

LH AND HCG

Luteinizing hormone and human chorionic gonadotropin: distinguishing unique physiologic roles

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Abstract

Luteinizing hormone (LH) and human chorionic gonadotropin (hCG) are integral components of the hypothalamic–pituitary–gonadal axis, which controls sexual maturation and functionality. In the absence of signaling through their shared receptor, fetal sexual differentiation and post-natal development cannot proceed normally. Although they share a high degree of homology, the physiologic roles of these hormones are unique, governed by differences in expression pattern, biopotency and regulation. Whereas LH is a key regulator of gonadal steroidogenesis and ovulation, hCG is predominantly active in pregnancy and fetal development. Emerging evidence has revealed endogenous functions not previously ascribed to hCG, including participation in ovulation and fertilization, implantation, placentation and other activities in support of successful pregnancy. Spontaneous and induced mutations in LH, hCG and their mutual receptor have contributed substantially to our understanding of reproductive development and function. The lack of naturally occurring, functionally significant mutations in the β -subunit of hCG reinforce its putative role in establishment of pregnancy. Rescue of reproductive abnormalities resulting from aberrant gonadotropin signaling is possible in certain clinical contexts, depending on the nature of the underlying defect. By understanding the physiologic roles of LH and hCG in normal and pathologic states, we may better harness their diagnostic, prognostic and therapeutic potential.

Keywords

Function, hCG, infertility, LH, *LHCGR*, mutation, ovulation, polymorphism

History

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Introduction

Luteinizing hormone (LH) and human chorionic gonadotropin (hCG) serve different roles in reproductive physiology: LH contributes to the driving force behind gonadal steroidogenesis and regulation of ovulation, whereas hCG (in the absence of pathologic abnormalities) is secreted in large amounts only during pregnancy [1]. The expression profile differences manifest early in fetal development and are maintained throughout the life span [2–4]. Although LH and hCG share the same receptor, many of their actions remain distinct [1,5,6]. A wealth of information regarding the endogenous functions of LH and hCG has been ascertained through naturally occurring and induced mutations, yet data are still emerging that shed new light on the involvement of LH and hCG in various physiologic processes.

By understanding how LH and hCG affect normal and abnormal human development and reproduction, we may be able to improve on current treatments for reproductive disorders while uncovering other areas where assessment of these gonadotropins may be of use, such as the management of certain cancers. This review describes the current state of knowledge regarding the physiology of LH and hCG throughout the stages of life and the impact of disrupting their normal expression profiles and functionality.

Physiology of LH and hCG through the life stages

Fetal period

Fluctuations in circulating LH and hCG concentrations are observed throughout fetal development (Figure 1) [1,3,6,7]. In the male fetus, initially high levels of plasma hCG decrease sharply between weeks 10 and 20 and then gradually decline for the remainder of gestation [6]. Expression of LH, in contrast, increases from week 10, reaching a peak before week 20 and decreasing slowly thereafter. The amount of hCG present at its nexus far exceeds that of LH [1,6]. Although fetal cells that are destined to become Leydig cells begin to produce testosterone as early as 6–7 weeks of gestation, it is not until after this period that hCG and LH are believed to be important to the process [8]. Indeed, the LH/choriogonadotropin receptor (*LHCGR*) is not detected in Leydig cells until 10–12 weeks after conception [6]. As the more abundant and biologically active species, hCG likely plays a larger role in testosterone production by Leydig cells than does LH during early fetal development [6,9]. Testosterone is responsible for virilization of the reproductive tract, promoting the formation of the ductus deferens, epididymides, seminal vesicles and ejaculatory ducts [1,6]. Dihydrotestosterone, a derivative of testosterone, is active in the differentiation of the prostate and external genitalia. At ~15–20 weeks of gestation, testosterone regulation shifts to the fetal pituitary gland, as LH secretion takes over from placental hCG in driving testosterone production [9]. This transition is evident in LH-deficient anencephalic male fetuses, in whom normal masculinization of the reproductive tract occurs while high levels of hCG are present, but further development of the external

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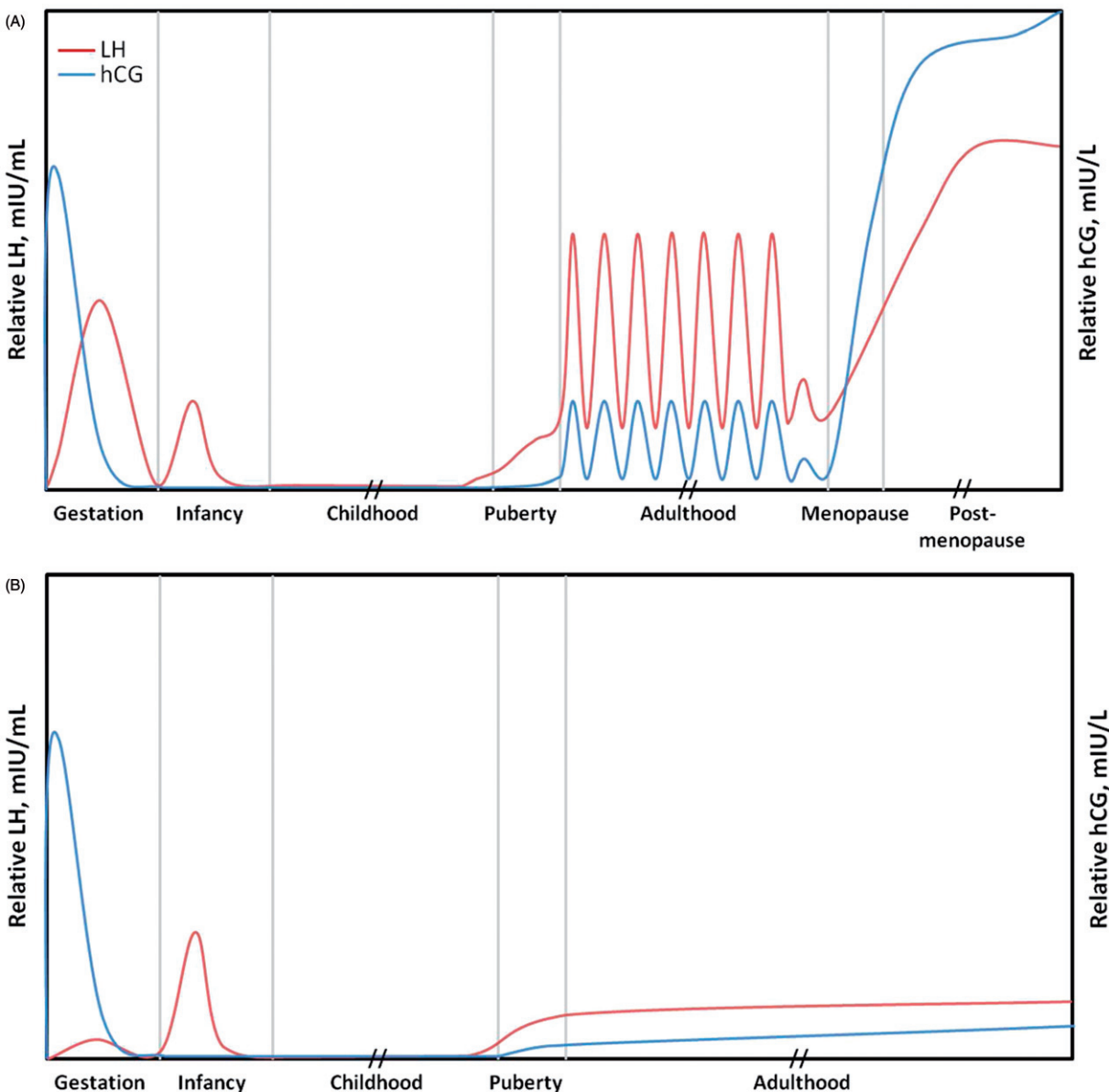


Figure 1. Relative expression of luteinizing hormone (LH) and human chorionic gonadotropin (hCG) during the stages of life in females (A) and males (B). Note that patterns of LH and hCG expression will vary substantially from person to person. This figure is a representation of which molecule is predominant at the different stages of life. It is not an exact measurement.

genitalia is hindered by the lack of LH when hCG levels decrease [9]. The pattern of pituitary LH expression during fetal development mirrors that of serum LH levels [3].

Peak concentrations of pituitary and circulating LH are higher in female fetuses relative to that of males [3,7]. It has been postulated that negative feedback from testosterone and inhibin in males lead to their lower LH levels, which is borne out by the higher levels of testosterone and inhibin B detected during gestation in males compared with females [7]. Development of the female fetal reproductive tract does not depend on the presence of LH or hCG. In fact, *LHCGR* is not expressed by the developing ovary until after the 16th week of gestation [6]. In general, minimal steroidogenesis occurs in the ovary during fetal development.

Detection of *LHCGR* in fetal organs, including the kidney, liver, lung, pancreas and gastrointestinal tract, has led to speculation that hCG may have a further role in fetal organ growth and differentiation [5,10]. No specific function in fetal organ development has yet been ascribed to hCG [5].

Infancy and childhood

In term infants, circulating LH and hCG concentrations are below the limits of detection [7]. After delivery, both sexes experience a surge in gonadotropin levels due to the withdrawal of maternal-derived estrogen. The magnitude of LH elevation is greater in male than in female infants [2,11,12]. In male infants, LH peaks at 1–3 months of age, declining rapidly thereafter and reaching a nadir at ~4–9 months of age. Testosterone levels, which are also elevated at 3 months of age in boys, decrease more precipitously, falling below the limit of detection by 6 months of age [12]. The testosterone peak may be driven by a coinciding increase in Leydig cell number and is believed to trigger germ cell proliferation and sexual differentiation of the central nervous system.

Infant girls demonstrate greater variability in LH expression patterns [12]. Generally, a peak in LH concentration is reached at 1–3 months of age, followed by a decrease to childhood levels and a possible small resurgence at 1 year [2,12]. The significance of transient hypothalamic–pituitary–gonadal axis activation is as

yet unknown. After the temporary surge in boys and girls, gonadotropin levels remain low until prepuberty. This period is sometimes referred to as the juvenile pause [6,13].

Prepuberty and puberty

In the year or two preceding puberty, the gonadotropin-releasing hormone pulse generator begins to mature and escape its central inhibition. In response, there is a gradual increase in the frequency and amplitude of nocturnal LH pulsatile secretion [14,15]. With pubertal progression, this diurnal pattern of LH secretion abates, and LH is released in a more regular pulsatile manner throughout the day [13,16]. Concurrently, the proportion of bioactive to immunoreactive LH increases [17,18]. Phillips et al. [19] studied the shift in LH and follicle-stimulating hormone (FSH) iso-hormone profile in puberty. In boys, there was an increased prevalence of acidic FSH and LH isoforms observed at pubertal stage II. In contrast, the median charge of LH was largely unchanged in girls during pubertal stages I through IV.

The increase in gonadotropin activity during puberty drives gonadal steroidogenesis – primarily the production of testosterone by Leydig cells in males and testosterone and progesterone by thecal cells in females [1]. Most of the testosterone generated by thecal cells are converted to estradiol by granulosa cells. Testosterone, estradiol and adrenal androgens produce the physical changes associated with puberty, including the development of secondary sex characteristics. As estradiol production increases in girls, stimulation of the endometrium occurs, eventually leading to menarche (~2–3 years after the onset of puberty). The hypothalamic–pituitary–ovarian axis matures in middle-to-late puberty, with the development of estradiol's positive feedback effect on stimulating an LH surge [13]. More regular, ovulatory cycles do not become established until several years after menarche.

Adulthood

In women, LH and hCG play crucial roles in ovulation and pregnancy (discussed in the next section). After puberty, the pattern of LH secretion during the menstrual cycle becomes more regular in normo-ovulatory women. In women with polycystic ovarian syndrome (PCOS), however, higher basal levels of LH are observed with increased pulse frequency and amplitude throughout the cycle [20–22]. The lack of variation in LH secretion pattern contributes to the anovulatory cycles frequently found in women with PCOS.

In men, LH stimulates testosterone production by Leydig cells. Secretion of LH is pulsatile, but it does not demonstrate the cyclic variations observed in women. Low levels of hCG (presumably of pituitary origin) are also present in men [4], the function of which is unknown. Although not the key impetus for endogenous steroidogenesis, in conditions such as male hypogonadism and infertility, exogenous hCG may be administered to drive testosterone production [1].

Menopause and post-menopause

A decline in ovarian function during the perimenopausal period, which can last from 2–8 years [13], is marked by a gradual increase in FSH, a pronounced decrease in the follicular pool, and a reduction in early follicular phase inhibin secretion [1]. As menopause approaches, estradiol and estrone levels decline [1]. The subsequent lack of ovarian steroid negative feedback results in a sharp increase in LH and FSH secretion, with a gradual decline during the post-menopausal period [1,6].

During the perimenopausal period, serum hCG levels increase substantially in women [23]. The finding that hCG measurements

in women 55 years of age and older are significantly greater than those in non-pregnant women aged 18–40 years or 41–55 years ($p < 0.0001$) could have diagnostic implications when interpreting hCG tests. After the onset of menopause, hCG levels seem to stabilize. The elevated levels of hCG in perimenopausal and menopausal women are believed to be pituitary in origin [23]. It should be noted that LH and hCG levels during and after the menopausal transition demonstrate a high degree of interindividual variability.

Although loss of reproductive capability akin to female menopause does not occur in men, they do experience a progressive decline in spermatogenesis and fertility with age. Leydig cells decrease in number and are less capable of producing testosterone in response to LH or hCG stimulation [6,24]. Aging is generally associated with a decrease in circulating total and free serum testosterone levels, but this phenomenon is not observed in all men [6,24,25]. On an average, testosterone levels decrease by 1–2% per year [25]. Levels of LH and hCG, in contrast, gradually increase with age [25,26]. The increases in LH and hCG levels in men are much less pronounced than those observed during the perimenopausal and post-menopausal intervals in women. Nonetheless, reference ranges for normal LH and hCG values in men are typically stratified by age group.

Roles of LH and hCG during ovulation and pregnancy

Ovulation

Luteinizing hormone regulates ovulation through changes in expression levels and the proportions of glycosylated isoforms. Both LH and hCG exist as compilations of isohormones that differ with respect to post-translational modification (predominantly glycosylation) and state of degradation, which influences their biological activity and half-life in circulation [27,28]. Early in the follicular phase, estradiol exerts a negative feedback effect on LH; however, some LH activity occurs to stimulate thecal cell production of androgens that serve as substrates for estradiol production by granulosa cells. As estradiol levels rise in the late follicular phase, the relationship with LH becomes one with a positive feedback effect, leading to the LH surge and subsequent ovulation [6]. This transition corresponds with a shift toward less glycosylated and more biologically active LH isoforms [29,30]. With ovulation, the ovulatory oocyte progresses through to meiosis II while the corpus luteum forms in the ovarian stroma. LH drives progesterone production and secretion from the corpus luteum and, if pregnancy occurs, hCG takes over progesterone regulation. The hyperglycosylated isoform of hCG, which is abundant in early pregnancy, does not seem to play a role in the promotion of progesterone secretion [31].

Low levels of pituitary hCG parallel the dynamics of LH secretion during the menstrual cycle [4]. Pituitary hCG secretion is responsive to stimulation by GnRH analogs and is suppressed by oral contraceptives [32–34]. The role of this pituitary hCG is unclear, but the pattern of expression is consistent with overlapping function to that of LH [5]. It has been suggested that hCG expression may elevate the peak range of LH, thereby aiding in the promotion of ovulation [35]. In addition, lingering hCG could enhance progesterone production at luteal phase onset.

Fertilization and implantation

The presence of *LHCGR* in human fallopian tubes and in sperm suggests a role for LH and hCG in fertilization [36,37]. Consistent with this putative function, expression of *LHCGR* is greater in fallopian tubes during the luteal phase compared with the proliferative phase of the menstrual cycle or fallopian tubes from postpartum or post-menopausal women [36]. Studies using

a porcine model demonstrated that LH was capable of inducing relaxation of the oviduct, most notably during the periovulatory interval [38]. It is not known what the function of gonadotropin signaling is in sperm; however, a recent study reported correlations between polymorphisms in *LHCGR* and sperm quality (e.g. concentration and motility) in cattle [39]. Investigators have speculated that hCG present in the female reproductive tract could activate the *LHCGR* on sperm, thus promoting motility and capacitation [37].

Blastocyst secretion of hCG may contribute to endometrial cross-talk to enable implantation [40,41]. Endometrial expression of *LHCGR* increases mid-luteal phase, during a short period in which the endometrium is receptive to implantation (i.e. the implantation window) [41]. Investigators hypothesize that a blastocyst capable of producing locally high levels of hCG could extend the implantation window, thereby increasing the chances for successful pregnancy [40]. A similar phenomenon of increased endometrial *LHCGR* expression during the implantation window has been observed in mice [42]. Given that the mouse genome does not include a chorionic gonadotropin gene, LH would need to functionally substitute for hCG in this system. Preliminary evidence suggests that this may indeed be the case – a bioactive LH signal has been reported at the time of murine blastocyst implantation.

During early pregnancy, hCG is also believed to support implantation and placentation by modulating endometrial tissue remodeling, fostering maternal immunotolerance of fetal tissue, promoting neoangiogenesis and increasing the uterine natural killer cell population [5,40,41]. These functions all contribute to endometrial receptivity – a key component to successful pregnancy. Emerging evidence suggests that hCG expressed by the blastocyst stimulates receptors on the endometrium, eliciting a variety of effects on downstream molecules, including growth factors (vascular endothelial growth factor [VEGF], transforming growth factor beta), cytokines (leukemia inhibitory factor) and proteinases (matrix metalloproteinase 9 [MMP-9]), which contribute to different aspects of endometrial receptivity [40,41,43]. For example, hCG-mediated upregulation of VEGF is believed to promote angiogenesis, whereas stimulation of MMP-9 expression by hCG is involved in regulation of tissue remodeling. The role of hCG in fostering endometrial receptivity appears to begin even before embryonic hCG expression. It has been shown that epithelial hCG is expressed and produced in human endometrium biopsy specimens during the early to mid-secretory phase of the menstrual cycle [44]. Elucidating the precise role of hCG in endometrial functions related to implantation remains an active subject of investigation.

Maintenance of pregnancy

Expression of hCG continues throughout pregnancy, with peak levels occurring at ~10 weeks' gestation [5]. As many as 20–30 isoforms of hCG can be detected during pregnancy [45]. Hyperglycosylated hCG (hCG-H) secreted by root or extravillous cytotrophoblasts is the predominant species early in gestation, but it is gradually surpassed in proportion by regular hCG, which is produced by fused and differentiated syncytiotrophoblast cells [5]. It has been well established that in early pregnancy, hCG sustains progesterone production by the corpus luteum. Placental production of progesterone takes over in the later part of the first trimester, at a time when hCG levels are in decline [6]. Beyond its role in luteal support, hCG is believed to promote angiogenesis, thereby supporting blood flow to the placenta and nutrition for the fetus [46,47]. Emerging evidence also suggests that hCG is involved in umbilical cord growth and development, synchronizing uterine growth with that of the developing fetus and relaxation

of myometrial contractions [5]. In addition, the presence of *LHCGR* in the brain has led to speculation that gonadotropin signaling is involved in the nausea and vomiting experienced during pregnancy [48].

Quantification of hCG species is a valuable diagnostic and prognostic tool during pregnancy. For example, measuring hCG-H levels, which increase rapidly during the initial stages of pregnancy, allows for earlier detection than standard pregnancy tests. A recent study showed that an ultrasensitive hCG-H assay was capable of detecting pregnancy 6 days after embryo transfer in women undergoing *in vitro* fertilization [49]. At 12 days, lower levels of hCG-H distinguished biochemical from clinical pregnancies. Insufficient hCG-H levels (i.e. urinary hCG-H <50% of total hCG) have also been detected in a large proportion of early pregnancy losses in spontaneously conceived cycles [50]. Low circulating concentrations of another form of hCG, the disassociated β -subunit, have been linked to an increased probability of ectopic pregnancy in symptomatic patients [51]. During the later stages of pregnancy, inadequate amounts hCG-H are associated with the development of preeclampsia [52]. Preeclampsia itself is attributed to abnormal placentation and trophoblast invasion [53]. On the other end of the spectrum, elevated levels of hCG-H or hCG free β -subunit in maternal serum during the first trimester are markers of Down syndrome pregnancy [54]. Triploid abnormalities may be discernible as early as the pronuclear stage by the presence of hCG-H [55]. Notably, most methods currently used for hCG quantification in clinical laboratories underestimate hCG-H levels.

Pathology of LH, hCG and LHCGR

Loss- or gain-of-function mutations have helped to establish the extent to which gonadotropin signaling is necessary for sexual development and reproductive success, while also providing insights into pathologic processes. These gene alterations may be naturally occurring, as is the case for human mutations/polymorphisms, or induced in model systems (most commonly in mice). The effects of targeted mutations in LH or overexpression of hCG on reproductive structure and function in mice are presented in Table 1. A description of human phenotypes associated with changes in LH, hCG and *LHCGR* functionality or expression are provided below and summarized in Table 2.

Human mutations/variants

LHB

Naturally occurring mutations that result in inactive LH are rare in humans, particularly in women. Only two cases in female patients with inactivating *LHB* mutations have been described to date [63,64]. Characterization of one of these individuals revealed normal development and appropriate pubertal milestones followed by secondary amenorrhea and infertility [63]. Uterine volume was normal, although the endometrium was atrophic. The absence of detectable LH did not seem to adversely affect FSH, hCG, testosterone, or prolactin levels; estradiol and progesterone levels were in the low-to-normal range for the follicular phase of the menstrual cycle. Supplementation with estrogen and progesterone was capable of inducing endometrial thickening and follicle enlargement; however, normal ovulation was not restored and no corpus luteum was observed. The second patient was reported to have experienced menarche at age 14 years, with subsequent oligomenorrhea and secondary amenorrhea [64]. Residual LH activity described in an affected male sibling suggests that this mutation did not result in the complete absence of LH, although serum levels were below the limit of detection. The reproductive findings in these women confirm that adequate

Table 1. Phenotypes in knockout and transgenic mice.

Model	Gender	Reproductive phenotype
Disrupted pituitary glycoprotein hormone α -subunit [56]	Female	Prepubertal external genitalia, underdeveloped ovaries and uterus, limited follicle development, absence of ovulation, failure of vaginal orifice opening, infertility
	Male	Prepubertal external genitalia, reduced testes size, impaired spermatogenesis, testosterone deficiency, infertility
LH receptor null [57,58]	Female	Underdeveloped genitalia, ambiguous vaginal opening, arrested follicular growth, decreased estradiol and progesterone levels, infertility
	Male	Underdeveloped genitalia, abdominal testes, micropenis, Leydig cell hypotrophy, disarray of seminiferous tubules, spermatogenic arrest, modestly elevated estradiol levels, infertility
LH β -subunit null [59]	Female	Hypogonadism, decreased serum estradiol and progesterone levels, defects in folliculogenesis, gene expression abnormalities, uterine hypoplasia, infertility
	Male	Decreased testicular size, Leydig cell hypoplasia, gene expression abnormalities, reduced testosterone levels, impaired spermatogenesis, infertility
hCG α -subunit overexpression [60]	Female and male	Normal and fertile*
hCG β -subunit overexpression [60–62]	Female	Precocious puberty, enhanced ovarian steroidogenesis, abnormal uterine structure, hyperprolactinemia, infertility†
	Male	Mild hypogonadism, fertile† Infertility*
hCG α - and β -subunit overexpression [60,61]	Female	Elevated levels of serum estradiol, hemorrhagic and cystic ovaries, thecal layer enlargement, stromal cell proliferation, infertility*, tumorigenesis*
	Male	Increased testicular androgen production, focal Leydig cell hypertrophy, progressive seminiferous tubule degeneration, urethral obstruction, infertility† Leydig cell hyperplasia, very high serum testosterone levels, reduced testis size, enlarged seminal vesicles, infertility*

LH, luteinizing hormone; hCG, human chorionic gonadotropin.

*Transgene expression was driven by the ubiquitin promoter.

†Mice expressing high levels of hCG, with transgene expression driven by the metallothionein 1 promoter.

Table 2. Phenotypes associated with mutations in human *LHB*, *CGB* and *LHCGR* genes*.

Gene and type of mutation	Sex	Phenotype	Effect on fertility	
<i>LHB</i>	Inactivating	Women	Oligomenorrhea, secondary amenorrhea	Infertile
		Men	Hypogonadism, Leydig cell hypoplasia, testosterone deficiency, azoospermia	Infertile
	Polymorphisms	Women	Endometriosis, hyperprolactinemia, luteal insufficiency, menstrual disorders, PCOS, premature ovarian failure	Reduced fertility
Men		Increased prostate cancer risk	Unknown	
<i>CGB</i>				
Polymorphism	Women	Recurrent miscarriage	Reduced fertility	
<i>LHCGR</i>	Activating	Men	Familial male-limited gonadotropin-independent precocious puberty Leydig cell adenoma	Not affected Reduced fertility
	Inactivating	Women	Oligomenorrhea/amenorrhea, empty follicle syndrome	Infertile
		Men	Leydig cell hypoplasia	Infertile
Polymorphism	Women and men	Risk factor for certain cancers	Unknown	

LHB, luteinizing hormone β -polypeptide; *CGB*, chorionic gonadotropin β -polypeptide; *LHCGR*, luteinizing hormone/choriogonadotropin receptor; PCOS, polycystic ovary syndrome.

*Sources: references [63–81].

LH is not required for normal sexual differentiation and pubertal development, but it is necessary for ovulation and development of a corpus luteum.

Men with homozygous inactivating *LHB* mutations have a more severe phenotype characterized by hypogonadism, severe testosterone deficiency and azoospermia [63,65,66]. Leydig cells are absent or hypoplastic. Sexual differentiation and development proceed normally through gestation and childhood, but pubertal maturation does not occur. Male heterozygotes display a milder phenotype, with normal pubertal development but altered steroidogenesis and increased risk of infertility [65]. Long-term treatment with hCG is capable of rescuing the hypogonadal phenotype in men with inactivating *LHB* mutations, resulting in virilization, increased testicular volume, elevated testosterone levels and improved spermatogenesis [65–67]. Restoration of spermatogenesis allowed one of these men to father a child

through intracytoplasmic sperm injection [67]. There has been one reported case of an *LHB* mutation that does not completely abrogate LH activity and is compatible with complete spermatogenesis even in the absence of virilization and in the presence of low serum testosterone levels [64]. Despite a reduced number of Leydig cells compared with an age-matched control, sperm production in this patient was quantitatively normal. These observations suggest that the LH threshold for sperm production is relatively low.

One common variant of *LHB* (often referred to as ‘‘variant LH’’) has been detected in 7.1–41.9% of the world’s population [82,83]. This polymorphic isoform contains two point mutations, resulting in a functional LH with a shorter half-life and possibly decreased bioactivity relative to normal LH. Amino acid sequencing of variant LH suggests a closer homology to hCG than to normal LH. Current LH antibody assays are less able to

detect variant LH, which may pose difficulty in ovulation testing. In certain patient cohorts, variant LH has been linked to ovulatory disorders, including hyperprolactinemia, premature ovarian failure, menstrual disorders, luteal insufficiency and PCOS [68–70]. Variant LH allele carriers may be at increased or reduced risk for developing ovulatory dysfunction, depending on the specific disorder and population evaluated. Separate (non-variant LH) polymorphisms have also been associated with PCOS susceptibility and phenotype [71,72], as well as with endometriosis, premature ovarian failure and luteal insufficiency [71].

hCG

Sequence changes that influence the function of hCG are rare. It has been suggested that mutations with a significant effect on hCG would not be compatible with successful pregnancy and are, therefore, not observed in the population at large [73]. This hypothesis is consistent with the postulated importance of hCG signaling from the blastocyst for implantation and the additional functions of hCG during gestation. It seems intuitive then that polymorphisms in the hCG β -subunit (i.e. the *CGB* gene) are associated with increased risk of recurrent miscarriage [73].

LHCGR

A variety of naturally occurring activating and inactivating mutations have been identified in the *LHCGR* gene. In men, activating mutations of *LHCGR* result in autosomal dominant familial male-limited gonadotropin-independent precocious puberty (i.e. testotoxicosis) [74]. Affected individuals develop Leydig cell hyperplasia and demonstrate evidence of pubertal development in early childhood. Of the variety of gain-of-function *LHCGR* mutations reported, only D578H is known to cause Leydig cell adenomas in addition to precocious puberty [84]. Whereas the other *LHCGR* activating mutations have a familial or germline origin, D578H is somatic [74]. Surprisingly, women with activating *LHCGR* mutations display no reproductive abnormalities in structure or function. Women with inactivating mutations of *LHCGR*, on the other hand, have a similar phenotype to that of inactivating *LHB* mutations, including oligomenorrhea/amenorrhea and infertility [75]. In addition, an *LHCGR* mutation that is believed to reduce receptor expression and binding capacity has been implicated in empty follicle syndrome [76]. Bentov et al. [85] recently reported a reproductive phenotype in a woman who was heterozygous for an inactivating *LHCGR* mutation. Previously identified loss-of-function *LHCGR* mutations had only generated overt reproductive pathology in the homozygous state (i.e. autosomal recessive inheritance). This patient presented with amenorrhea and had a history of irregular periods, endometriosis and recurrent ovarian cysts. Attempts at *in vitro* fertilization resulted in poor egg yield and multiple biochemical pregnancies.

Inactivating mutations of *LHCGR* cause Leydig cell hypoplasia in men [74]. There are degrees of retained *LHCGR* activity among the inactivating mutations, which influences the patient's phenotype. Genetically, males with complete loss of *LHCGR*-mediated signaling develop Type I Leydig cell hypoplasia, wherein male sexual differentiation does not progress normally during fetal development, resulting in pseudohermaphroditism. Partial loss of *LHCGR* function yields a milder and more variable form of Leydig cell hypoplasia (Type II) that may include micropenis and hypospadias. In one unusual case of Leydig cell hypoplasia Type II, a patient presented with hypogonadism, azoospermia and pubertal delay, despite otherwise normal prepubertal male development [86]. Functional analysis revealed that the *LHCGR* mutation in this patient rendered the receptor insensitive to LH but not to hCG [87]. Consequently, unlike

typical inactivating *LHCGR* mutations, treatment with hCG was effective for treating hypogonadism and restoring spermatogenesis in this patient [86]. This case underscores the inherent divergence in the physiologic roles of endogenous hCG and LH: continued hCG sensitivity allowed for normal fetal sexual differentiation, but lack of LH response prevented pubertal development and sperm production.

Sequence alterations in components of the gonadotropin signaling pathway have also been linked to cancer risk and prognosis. Polymorphisms in *LHCGR*, for example, are associated with an increased risk of testicular germ cell cancer and endometrioid adenocarcinoma [77,88], whereas variant LH is considered a weak risk factor for prostate cancer [78]. Moreover, increased *LHCGR* activity resulting from a common polymorphism has been correlated with shortened disease-free survival in patients with breast cancer [79,80]. Investigators postulate that the negative influence on cancer outcome of this *LHCGR* allele results from an increase in estrogen exposure. Further investigation is needed to better understand the role of aberrant gonadotropin signaling in cancer etiology.

Conclusions

Despite a high level of homology and action at a common receptor, LH and hCG play unique roles in development and reproduction. LH and hCG act during specific windows of opportunity during fetal and post-natal development, at times coordinately, to promote proper sexual differentiation, maturation and functionality. Although long known to support pregnancy through its effect on progesterone production, hCG is increasingly recognized for its multitude of activities that foster implantation and subsequent maintenance of pregnancy. Loss-of-function mutations prove that the absence of one gonadotropin is not fully compensated by endogenous production of the other, yet rescue through exogenous administration is possible. Success of supplementation with hCG or downstream hormones in the gonadotropin cascade for spurring pubertal development, treating hypogonadism or managing infertility depends on the nature of the underlying molecular abnormality. The ongoing study of LH and hCG physiology will aid in the development of diagnostic tests, prognostic assessments and therapeutic approaches relevant to human disease and reproduction.

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