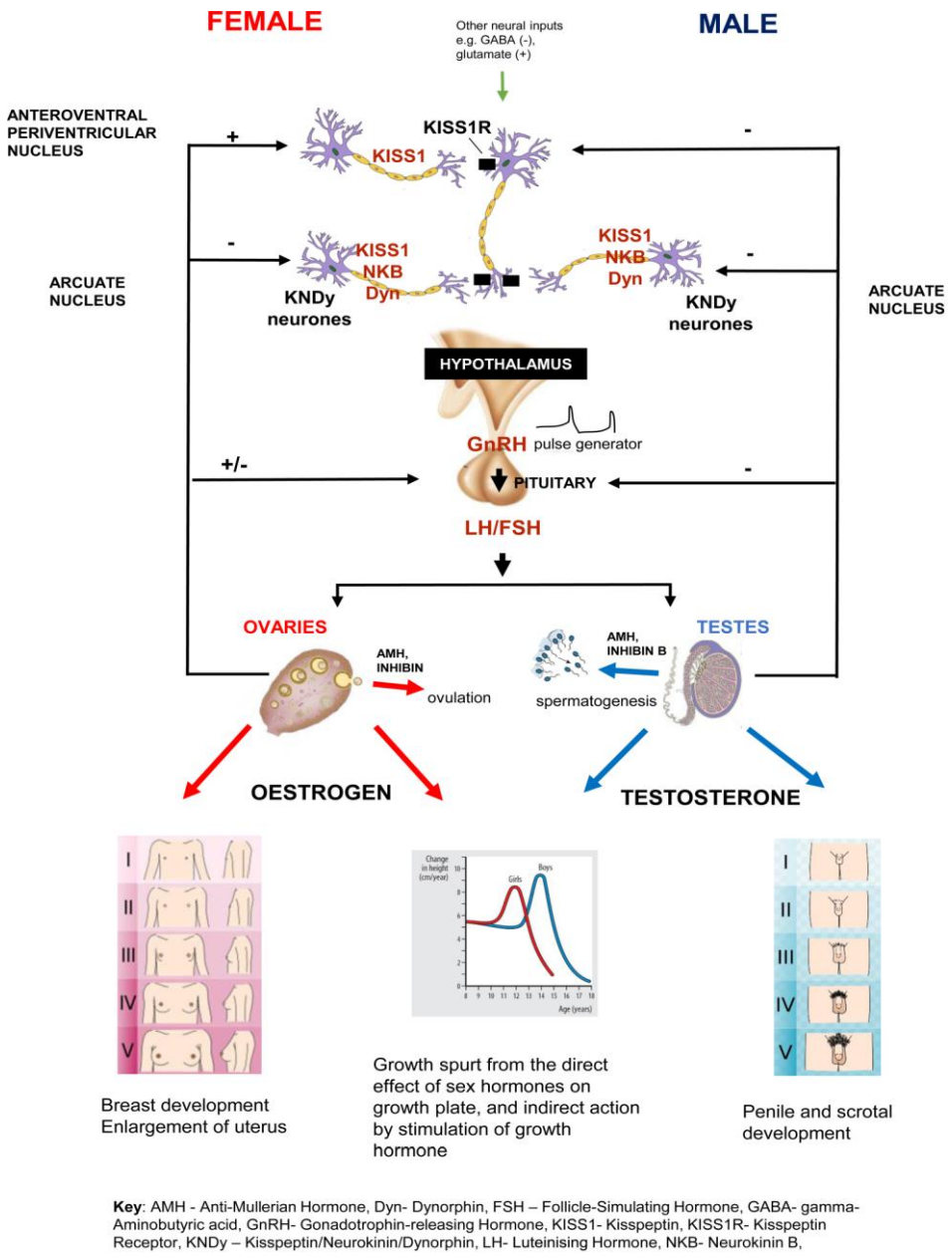

Figure (1): Physiology of hypothalamic–pituitary–gonadal axis in puberty ***(Wei and Crowne, 2016).***

GnRH is a decapeptide that is synthesized by a loose network of neurons located in the medial basal hypothalamus

(MBH) and the arcuate nucleus of the hypothalamus. Some GnRH neurons are found outside the hypothalamus in the olfactory lobe, reflecting their common embryological origin. Developmentally, GnRH neurons originate from the olfactory placode/vomeronasal organ of the olfactory system and migrate along the vomeronasal nerves to the hypothalamus, where they extend processes to the median eminence and pituitary gland. GnRH is synthesized as a precursor hormone that contains 92 amino acids and is then cleaved to a prohormone with a length of 69 amino acids. The prohormone is further cleaved in the nerve terminals to form the active decapeptide. GnRH activation is achieved when specific receptors (i.e., the KiSS1-derived peptide receptor, also known as GPR54 or the kisspeptin receptor) are occupied by kisspeptin protein, which is also produced in the hypothalamus ***(Popa et al., 2008)***. During puberty, the KISS1 system undergoes neuroanatomical and functional activation under neuronal control and influence from environmental factors that are critical for brain sexual maturation and the generation of pulsatile GnRH to enable HPG-axis activation ***(Kaur et al., 2012)***. Androgens (testosterone and dihydrotestosterone) exert negative feedback by activating specific receptors that are located on the kisspeptin-secreting neurons of the arcuate nucleus. Other substances also influence GnRH secretion. Noradrenaline and leptin have stimulatory effects, whereas prolactin, dopamine, serotonin, gamma-aminobutyric acid (GABA) and interleukin-1 are inhibitory ***(Popa et al., 2008).***

The GnRH pulse generator is the main regulator of puberty, and the production of GnRH starts early in fetal life. As a result, gonadotropin levels change drastically during fetal development, childhood, puberty and adulthood. Male infants exhibit what is called a "window period" during the first six months of life, during which gonadal function can be clinically detected in response to gonadotropin stimulation. After that period, serum gonadotropin levels drop and can only be detected again with the onset of puberty ***(Layman, 2007).*** The essential function of GnRH is to stimulate the secretion of LH and FSH from the anterior pituitary gland. LH and FSH are glycoproteins consisting of alpha and beta polypeptide chains (α and β subunits). They have identical alpha subunits but differ in their beta subunit, which determines receptor-binding specificity. Once synthesized, LH and FSH are stored in granules in the pituitary gland. GnRH induces exocytosis of the granules and the release of these hormones into the circulation. A low GnRH pulse frequency tends to preferentially release FSH, whereas higher frequencies are associated with preferential secretion of LH ***(Ferris and Shupnik, 2006)***.

Gonadarche refers to the onset of gonadal sex steroid production during puberty. Gonadarche results from pulsatile GnRH secretion from the hypothalamus. GnRH secretion occurs every 60 to 90 minutes ***(Viswanathan and Eugster, 2011).*** GnRH pulsatility causes pulsatile pituitary gonadotrophins production initially at night, then across 24 h.

Pulsatile LH stimulates testosterone production from Leydig cells while FSH stimulates germ cell maturation and spermatogenesis in the seminiferous tubules, resulting in testicular enlargement ***(Wei and Crowne, 2016).*** Sertoli cells have receptors for FSH and testosterone. It is therefore believed that both FSH and testosterone support the initiation of spermatogenesis and that both are necessary for the maintenance of quantitatively normal spermatogenesis. Testosterone or its metabolite dihydrotestosterone binds to androgen receptors on Sertoli cells and then modulates gene transcription ***(Raivio et al., 2007)***. FSH binds to FSH receptors on Sertoli cells and initiates signal transduction events that ultimately lead to the production of inhibin B, which is a marker of Sertoli cell activity. Inhibin B and testosterone in turn regulate pituitary FSH secretion. The dual hormonal dependence of normal spermatogenesis can be appreciated in males with hypogonadotropic hypogonadism. Sperm production is restored to approximately 50% of the normal level with either FSH or hCG alone; only the combination of hCG plus FSH leads to full quantitative restoration ***(Farietta et al., 2013)***.

Development of secondary sexual characteristics and growth spurt reach the peak in the second half of puberty (testicular volumes >10 mL). The growth spurt is due to oestrogen-primed increase in growth hormone (GH) production, with the additional effect of androgens in boys.

Oestrogen is responsible for the maturation and eventual fusion of the growth plate in both sexes ***(Wei and Crowne, 2016).***

It has been suggested that testicular function is also regulated by other factors. For instance, Sertoli cells are influenced by factors secreted by the germ cells. The testes are a major site of estrogen production; however, direct evidence for a role of estrogen in spermatogenesis has not yet been identified ***(Maffei et al., 2004).***

Although gonadotropins are the major regulators of testicular function, there is controversy as regard to the relationship between hypo- and hyperthyroidism and LH and FSH levels in men. T3 is likely to represent a major hormonal signal to Sertoli cell proliferation during testicular development, and ultimately affecting the establishment of the adult Sertoli cell population ***(Wajner et al., 2009).***

Puberty examination in males:

Pubertal maturation can be described in terms of sequence, timing, and tempo (Puberty consists of a series of predictable events, and the sequence of changes in secondary sexual characteristics). The staging system utilized most frequently is that published by Marshall and Tanner and the sequence of changes, commonly referred to as **"Tanner stages"**. The Tanner scale (also known as the Tanner stages) is a scale of physical development in children, adolescents and adults. The scale defines physical measurements of development based on external primary

and secondary sex characteristics, such as the size of the breasts, genitals, testicular volume and development of pubic hair. This scale was first identified by James Tanner, a British pediatrician, and thus bears his name ***(Marshall and Tanner, 1970)***.

Table (1): Sexual Maturity Rating (SMR) Stages in Males ***(Marshall and Tanner, 1970):***

Tanner stage	Pubic hair	Penis	Testes
1	None	preadolescent	preadolescent
2	Scanty, long, slightly pigmented	Minimal change/enlargement	Enlarged scrotum, pink, texture altered
3	Darker, starting to curl, small amount	Lengthens	Larger
4	Resembles adult type, but less quantity, coarse, curly	Larger; glans & breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

Factors controlling the timing of puberty:

There is increasing evidence of the impact of genetic and environmental factors on pubertal timing.

Genetics:

The heritability of pubertal timing is supported by observations from clinical practice, large case series of delayed puberty and ethnic differences in the age of pubertal onset

(He and Murabito , 2014). The concordance of timing in monozygotic twins suggests that genetic factors account for 50%–80% of variation in pubertal timing ***(Parent et al., 2003)***. Inheritance of pubertal timing with autosomal dominant pattern has been described ***(Wehkalampi et al., 2008).*** Several single gene defects affecting GnRH development, migration or action causing isolated hypogonadotropic hypogonadism (IHH) have been identified ***(Bonomi et al., 2012).***

Multiple regulatory genes are more likely to explain the continuous distribution of pubertal timing in populations, and this has been explored recently with genome-wide association studies (GWAS). GWAS can investigate heritability of puberty by studying thousands of single nucleotide polymorphisms across the entire genome in large populations. Thirty-two genetic loci that regulate timing of puberty were identified using GWAS ***(Elks et al., 2010).*** Specific gene loci, *LIN28B* on chromosome 6 is associated with earlier signs of sexual maturation and signs of growth in both genders ***(Ong et al., 2009).*** *MKL2* on chromosome 16 is associated with both the timing of sexual development and the pubertal height growth spurt. Loci associated with increasing body mass index were also associated with earlier puberty in girls, and either earlier or later pubertal timing in boys, consistent with epidemiological data in body composition and pubertal timing ***(Cousminer et al., 2014)***.

Environmental factors:

Environmental factors may affect pubertal timing through epigenetic mechanisms at specific windows of development in neonatal or early postnatal life. It is proposed that environmental risk factors that threaten species survival may cause early puberty to ensure the reproductive cycle is expedited, while those occurring later (for instance, chronic disease, malnutrition) cause delayed puberty, postponing reproduction until circumstances improve. For example, stress in early childhood (birth–7 years) is associated with early puberty, whereas later exposure results in delayed puberty. The impact of endocrine disruptors, which are environmental chemicals such as, industrialized chemical, pesticides, phytoestrogens are currently under close observation of their effect on the timing of puberty, potentially via interactions with sex steroid receptors. Results in their influence on pubertal timing are variable, with some suggesting early and others with no change ***(Parent et al., 2015).***

Delayed puberty

Puberty involves the interplay of multiple genetic and endocrine controls to produce the gradual development of secondary sexual characteristics and ultimately reproductive capability, growth spurt and completion of growth. As puberty occurs at a key time in terms of social and educational development, any aberrations in timing, whether pathological or not, may have significant impacts on physical and psychological health. Associations between earlier or later

timing in puberty in both genders have been linked with a wide range of adverse health outcomes, including cancers, cardio metabolic, gastrointestinal, musculoskeletal and neurological pathologies ***(Day et al., 2015).***

Delayed puberty is defined as the lack of the initial signs of puberty (testicular enlargement to ≥4 mL in boys) at an age that is 2–2.5 SDs beyond the population mean ***(Marshal and Tanner, 1970).***

The presence or absence of pubic hair is not part of this definition because it can be due to androgen production from the adrenal gland (adrenarche) instead of the gonad. Traditionally, the age cut-offs for delayed pubery are a chronological age of 13 years in girls and 14 years in boys ***(Palmert and Dunkel, 2012).***

Delayed puberty in boys is one of the commonest reasons for referral to a pediatric endocrinologist. The prevalence in Paris is approximately 2% at 14 yr of age, with 0.4% remaining prepubertal 1 yr later. The differential diagnosis lies between constitutional delay of puberty (CDP) and isolated hypogonadotropic hypogonadism (IHH), with an estimated prevalence of 0.1 to 0.25% in males ***(Coutant et al., 2010).*** It is difficult to differentiate between HH and delayed puberty, as low gonadotropin and testosterone levels are found in both conditions. Therefore, a definitive HH diagnosis must be confirmed only after the patient is 18 years of age ***(Fraietta et al., 2013).***

Table (2): Causes of Delayed Puberty

Causes	Examples
Constitutional delayed growth and puberty CDGP	
Functional delayed onset of HPG-axis activity	**Physical conditions:** Isolated growth hormone deficiency, hypothyroidism, asthma, coeliac disease, inflammatory bowel disease, chronic renal failure, cystic fibrosis. **Malnutrition:** Anorexia nervosa, poverty and starvation **Overtraining:** Athletes, gymnastics
Hypogonadotrophic hypogonadism	**Idiopathic Hypogonadotrophic Hypogonadism.** **Intracranial disorders:** Tumours, other acquired disorders, congenital disorders **Congenital gonadotrophic deficiency:** -Monogenetic mutation for isolated gonadotrophin deficiency (GnRH1, GnRH Receptor, Kiss1R, Kiss1, TAC3 neurokinin B, TACR3). -Kallmann syndrome (KAL1, FGF8, FGR1, PROK2, PROKR2). -DAX1 mutations (adrenal hypoplasia congenita) **Multiple pituitary hormone deficiencies associated with mutations of transcription factors:** HESX1, PROP1, SOX2, SOX3, LHX3, LHX4 **Part of a genetic syndrome:** Prader–Willi, Laurence–Moon or Bardet–Biedl syndromes **Permanent damage secondary to chronic disease:** Iron deposition from transfusion-dependent haemoglobinopathies.
Hypergonadotropic hypogonadism	

Different causes of delayed puberty ***(Wei and Crowne, 2016)***