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Editorial

Luteinizing Hormone Deficiency: Historical Views and Future Perspectives

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Editorial

Fertility in men requires normal testicular development, which is controlled by chorionic gonadotropin (hCG) *in utero* and thereafter by luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [1]. Some rare observations, such as, mutations in the luteinizing hormone subunit beta gene [2] have contributed substantially to our understanding of reproductive development and male infertility.

In Argentina in 1950, Pasqualini and Bur described a 24-year-old man with a well-defined syndrome of clinical and hormonal hypoandrogenism who had a eunuchoid body habitus [2-4]. A testicular biopsy demonstrated that in 82 percent of the seminiferous tubules there was full spermatogenesis, whereas in 5 percent, only a Sertoli syncytium was present; in the remaining tubules there was incomplete spermatogenesis and scarce Leydig cells [3,4]. The salient characteristics of the syndrome were the presence of spermatogenesis despite moderate to severe androgen deficiency. Treatment with chorionic gonadotropin increased the secretion of androgens [3,4].

In the United States in 1953, McCullagh et al. described five other men with similar characteristics [5]. They coined the term "fertile eunuch" to describe these men. Both research teams suggested that these patients could have a decrease in interstitial-cell stimulating hormone (or LH) with a probably normal elaboration of FSH.

A first step in the understanding of the physiopathology of Pasqualini syndrome was the demonstration of isolated luteinizing hormone deficiency (both in plasma and in urine) in a patient studied by Faiman et al. [6]. Although it could be foreseen that more cases of this syndrome would come to light, the cause of LH deficiency remained elusive until the advent of the genetic era.

The next breakthrough came with functional and genetic studies that validated the hypothesis of a functional deficit of LH in these men. In 1992, Weiss et al. identified, among a consanguineous family, a hypogonadal male [7]. He had high FSH and LH levels but LH had a reduced biological activity. Klinefelter syndrome was ruled out. Sequencing of *LHB* gene demonstrated a homozygous mutation (p.Gln54Arg), explaining both the immunological activity but biologically reduced activity. In 2004, we described, in collaboration with a Swiss group, a man with a homozygous missense mutation (p.Gly36Asp) in the *LHB* subunit gene that abrogated subunit dimerization and rendered LH biologically and immunologically inactive [8]. Treatment with human chorionic gonadotropin (hCG) induced near normalization of testicular structure [8,9]. Recently we studied another family of two affected brothers. Both patients harbored a new beta LH mutation (p.Lys40del) impairing the intracellular exportation and secretion of LH by gonadotrophs [10].

Several groups [7-14], including ours demonstrated in these hypogonadal patients that LH was hormonally inactive but had varying degrees of immunological activity due to one or more inactivating mutations in the *LHB* gene. In patients with LH deficiency, sexual differentiation is normal, due to placental hCG effects. This is in line with LH-deficient anencephalic male fetuses; in which normal masculinization of the reproductive tract occurs while high levels of hCG are present [15]. However, the absence of or the reduction in LH secretion in males with *LHB* gene mutations impairs puberty and alters Leydig cell proliferation and maturation. LH deficient males have reduced spermatogenesis, ranging from azoospermia to oligospermia, which has been linked to the lack of LH stimulation and low intratesticular testosterone action [2-14].

An immunologically anomalous form of LH, due to two point mutations (p.Trp28Arg) and (p.Ile35Thr): was called V-LH. The variant V-LH was identified in Finland [16], then in Japan [17]. The p.Trp28Arg polymorphism creates an additional glycosylation site in the beta LH protein. Thereby, this LH variant has an increased *in vitro* bio activity, while its half-life in circulation is longer. Current LH antibody assays are not designed to detect variant LH, which may pose difficulties when testing [16,17]. The prevalence of different polymorphisms of LH can range from 11% to 26% in selected populations, such as males with infertility and/or abnormalities in testicular descent [18,19]. As more physicians are able to diagnose luteinizing hormone (LH) deficiency, the issue of the best therapeutic strategy to offer to these patients is unresolved. Although testosterone administration may render the secondary sexual characters, it does not promote testicular development [14]. Through mimicking of the "mini puberty" state, gonadotropin treatment may develop the fertility potential of these patients if it is done early after the diagnosis of hypogonadotropic hypogonadism [16]. Five [7,8,10,13] of eight LH deficient patients (including our three male patients) with documented *LHB* mutations were treated with human chorionic gonadotropin. After one to two years of treatment, they had virilization and testicular growth with somehow impaired spermatogenesis [2-3,7-14]. Our first male patient successfully underwent assisted reproduction [9]. He had recently a second child via the same reproductive method [20].

According to this experience and the available literature on this very rare disorder, we propose that young pubertal males with LH deficiency due to a documented *LHB* mutation should be

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first managed with gonadotropins (hCG, recombinant LH) rather than testosterone. This strategy can promote Sertoli and Leydig maturation, and it may improve spermatogenesis and maximize the potential for fertility [20]. More studies are needed in infertile male patients with LH variants to demonstrate if recombinant LH or hCG treatment could be beneficial in selected populations.

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