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Chapter 5

The Role of the Human Growth Hormone Gene Family in Pregnancy

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Abstract

A pregnant woman´s body undergoes profound anatomical and physiological changes to accommodate the needs of the maternal-fetal unit required for a successful pregnancy. During normal pregnancy, the placenta produces a variant of human growth hormone as well as a chorionic somatomammotropin hormone. These are the placental members of the human growth hormone gene family and play a crucial role in the regulation of maternal and fetal metabolism, as well as in the growth and development of the fetus. For this reason, the scope of this chapter is to describe the differences of the biochemical and physiological roles of the hormones coded in this locus during pregnancy, the repercussions of their deficiencies, and role in some of the most prevalent pathologies during pregnancy affecting either the mother or the fetus and also to describe how pioneering sequencing of this locus allowed our laboratory to invent the first companion diagnostics test and thus contributed to the dawn of the personalized medicine era.

Keywords: placenta, growth hormone family, HGH physiology, placental variant HGH, chorionic somatomammotropin hormone, hormonal deficiencies, companion diagnostics, personalized medicine

1. Introduction

The first correlation between growth disorders and the pituitary gland occurred at the beginning of the twentieth century. Human growth hormone (HGH) was later identified as the main promoter of postnatal body growth. Its availability as a recombinant drug at the end of

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The 1980s sparked many investigations aimed at exploring many alleged roles in adult health and even in longevity. Likewise, the cloning of its gene and the discovery that it belongs to a gene family along with genes for variant or placental HGH (HGH-V) and chorionic somatomammotropin hormone (CSH: previously referred as placental lactogen) accelerated the understanding of the role of this family in human biology and medicine [1]. Today we understand in detail the molecular mechanisms of their functions, either direct or via mediators, and the role they play in many physiological and pathological processes, although other possible but suspected roles remain unknown. One of the most interesting and fascinating functions of this family of hormones is their contribution to fetal health during pregnancy, although, surprisingly, normal pregnancies with total or partial absences of one or both of the placental hormones have been reported.

2. The HGH family: anatomy, physiology, and homeostasis

In humans, the growth hormone (GH) family includes the pituitary HGH (referred as HGH-N), the placental HGH (named HGH-V), and the CSH; along with prolactin (PRL; a more evolutionarily distant relative) they are collectively referred as somatolactogens. By virtue of their similarities, it was proposed that their genes were derived by gene duplication from a common ancestor dating from the first vertebrates [2]. Over time the members of this family became specialized, developing specific functions: HGH-N has been attributed metabolic and

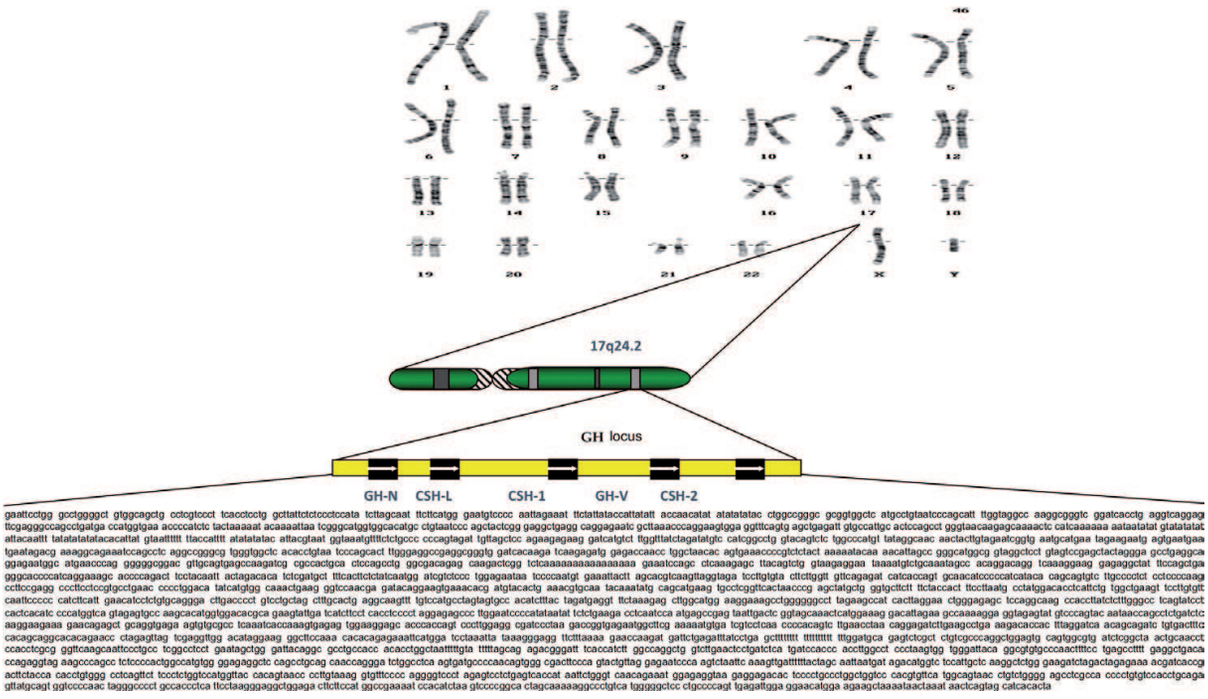


Figure 1. The hGH chapter of the human genome encyclopedia. The *hGH* locus was the first non-highly repetitive DNA element to be localized in the human karyotype. It turned out to harbor the five genes here described. Its sequencing was a world record back in 1988.

somatogenic functions after birth, HGH-V has been attributed metabolic and somatogenic functions during pregnancy, and CSH is considered a lactogenic hormone. PRL is considered a multifunctional hormone [3].

In humans, the *hGH* locus, which includes *hGH* and *hCSH*-type genes, spans approximately 50 kb of band 24.2 at the long arm of chromosome 17. PRL is coded by a single gene that is located on chromosome 6 [4, 5]. The locus′ five genes are arranged in tandem, all in same orientations, and exhibit very high sequence and organizational similarities. At the 5′-end of the locus is the *hGH-N* gene, followed by the pseudogene *hCSH-L*, then *hCSH-1*, next *hGH-V*, and CSH-2 in the end [5] (**Figure 1**).

While the *hGH-N* gene is expressed in the pituitary and yields at least two isoforms (22 and 20 kilo Daltons), the rest do so in the placenta and are responsible: one (*hGH-V*) of the placental variant of HGH or HGH-V and two (*hCSH-1* and *hCSH-2*) for a single mature isoform of HCS. The so-called *hCSH-L* is a pseudogene and thus is postulated to contribute no protein [5].

2.1. Human growth hormone (HGH)

HGH can exert metabolic effects either directly or indirectly through, in the latter case, the increase in hepatic production of the insulin-like growth factor 1 (IGF-1). Regarding their direct actions, the administration of HGH has been reported to antagonize the action of insulin, thus producing intolerance to carbohydrates in spite of elevated plasma insulin levels. In contrast, insulin sensitivity increases during the administration of IGF-1, which exerts hypoglycemic effects even with concomitant suppression of insulin secretion. Another important direct metabolic effect of HGH is to increase the mobilization and oxidation of fat and therefore to reduce total body fat; there is no evidence that IGF-1 acts directly on adipose tissue in vivo. The administration of HGH results in the retention of sodium through the stimulation of Na-K-ATPase. It is suggested that part of the effects of HGH on tubular function (e.g., phosphate reabsorption) is mediated through IGF-1 [6].

The administration of HGH increases the circulating levels of IGF-1 through the stimulation of its hepatic synthesis and secretion; it can also improve the synthesis of local IGF-1 in peripheral tissues, where it exerts autocrine or paracrine effects [6]. While HGH increases lipolysis, as a direct effect on the adipocyte, as well as the oxidation of lipids by increasing substrate availability, IGF-1 increases lipid oxidation only when administered chronically, most likely as a result of chronic insulinopenia. These metabolic regulators have been tested in a variety of catabolic conditions in man, and both hormones have been effective in reducing protein loss caused by glucocorticosteroids and in mitigating some of the catabolic effects of severe hypogonadism in men [7].

Another function of IGF-1 is to increase myelination by increasing the number of myelinated axons and the thickness of myelin sheaths. The latter is by mechanisms involving the stimulation of myelin protein gene expression and by increasing the number of oligodendrocytes [8]. For this reason, people with IGF-1 deficiency, caused by a homozygous mutation in the *IGF-1* gene at the 12q22 locus, present, in addition to intra- and extrauterine growth retardation, mental retardation and sensorineural deafness [9].

Some studies have compared the phenotypes of dwarfism manifested in mutant mice lacking the HGH receptor, or IGF-1, or both, and have provided conclusive evidence that HGH and IGF-1 promote postnatal growth, both by independent and by common functions, given that the delay in the growth of double nullizygotes HGHR/IGF-1 is more severe than that observed with any of the mutant classes separately [10].

2.1.1. Physiological regulation

2.1.1.1. Somatomedins

The insulin-like growth factors, IGF-1 and -2, share structural and functional similarities with insulin. Together with insulin, they make up a family of phylogenetically conserved molecules important in the regulation of both growth and metabolism. IGF-1 and IGF-2 (constitute a small proportion of the total IGFs present in plasma) function predominantly as growth regulators. While it is true that the liver is the source of most (75%) of plasma IGF-1, it is also synthesized by multiple mesenchymal cell types [11]. As a result, there are two main mechanisms of IGF-1 regulation: (1) The IGF-1 that is synthesized in the liver and secreted to the blood is under the control of HGH, and (2) autocrine/paracrine IGF-1 synthesized in peripheral tissues, such as bone, is controlled by HGH and by factors that are secreted locally by the surrounding cell types.

IGF-1 exerts its effects through the activation of the IGF-1 receptor. This receptor is present in multiple types of cells and tissues, which probably explains its ability to stimulate balanced and symmetric growth [12].

2.1.1.2. HGHRH

The role of a GH-releasing hormone (GHRH) in the regulation of HGH secretion has been recognized since the late 1950s, based on several lines of evidence that postulated its existence. These lines of evidence include that the interruption of the connection between the hypothalamus and the pituitary gland leads to a decrease in HGH secretion; that the electrical stimulation of the ventromedial nucleus and the basal hypothalamus stimulates the secretion of HGH; and that hypothalamic crude extracts stimulate the release of HGH from anterior pituitaries in culture [13]. The cell surface receptor for HGHRH (HGHRH-R) has been incompletely characterized. More is known about the post-receptor events triggered by HGHRH. The binding of HGHRH to its receptor stimulates the formation of cyclic AMP, which stimulates an AMPc-dependent protein kinase located in the secretory granules of the pituitary gland, which increases exocytosis of granules and causes the acute release of preformed HGH [13]. HGHRH not only stimulates the release but also stimulates the synthesis of HGH. It has been shown that HGHRH can alter the transcription of the *hGH* gene both in vitro and in vivo, with an increase of 2.5 times 30 minutes after the injection of HGHRH [14].

2.1.1.3. Somatostatin

Somatostatin (SST) is one of the oldest peptides in neurobiology. It was originally discovered in 1972 as part of the hormone-releasing family because of its property to inhibit the secretion of

HGH in monolayers of pituitary cells in vitro. Despite its well-known neuroendocrine effects, it was quickly shown to inhibit a series of endocrine and exocrine secretions along the neural-gut axis including, for example, pancreatic insulin and glucagon or myenteric acid secretions [15].

SST is a cyclic tetradecapeptide synthesized in the hypothalamus, from where it is transported to the anterior pituitary gland where it is responsible for the pulsatile release of HGH and for inhibiting tonically the secretion of HGH and TSH. Several loops of internal feedback, sleep, exercise, and chemical agents control and influence the release of SST [16]. SST acts through six separate surface receptors (SSTR-1, SSTR-1-2A, SSTR-1-2B, SSTR-1-3, SSTR-1-4, SSTR-1-5), members of the family of G protein-coupled receptors, characterized by seven transmembrane-helical domains, creating three intra- and extracellular loops. The binding of the receptor and the ligand (SST/SSTR) results in specific cellular activities for each receptor, or combinations of receptors, and their cellular/tissue localization, although it is known that the common effect is a reduction in cyclic adenosine monophosphate (cAMP) and Ca^{++} with activation of protein phosphatases [16].

3.1.1.4. Other important elements of the pathway

There are many elements whose correct functioning is necessary for the hormonal system of the HGH family to work properly; among the most important of these, we have the transcription factor Pit-l, a member of a POU-domain family of binding factors of DNA; it is a specific pituitary factor that binds to and activates the promoters of both *hGH* and *hPRL* genes. It has also been speculated that Pit-I could play a critical role in the ontogeny of HGH, PRL, and thyroid-stimulating hormone (TSH) producing cells [17].

Another no less important element is prophet of Pit-1 (PROP-1), which is a transcription factor capable of binding to the sites in an early promoter of the *PIT-1* gene and regulating its expression, which is necessary for the development of the pituitary gland and the expression of the hormone [18]. Mutations in this gene have been associated with a combined pituitary hormone deficiency, as well as deficiencies in luteinizing hormone, follicle-stimulating hormone, HGH, PRL, and thyroid-stimulating hormone [18].

2.2. The growth hormone receptor (GHR)

The cloning of the HGH receptor (HGHR) gene in 1987 opened the door for the study of HGH signaling at the molecular level. Its mRNA encodes a protein of 638 amino acids (aa) with single extracellular, transmembrane, and cytoplasmic domains [19]. HGHR belongs to the transmembrane superfamily of proteins that includes the PRL receptor (PRLR) and a number of cytokine receptors [20].

The determination of the structure of HGH bound to the extracellular domain of HGHR has led to the model where a single molecule of HGH binds to two molecules of HGHR. This binding of HGH leading to the HGHR (2)-HGH complex is thought to be sequential. The initial step is the binding of HGH to a high-affinity HGHR monomer, whereby a different face of HGH is contacted by a second HGHR monomer, stabilizing the HGHR dimer. This binding of HGH to its receptor dimer is thought to be an initial and crucial event in the HGH signaling [19]. Subsequent to this, a conformational change in the extracellular domain of the receptor

is important for signaling. At present, virtually nothing is known about the structure of the cytoplasmic domain of the HGHR; a clue to the mystery of the signaling mechanism came with the discovery that HGH promotes the tyrosine phosphorylation of receptors and other cellular proteins. The current working model of the signal transduction of HGH action is that its binding to two HGHR monomers increases the affinity of each receptor for JAK2. The dimerization brings two JAK2 molecules in proximity so that each JAK2 can phosphorylate the activation tyrosine of the other JAK2 molecule, blocking it in an active conformation. This allows the activated JAK2 to phosphorylate itself and the cytoplasmic domain of the HGHR in the tyrosine residues, in order to activate the signaling pathway required for the specific function of the HGH that needs to develop: regulation of gene transcription, metabolic actions, etc. [19].

2.3. The IGF receptor

The components of the IGF system include IGFs (IGF-1 and IGF-2), IGF type 1 (IGF-1R), and type 2 (IGF-2R) receptors, a family of six secreted IGF binding proteins (IGFBP) and IGFBP proteases [21]. The two IGF receptors are structurally and functionally related. The signaling of the IGF ligand is mediated by IGF-1R, which is a transmembrane glycoprotein with tyrosine kinase activity. IGF-2R is a single-chain protein with no kinase activity. IGF-1R binds to IGF-1 with up to 20 times higher affinity than with IGF-2, while IGF-2R binds strongly to IGF-2 but hardly recognizes IGF- 1. The genes for IGF2 and IGF2R have imprinting, expressing themselves in a monoallelic way depending on the parental origin [21].

IGF-1R is activated by two ligands, IGF-1 and IGF-2, and by insulin at supraphysiological concentrations [22]. After the binding of IGF-1 to its receptor, it undergoes a conformational

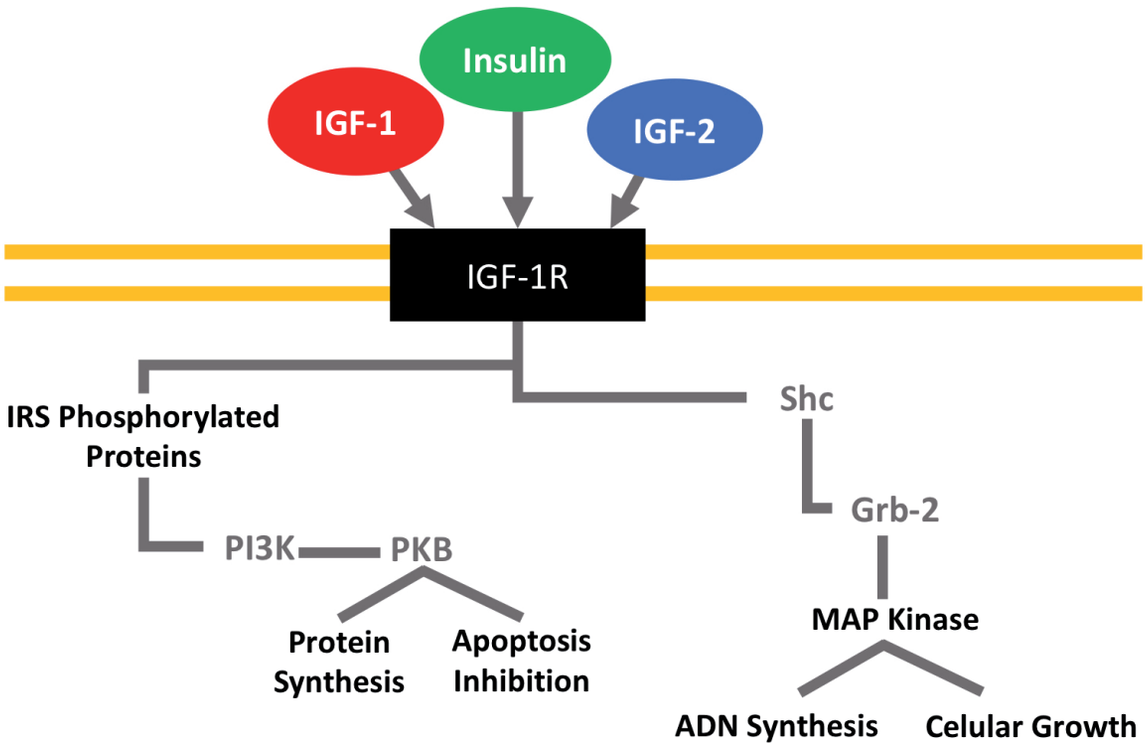


Figure 2. Molecular mechanism of IGF-1R. The signal transduction elicited by insulin and insulin-like growth factors is depicted.

change that unleashes its tyrosine activity kinase (TK). This autophosphorylates tyrosines which act as coupling sites for Shc (a signaling adaptor protein) and IRS-1 or IRS-2 signaling proteins. The IRS proteins are phosphorylated by the TK activity of the receptor and then binds to the p85 subunit of phosphatidylinositol 3-kinase (PI3K), which is the type A regulatory/subunit of the isoforms of class 1 of the PI3K, leading to the activation of protein kinase B (PKB) and the stimulation of protein synthesis, as well as the inhibition of apoptosis. The Shc signaling protein is also phosphorylated, which allows it to bind to growth factor receptor-bound protein 2 (Grb-2), leading to the activation of MAP kinase and the stimulation of DNA synthesis and cell growth (**Figure 2**).

The critical importance of this receptor for normal development and physiology is underlined by neonatal lethality as a result of its complete absence. Conversely, IGF-2R, also called mannose-6-phosphate receptor independent of cations, is less important for growth stimulation but is important for the regulation of IGF-1 and IGF-2 activities, both by sequestration of hormones, as by promoting their degradation [23].

IGF-2 is a key regulator of cell growth, survival, migration, and differentiation. Its fundamental role in these processes requires strict regulation, both of expression and activity. The IGF-1R mediates the actions of IGF-2, and a family of six high-affinity binding proteins of IGF (IGFBP-1 to IGFBP-6) regulates the circulating half-life of IGF-2 and its availability to bind to IGF-1R. In addition, IGF2-R modulates circulating and tissue levels of IGF-2, directing it to lysosomes for degradation [23].

An example of the growth regulation function of IGF-2 is the Beckwith-Wiedemann syndrome (BWS), which is a pediatric overgrowth disorder with predisposition to form embryonic tumors. Individuals with BWS can grow at a higher rate during the second half of pregnancy and in the first years of life [24]. BWS results from alterations in the imprint control region 1 (ICR1), either by deletion or by DNA methylation. The ICR1 region controls the genomic imprint of the *H19* gene, a gene that, unlike many others, does not code for a protein but rather a noncoding RNA molecule whose function is unknown, although it is suspected that it acts as a suppressor of the tumor and of the *IGF-2* gene, which has already been mentioned previously. This anomaly alters the regulation of both genes; specifically, it leads to a loss of the activity of the *H19* gene and an increase in the activity of the *IGF-2* gene in many tissues [25].

3. HGH and IGF-1 during pregnancy

The pregnant woman undergoes profound anatomic and physiologic changes in almost every organ system. These adaptations to the pregnant state begin just after conception and evolve through delivery, after which they almost completely revert to the nonpregnant state over a period of weeks. The purpose of these alterations is to accommodate the needs of the maternal-fetal unit.

During pregnancy, pituitary HGH-N synthesis in the mother is suppressed, and HGH-V starts to be synthesized by the placenta, becoming the predominant HGH in the pregnant women [26]. There is no precise explanation in the literature of the differential actions of HGH-N and HGH-V. It is considered that HGH-V plays an essential role for healthy intrauterine development by

increasing the levels of IGF-1, favoring its bioavailability for the fetus, and generating an insulin resistance through its lower lactogenic effects to ensure a contribution of constant glucose.

The evolution of serum HGH-N in pregnant women has been studied with radioimmunoassays (RIA) unreactive to CSH. In such women, serum HGH-N levels progressively decline to undetectable levels during the second half of pregnancy, while HGH-V appears in the circulation at midpregnancy and increases thereafter up to term [27]. HGH-V is secreted by the placenta in a non-pulsatile manner. This continuous secretion appears to have important implications for physiological adjustment to gestation and especially in the control of maternal IGF-1 levels [5]. The "normal" episodic peak activity of HGH-V in first-trimester pregnant women is dramatically changed into a continuous very stable secretion during late pregnancy. This change is first observed at 17 weeks of gestation. It is concluded that during the second half of pregnancy, serum measurements of HGH reflect a major contribution from a non-episodically secreted placental HGH-V and concomitant suppression of pituitary HGH-N. This specific signal, i.e., a continuous HGH secretion, may be an important regulator of maternal liver metabolism during pregnancy and is directly involved in the insulin resistance of pregnancy [28, 29].

Placental HGH-V is the same length (191 aa) as pituitary HGH-N but contains 13 different aa, is more basic, and possesses one glycosylation site. These small differences are thought to be responsible for the reduced lactogenic and high somatogenic activities of placental HGH-V compared with pituitary HGH-N [5, 30]. In vitro placental HGH-V binds to HGHR with similar affinity than pituitary HGH-N. However, placental HGH-V has considerably lower affinity than pituitary HGH for lactogenic receptors [5]. CSH and PRL increase maternal food intake by induction of central leptin resistance and promotion of maternal beta-cell expansion and insulin production to defend against the development of gestational diabetes mellitus. It is probable that as a result of the lower affinity of placental HGH-V for lactogenic receptors than pituitary HGH-N and the fact that its secretion is not suppressible by high glucose levels, pregnancy is a well-known period of susceptibility for the development of diabetes and other metabolically alterations. HGH-V is equipotent to pituitary HGH-N as a ligand for circulating HGH binding protein and therefore circulates in the maternal circulation as both free and bound HGH-V [5].

3.1. Growth hormone-releasing hormone

HGH releasing hormone (HGHRH) is a 44 aa peptide. Its concentration throughout pregnancy is similar to that in nonpregnant women despite fluctuations in HGH values, which are always higher than in nonpregnant levels [31], thus supporting the idea that HGH values are higher during pregnancy due to the placental secretion of HGH-V not regulated by HGHRH [29].

After delivery, placental HGH-V disappears from maternal serum within an hour. Amniotic fluid contains low HGH concentrations; cord serum contains high HGH levels, but not because of HGH-V (we assumed that the material responsible for the GH immunoreactivity in late pregnancy maternal serum was of placental origin, since it rapidly disappeared after delivery); thus, it appears to be secreted selectively into the maternal compartment [27].

HGH-V does not appear to have a direct effect on fetal growth as it is secreted only in the maternal circulation and is not detected in the fetal blood [5]. Secreted continuously by the placenta, it seems to control the synthesis of maternal IGF-1; indeed, maternal IGF-1 levels are correlated with placental HGH levels [30]. Its continuous secretion by syncytiotrophoblast villous into the maternal compartment may alter maternal metabolism during pregnancy. In the maternal liver and other organs, HGH-V strongly stimulates gluconeogenesis, lipolysis, and anabolism, thereby increasing nutrient availability for the fetoplacental unit [5]. HGH-V acts in vivo as an HGH-N agonist sharing most of its biological properties [27]. HGH-N, which is synthesized by the fetal pituitary gland (levels of which rise to a maximum at mid-gestation) [26], has little or no physiological action on the fetus until the end of pregnancy, because of the lack of functional HGH receptors in fetal tissues.

Growth, prenatal development, and size at birth are normal in animal fetuses of specimens subjected to hypophysectomy and HGH deficiency, including human fetuses with mutant genes for this and their receptors. However, this pattern is not maintained in the postnatal period, in which the individual manifests abnormal development and growth [21]. HGH deficiency does not eliminate the normal increase in IGF-1 induced by pregnancy and does not reduce fetal weight [30]. Unlike IGF-2 levels, the levels of HGH-V do not correlate with birth weight or placental weight [32].

In humans and mice, mutations or specific deletions of the genes for IGFs, IGF1, and IGF2, as well as IGF1R and for its main signaling molecule IRS, lead to a restriction in fetal growth [33]. The targeted inactivation of the mouse gene for IGF-2 results in a 40% reduction in fetal growth, but postnatal growth remains normal so that alterations in development occur exclusively in the prenatal period. On the other hand, the interruption of the *IGF-1* gene leads to a similar decrease in fetal growth than the alteration of the *IGF-2* gene, but it is also characterized by the lack of persistent postnatal growth [34]. Most surprising, however, are the phenotypic consequences of the deletion of the gene for the IGF-1 receptor (IGF-1R), which as described above, is a transmembrane tyrosine kinase that mediates the growth promotion actions of both IGFs. Mice with this suppression have a birth weight that is only 45% of normal and usually die in a matter of hours after birth due to respiratory failure as a result of muscle hypoplasia [34].

3.2. Growth hormone replacement therapy during pregnancy

A retrospective study of 25 women with HGH-N deficiency (HGHD), who underwent pregnancy without HGH replacement therapy (HGHRT), concluded that unsubstituted HGHD during pregnancy is not detrimental to the fetus [35]. Another publication described four HGHD women who stopped HGHRT immediately after confirmation of pregnancy and remained off treatment throughout the pregnancy while having no pregnancy complications and gave birth to healthy babies of normal height and weight [36]. In a case report, physiologic HGHRT until there was evidence of sufficient HGH-V production also led to normal pregnancy and a healthy fetus [37]. This regimen of maintaining HGHRT during the first trimester, gradually decreasing it during the second trimester, and discontinuing it during the third trimester was reported to lead to successful outcomes in 12 pregnancies [38]. In addition, replacement with HGH-N during pregnancy did not suppress the physiologic increase in HGH-V [32].

Author	Pregnancy outcome	Product outcome	Hormone level/ molecular characterization
Alexander *et al*.	Normal pregnancy with spontaneous labor at 39 weeks	Normal female infant; weighted 3300 g	CSH level < 0.006 mg/l. No molecular analysis
Barbieri *et al*.	Normal pregnancy	Normal product	CSH absent, confirmed by immunoperoxidase technique
Borody and Carlton	Normal pregnancy (second pregnancy)	Healthy female infant	CSH deficiency. No molecular analysis
Bradford and Hargreaves	Normal pregnancy (primigravida)	Term male infant, weighing 3420 g	CSH < 2.0 mg/l. No molecular analysis
Geade *et al*.	Normal pregnancy (primigravida). Medical induction of labor at term	Male infant weighing 3740 g	CSH < 1 mg/l. No molecular analysis
Giampietro *et al*.	Normal pregnancy (second pregnancy) with Cesarean section at 39th week for alterations in fetal heart rate	Healthy male infant, weighing 3060 g, 51 cm tall, cranial circumference of 34 cm.	CSH levels between 0.8 and 1.4 μg/ml. No molecular analysis
Hubert *et al*.	Normal pregnancy	Normal product	CSH levels low. Messenger RNA coding for CSH at low abundance
Moshirpur *et al*.	Normal pregnancy	Healthy male infant	CSH <1 μg/ml. No molecular analysis
Nielsen *et al*.	Normal pregnancy (fourth pregnancy). Spontaneous delivery	Healthy male infant, weighing 3000 g, 53 cm tall	CSH <0.025 mg/L. No molecular analysis
Parks *et al*.	Normal pregnancy, with spontaneous delivery at 38 weeks of gestation	Healthy female infant, weighing 2650 g, 49 cm tall	Isolated partial deficiency of CSH (peak CSH levels 1.1 μg/ml). Characterized by restriction endonucleases analysis (heterozygosity for two different deletions involving *hCSH* genes; the paternal *hGH* locus lacked the *hCS-1*, *hGH-V*, and *hCS-2* genes, while the maternal only the *hCS-1* gene)
Sideri *et al*.	Normal pregnancy (third pregnancy) with slight fetal growth impairment. Spontaneous labor at 38 weeks of gestation	Healthy female infant weighting 2600 g (a value just below the 10th centile by normal Italian standards)	No CSH could be measured by RIA. PRL and HGH levels were within the normal limits (137 and 14 ng/ml), and an oral glucose tolerance test at 30 weeks was normal
Simon *et al*.	Two normal pregnancies.	Patient 1: Healthy female infant, weighing 3640 g Patient 2: Healthy female infant, weighing 3250 g	DNA was investigated for the integrity of the *hGH* gene cluster by Southern blotting and hybridization with an *hCSH* cDNA probe. Patient 1 was found to be homozygous for a deletion involving *hCSH-1*, *hGH-V*, and *hCSH-2*. Patient 2 was a double heterozygote, with one chromosome bearing the same deletion as that of patient 1, while in the other, only the *hCSH-1* gene was missing

Table 1. Comparison of reported pregnancy cases with absence of CSH or very low concentrations in maternal plasma [40–51].

A study describing pregnancies in a large group of patients (173 pregnancies in 144 women with HGHD) in 15 countries using the Pfizer International Metabolic Database (KIMS) demonstrates that most patients conceived while receiving HGHRT. Details of HGHRT during pregnancy were reported in 170 out of 173 pregnancies. HGHRT was stopped at the beginning of the pregnancy (or had already been stopped before conception) in 81 cases (46.7%), partially continued in 42 pregnancies (24.7%), and continued throughout the entire pregnancy in 47 pregnancies (27.6%). The practice of partially continuing HGHRT during pregnancy and stopping it at the end of the second trimester was observed in nearly half of the countries but was more prevalent in Sweden (67% of all pregnancies in that country) and Denmark (55% of Danish pregnancies). Most physicians reported making their decisions about whether to continue HGHRT in agreement with the patient's wish. Outcome data were available for 139 pregnancies (80.3% of cases). In four cases the pregnancy was electively terminated (in three cases because of the patient's wish, in one case because of the doctor's advice given several concomitant diseases and the resulting need for multiple medications); these cases were excluded from further analysis. Live birth was observed in 107 pregnancies (79% of all known cases), with a total of 118 babies born. No congenital malformations were reported. No live births were reported in 28 pregnancies, including two extrauterine pregnancies, one blighted ovum (non-evolutive pregnancy), one malformation (severe cystic hygroma in ultrasound, which determined pregnancy termination in the second trimester), one stillbirth, and 23 non-elective abortions. Patients who partially or fully continued HGHRT during the pregnancy did not report any miscarriages happening after the first trimester of the pregnancy [39].

There are few reported cases in the literature of pregnancies with the absence of CSH or very low concentrations in maternal plasma throughout pregnancy, most of them progressing normally and resulting in delivery of normal babies, but only in a few cases have had the genetic background examined in detail using molecular analysis (**Table 1**).

4. Role of hGH locus in pioneering personalized medicine

Biotechnology has not only been a great ally in the diagnosis of diseases but has become part of the treatment, in the specific case of HGH through the development of HGH and CSH recombinant versions. With this, the era of personalized medicine begins, which refers to the design and application of prevention, diagnosis, and treatment strategies better adapted to the genetic-molecular specificities of each patient and each disease. That is, instead of all patients being treated in a similar way, more and more, the treatments will be adapted to groups of selected patients defined by molecular markers (**Figure 3**) [52].

The first step of this personalized medicine is to know the molecular substrate of the diseases that we face. The invention of the first companion diagnostic test was to screen for deletions in the *HGH* locus in search of explaining the failure of HGHRT due to immune rejection of the biosynthetic version of HGH. Using bioinformatics methods, our laboratory analyzed the *hGH* and *hCSH* genes. On the basis of the high sequence similarity displayed by these genes, we designed an ingenious strategy based on restriction enzyme characterizations that allow differentiating each gene's transcriptional unit. To simplify the gene analyses, gene regions

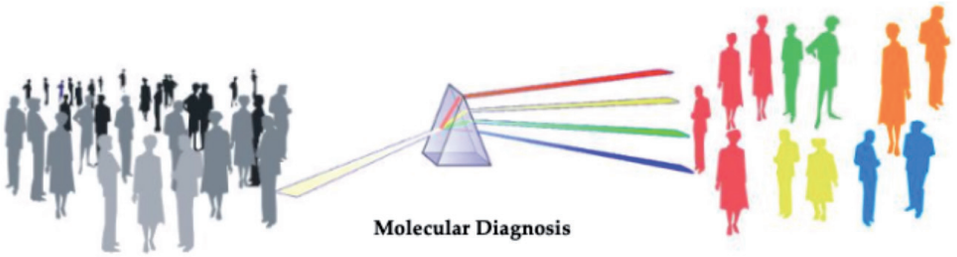


Figure 3. Stratification of patients by molecular diagnosis. Patients apparently with the same disease usually have genetic and thus physiological differences that influence their disease prognosis and prediction.

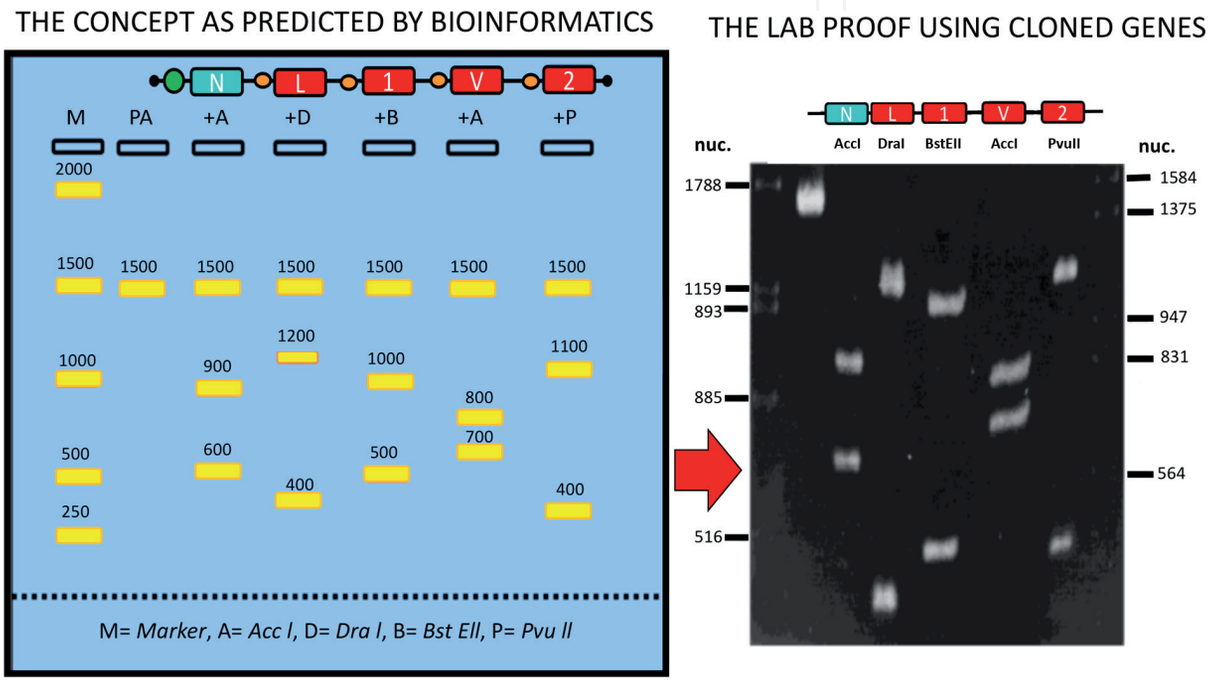


Figure 4. Diagnostic test for the *hGH* locus. Bioinformatics prediction and confirmation in the laboratory of the PCR + restriction enzymes test to differentiate each of the five genes constituents of the *hGH* locus. The gene-specific digestion patterns predicted *in silico* when amplifying all genes by a simple consensus primers PCR and then subjecting the pentagenic amplicon to "diagnostic" restriction enzymes were confirmed using cloned versions of all the gene members of this gene family.

of highest similarities were identified by means of the GENEALIGN program [53, 54]. This analysis resulted in the synthesis of a pair of consensus oligonucleotides complementary to the extremes of the five genes, allowing their simultaneous amplification by PCR. We chose as useful for this purpose what we call diagnostic restriction endonucleases: *Acc* I for *hGH-N* (0.9 and 0.6 kb) and *hGH-V* (0.8 and 0.7 kb), *Dra* I for *hCSH-L* (1.2 and 0.3 kb), *Bst* EII for *hCSH-1* (1.0 and 0.5 kb), and *Pvu* II for *hCSH-2* (1.1 and 0.4 kb) [53].

To test our bioinformatics-predicted test, we then used recombinant plasmids carrying the genes of the locus to confirm the presence of the restriction site for the chosen diagnostic endonuclease for each gene. Amplifications and digestion of each gene-carrying plasmid were performed. The digested PCR products were separated by 1.5% agarose gel electrophoresis. In all cases, we obtained the expected results (**Figure 4**). Fragments corresponding to the *hGH-N* gene (0.9 and 0.6 kb) and *hGH-V* gene (0.8 and 0.7 kb) were seen when *Acc* I was used to digest the amplified products of

plasmids containing *hGH-N* and *hGH-V* genes, respectively. Likewise, fragments of 1.2 and 0.3 kb were generated with *Dra* I upon digestion of the PCR product of recombinant plasmid carrying the *hCSH-L* gene. The digestion of the amplified product derived from the *hCSH-1* gene-carrying plasmid with *Bst* EII gave bands of 1.0 and 0.5 kb. Finally, the digestion with *Pvu* II of the amplified product of the cloned gene *hCSH-2* gave bands of 1.1 and 0.4 kb. No unexplained additional fragments were observed in both amplifications and cutting reactions, which reflects the specificity of the PCR and of the cuts with the chosen so-called diagnostic restriction endonucleases [53].

4.1. Application of the diagnostic test

4.1.1. A case of absence of CSH and HGH-V

In a pregnancy reported without HCS and HGH-V production, which was complicated by severe growth retardation of the fetus and mild preeclampsia and cardiotocogram abnormalities, the patient was given betamethasone, and Cesarean section was performed in week 35. A male baby was delivered with an Apgar score of 7/1, 10/5 and umbilical artery pH of 7.3, weight was 1270 g, and he measured 40 cm (the 10th percentile for weight for Danish male reference material at this gestational age is 2100 grams). Placenta weight was 250 g and was macroscopically normal. The umbilical cord contained only one artery. A thorough examination of the baby by a neonatologist revealed no physical abnormalities. The boy thrived; the only problem being a tendency to low blood sugar the first days, the lowest being 1.2 mM. He was discharged 26 days after delivery. Pediatric examination at discharge and 6 months later revealed no malformations or other problems [54].

Using the PCR method described before, the genes at the *hGH* multigene family were investigated in DNA isolated from the placenta of this case. We found that the placenta, and thus the baby, had two different DNA deletions along the 3′ half of the gene cluster, both of which eliminated the two active *hCSH* genes (*hCSH-1* and *hCSH-2*) and the placental *hGH* gene (*hGH-V*). The locus retained the pituitary *hGH-N* gene as well as the placental *hCSH-L* pseudogene (see **Figure 5**). The absence of CSH in this patient was caused by deletion of both copies in each chromosome of the active *hCSH* genes (*hCSH-1* and *hCSH-2*) in the placenta and, thus, in the child's genome. Both parents were heterozygous for the gene's deletion, lacking one copy of the three 3′ cluster genes: *hCSH-1*, *hGH-V*, and *hCSH-2*. In the first instance, the baby appeared to be a homozygote for deletion including the 3′ end of the *hGH* locus, but the PCR analysis revealed that the baby was, in fact, a double heterozygote for these deletions. Each chromosome lacks a different portion of the 3′ end of the *hGH* locus: one deletion begins between *hCSH-L* and *hCSH-1* genes and the other beginning at the first exon of the *hCSH-1* gene [54]. In the few previous reports where the molecular background for complete absence or very low levels of CSH have been examined [55], the cause has also been the deletion of *hCSH-1*, *hGH-V*, and *hCSH-2* genes or only of the last two genes, and in some cases both types of *hCSH* gene deletion have been found [49].

4.1.2. Cases of children treated with recombinant HGH to treat their severe growth retardation

Genomic DNA samples of 10 patients clinically diagnosed with isolated HGH deficiency (IGHD) were analyzed with our new diagnostic method, to establish if the *hGH-N* gene was absent and thus was the causal factor for this condition. Amplification products of all patients

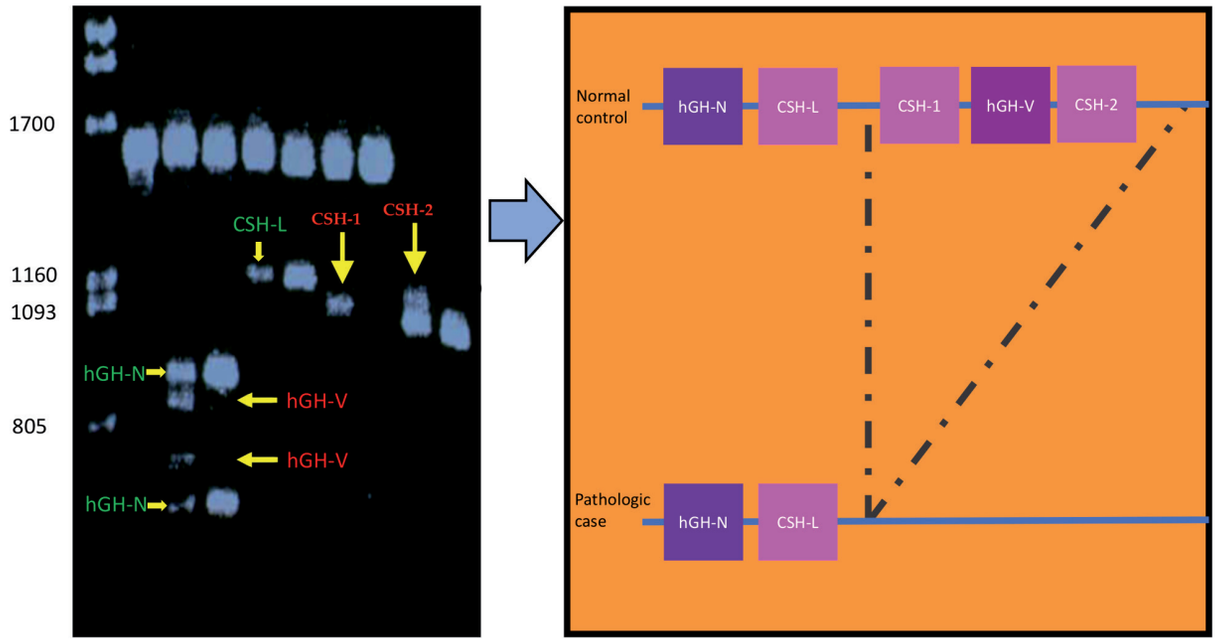


Figure 5. Molecular characterization of a case lacking CSH. Amplification by PCR with our consensus pair of primers capable of amplifying the five genes in the *hGH* locus, followed by digestion with "diagnostic" restriction enzymes, allowed to precise which genes were absent from the genome of the baby in this case of the complete absence of HGH-V and of CSH.

were digested with *Acc* I, which is specific for the *hGH-N* gene (0.9 and 0.6 kb) and for the *hGH-V* gene (0.8 and 0.7 kb) genes. This indicated to us that the former gene was absent in this child and, thus, the cause of this patient's disease, classifying her condition as IGHD type IA. Moreover, the pediatrician confirmed to us that this particular patient was not responding to the HGHRT [53] (**Figure 6**).

4.2. Anti-recombinant growth hormone antibodies

Pituitary HGH has been the preferred treatment for growth retardation in children since its efficacy was first reported 40 years ago. This treatment was discontinued in most countries in 1985 following the deaths from Creutzfeldt-Jakob disease of four patients who received the hormone recovered from cadavers in the period of 1965 through 1975. Application of recombinant (r) DNA technology has made the production of unlimited supplies of proteins possible, including HGH that has important therapeutic uses. But, the immunogenicity of commercially available rHGH is a matter of great concern. The adjuvant effects of unrelated contaminants associated with rHGH by disulfide, ionic and/or hydrophobic links, as well as the changes in the intrinsic primary and secondary structure, may occur during the production and/or recovery of the hormone and lead to potential immunogenicity. The main concern with anti-HGH antibodies could be their ability to neutralize circulating rHGH and inhibiting its growth-promoting effect. In a study evaluating 47 children treated with rHGH for up to 6 months, serum samples were examined for specific antibodies against it by ELISA, resulting in four patients positive for serum antibodies against the hormone [56]. Fortunately, new preparations have shown lower immunogenicity profile with no safety concerns [57].

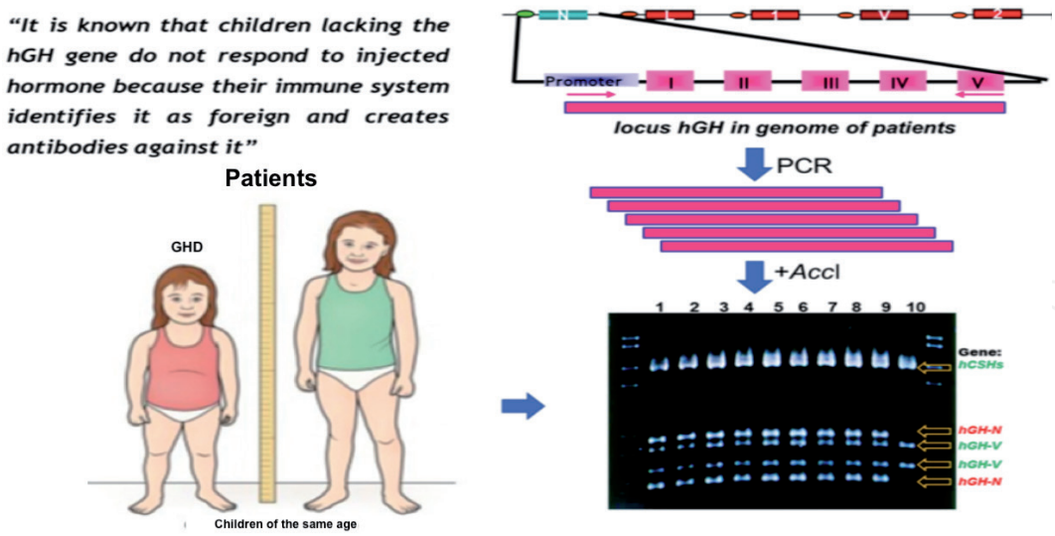


Figure 6. A genetic test to identify HGH-deficient patients that would not respond to replacement therapy from those that would. Bioinformatics analyses of the sequences of the five genes of the *hGH* locus allowed us to design a simple polymerase chain reaction with just one pair of consensus primers to amplify them. Digestion of the mixture of amplicons with *Acc* 1 restriction enzyme should render a ladder of four digestion bands: The first and last bands are digestion products of the gene responsible, in the hypophysis, for the synthesis of HGH (*hGH-N*), while the second and third bands are evidence of the presence of the placental gene counterpart (*hGH-V*) [52].

In a study of four patients with gene defects in the GH axis, the results showed that HGH substitution may be effective at the beginning, but development of HGH-Ab often occurs, resulting in a HGH-resistant state with sequelae similar to GHIS (HG insensitivity syndrome). One patient [58] developed high-affinity and high-avidity blocking of HGH-Ab during the first year of pituitary-derived human GH (pit-GH) treatment. Even plasmapheresis and immune modulating treatment to induce tolerance analogous to previous treatment regimes in hemophiliac patients with blocking antibodies did not result in HGH responsiveness, and HGH-Ab reappeared shortly thereafter [59]. The HGH growth response, even in patients with the identical genetic defect, may differ and is not clearly related to the presence of antibodies [60]. Factors contributing to immune response are complex and cannot be clearly demonstrated. Epidemiology and risk factors of HGH-Ab development have not been studied in depth, but analogous to hemophilia, there are various aspects that might be deduced: On a superior level, immune processes of self−/non-self-discrimination, i.e., the likelihood that antibodies will be formed appears to be influenced by the age at first antigen contact, the HLA haplotype, and other immune response genes. In particular, epitopes giving rise to antibody formation may differ and lead to various effects which are dependent on steric conformation changes or potency of complement activation [61]. Patients with genetic HGH defects who are exposed to exogenous rHGH will therefore generate different amounts of HGH-Ab with different affinities, thus compromising HGH binding to the receptor or HGHBP/HGHR (GH binding protein and GH receptor) dimerization kinetics [62]. In patients with different HGHR mutations, the extent of height deficit varies substantially and may be correlated with the presence or absence of HGHBP in plasma, although clear genotype–phenotype associations do not exist, thus suggesting an influence of additional genes or environmental factors [63–66]. The clinical outcome of treatment with

rHGH in patients with IGHD IA is quite variable. The amount and the affinity of GH-Ab modulated by genetic disposition for immune reactions may determine the overall response to HGH therapy [62].

5. Summary

During the prenatal period, the product has a very rapid development, for which it needs an adequate supply of nutrients by the mother. To date, many factors involved in this growth have been described. However, one of the most important without a doubt is the somatogenic and lactogenic hormones (collectively referred to as somatolactogens). Being the intrauterine period essential to define the health of the product throughout its extrauterine life, it is logical to think that there are biological mechanisms in nature that were evolving to assure the nutrient supply through the placenta. Many data point to the fact that HGH-V is one of these biological mechanisms.

During pregnancy, the expression of pituitary HGH is suppressed, and placental HGH becomes the predominant form of HGH in the mother [26]. This change in HGH production indicates that there must be some difference in their functions and surely have implications in the normal evolution of pregnancy. One of these differences is that HGH-V is secreted by the placenta in a non-pulsatile manner. This continuous secretion seems to have important implications in the physiological adjustment to gestation and especially in the control of maternal IGF-1 levels [5].

The lower affinity of HGH-V for the lactogenic receptors and the fact that its secretion is not suppressed by the high levels of blood glucose prevent glucose from being picked up by the mother's tissues and thus being available to the fetus. However, these effects also cause the pregnancy to be a period of susceptibility to the development of diabetes and other metabolic disorders, as is well known. HGH-V does not have a direct effect on fetal growth since it is secreted selectively into the maternal compartment and is not detected in fetal blood [27]. The effect on fetal growth apparently occurs indirectly through the IGF-1 maternal. HGH-V is secreted continuously by the placenta and that seems to control the synthesis of maternal IGF-1. This is supported by the fact that maternal IGF-1 levels are correlated with HGH-V levels. In addition, it binds to the hepatic receptors of HGH with a higher potency than HGH-N [27].

Unlike HGH-N, HGH-V does not increase the transcription of genes from the other components of the IGF system [IGF-2, IGF-2R, IGF-1R, a family of six IGF binding proteins (IGFBPs), and IGFBP proteases]. Therefore, during pregnancy, when HGH-V takes control over HGH-N, there is a greater amount of free IGF-1 available, which may be one of the reasons for the evolutionary divergence of the *hGH* locus for the creation of two GHs that will act in different periods of life.

Besides being the *hGH* locus a wonderful model to investigate gene spatial and temporal expression control, its world-record sequencing and pioneer translation into the first companion diagnostic ever invented, inaugurated the era of personalized medicine.

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