International Research Journal of Pharmacy and Medical Sciences
ISSN (Online): 2581-3277

Feedback Disruption in Infertile Men: How altered LH/FSH Testosterone Loops Contribute to Dysfunction

R. Purushothaman[1], K. Lokesh[2], P. Kamali Paul[3], M. Gayathri[4]
Dr. Borus Andro Lab and Research Center, Chennai, India

Abstract— *Male Infertility Contributes to Nearly Half of all Infertility Cases Globally and Represents a Major Public Health Concern [1, 3]. The Process of Spermatogenesis is Tightly Regulated by the Hypothalamic– Pituitary–Gonadal (HPG) Axis, in Which Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), and Testosterone (T) Act in Concert to Maintain Testicular Function and Sperm Production [1, 5]. Disruption of the LH/FSH–Testosterone Feedback Loops is a Key Factor in the Pathophysiology of Hormonal Infertility [6, 7]. The Feedback Loop Mechanism Operates Through a Coordinated Cascade: The Hypothalamus Secretes Gonadotropin-Releasing Hormone (GnRH) in a Pulsatile Manner, Stimulating Pituitary Gonadotrophs to Release LH and FSH [12]. LH acts on Leydig cells through the LH/choriogonadotropin receptor (LHCGR), promoting testosterone synthesis [19, 32]. FSH acts on Sertoli cells via the FSH receptor (FSHR) to stimulate germ-cell maturation and the production of nutrients and paracrine factors [17, 47]. Rising intratesticular testosterone and inhibin B then exert negative feedback on the hypothalamus and pituitary to suppress GnRH, LH, and FSH secretion, maintaining hormonal homeostasis [14–16]. Disruption at any level of this axis—hypothalamic, pituitary, or testicular— produces endocrine imbalance. Mutations in LHβ or LHCGR genes lead to reduced testosterone synthesis, Leydig-cell hypoplasia, and azoospermia [34–41]. Likewise, mutations in FSHβ or FSHR impair Sertoli-cell function, resulting in oligo- or azoospermia despite normal testicular structure [37, 49–53]. In primary testicular failure, LH and FSH are elevated while testosterone is low, reflecting failed negative feedback; in secondary (hypogonadotropic) hypogonadism, low GnRH output leads to reduced LH/FSH and testosterone [3–7]. Compensated hypogonadism is characterized by normal testosterone but raised LH, signifying subclinical Leydig- cell dysfunction [14]. Human genetic evidence demonstrates that even low intratesticular testosterone levels (≈ 5–10 % of normal) can maintain partial spermatogenesis when minimal LH stimulation persists [42, 46]. This challenges the traditional belief that full-range intratesticular testosterone is indispensable for sperm production. While FSH is not strictly required to initiate spermatogenesis, it markedly enhances quantitative sperm output by optimizing Sertoli-cell metabolism and germ-cell differentiation [47– 50]. Disruption of feedback integrity during critical developmental windows—fetal life, "mini-puberty," or puberty—can irreversibly impair Leydig- and Sertoli-cell function, predisposing to lifelong infertility [42–44]. Early hormonal therapy using human chorionic gonadotropin (hCG), recombinant LH/FSH, or pharmacological agents such as clomiphene citrate has restored spermatogenesis in selected hypogonadotropic or receptor-mutation cases when initiated within these windows [43, 44, 53]. Clomiphene works by blocking estrogen-mediated negative feedback at the pituitary, thereby increasing endogenous LH and FSH secretion to stimulate testosterone production and support spermatogenesis. In conclusion, the preservation of LH/FSH–testosterone feedback loops is essential for male reproductive capacity. Disruption of this finely tuned endocrine circuitry should be viewed not merely as hormonal deficiency but as a breakdown of regulatory feedback within the HPG axis. Understanding the molecular and genetic mechanisms of these loops provides the foundation for personalized, timing-sensitive hormonal therapies—including hCG, recombinant gonadotropins, and clomiphene—to restore spermatogenesis and fertility in affected men [37, 42, 43, 46, 83, 104, 107].*

Keywords— *Hypothalamic–pituitary–gonadal (HPG) axis;male infertility; Leydig cells; Sertoli cells; LHβ mutation;Feedback disruption;FSHβ mutation; hypogonadism; spermatogenesis; genetic mutations; hormonal regulation;LHCGR;FSHR;Clomiphene citrate;Intratesticular testosterone;Hormonal therapy*.

I. INTRODUCTION

Male infertility is a major public health concern, affecting nearly 15% of couples worldwide, with a male factor contributing to approximately half of these cases. Recent data indicate a global decline in sperm quantity and quality, highlighting the need to better understand the hormonal regulation of spermatogenesis and its disturbances [1].

Spermatogenesis is regulated through a complex interaction between endocrine, paracrine, and metabolic pathways involving Leydig cells, Sertoli cells, peritubular cells, and germ cells. Central to this process is the hypothalamic–pituitary–gonadal (HPG) axis, which governs testicular function via luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Both are heterodimeric glycoproteins composed of a common α subunit and a hormone-specific β subunit [1].

The feedback loop mechanism ensures hormonal balance within the HPG axis.

- The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which binds to receptors (GnRHR) on the anterior pituitary, stimulating the release of LH and FSH.
- LH acts on Leydig cells, promoting their proliferation and maturation, and inducing testosterone (T) synthesis.
- FSH targets Sertoli cells, stimulating the production of growth factors, signaling molecules, and nutrients essential for germ cell development and maturation within the seminiferous tubules.
- Testosterone and FSH act synergistically on Sertoli cells to maintain normal spermatogenesis and sperm maturation.
- Elevated testosterone and inhibin B from Sertoli cells exert negative feedback on the hypothalamus and pituitary to suppress further GnRH, LH, and FSH secretion, thereby

R. Purushothaman, K. Lokesh, P. Kamali Paul, and M. Gayathri, "Feedback Disruption in Infertile Men: Howaltered LH/FSH Testosterone Loops Contribute to Dysfunction," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 8, Issue 6, pp. 63-71, 2025.

maintaining hormonal equilibrium.

In adult men, intratesticular testosterone (ITT) levels remain approximately 100 times higher than in circulation, ensuring optimal spermatogenic activity and male virilization [1].

Recent advances from studies of genetic mutations in LHβ, FSHβ, and their receptors (LHCGR and FSHR) have provided valuable insights into how disruption of these feedback loops leads to impaired spermatogenesis and infertility. These findings have challenged classical endocrine models and offered new therapeutic perspectives for managing male hypogonadism and infertility.

Pharmacological agents such as clomiphene citrate can complement these approaches by blocking estrogen-mediated negative feedback at the pituitary, thereby increasing endogenous LH and FSH secretion, stimulating Leydig cell testosterone production, and supporting spermatogenesis without suppressing testicular function[1].

Aim

To study the impact of correcting altered LH/FSH–testosterone feedback loops on spermatogenic function and fertility potential in men diagnosed with hormonal infertility.

Objectives

To evaluate how disruption in LH/FSH–testosterone feedback mechanisms affects spermatogenesis and fertility potential, and to assess whether restoring hormonal equilibrium can improve fertility outcomes in men with hormonal infertility.

Need for the Study:

- Global decline in sperm count and fertility rates demands understanding of endocrine causes of male infertility.
- Current treatments often address symptoms rather than hormonal root causes.
- Feedback disruption in the HPG axis, due to receptor mutations or hormonal dysregulation, is often underdiagnosed.
- Studying how LH and FSH defects affect testosterone production can guide personalized hormonal therapy and early intervention strategies.

II. Methodology

Study design - Asystematic Review

Search Strategy:

The strategy combines literature review and clinical evidence to examine LH/FSH–testosterone feedback disruption in male infertility and the effects of interventions like clomiphene citrate on spermatogenesis and fertility.

Databases searched:

PubMed, Springer, web of science, google scholar, CrossRef.

Search terms/keywords used : Hypothalamic–pituitary–gonadal (HPG) axis;male infertility; Leydig cells; Sertoli cells; LHβ mutation; Feedback disruption; FSHβ mutation; hypogonadism; spermatogenesis; genetic mutations; hormonal regulation; LHCGR; FSHR; Clomiphene citrate; Intratesticular testosterone; Hormonal therapy.

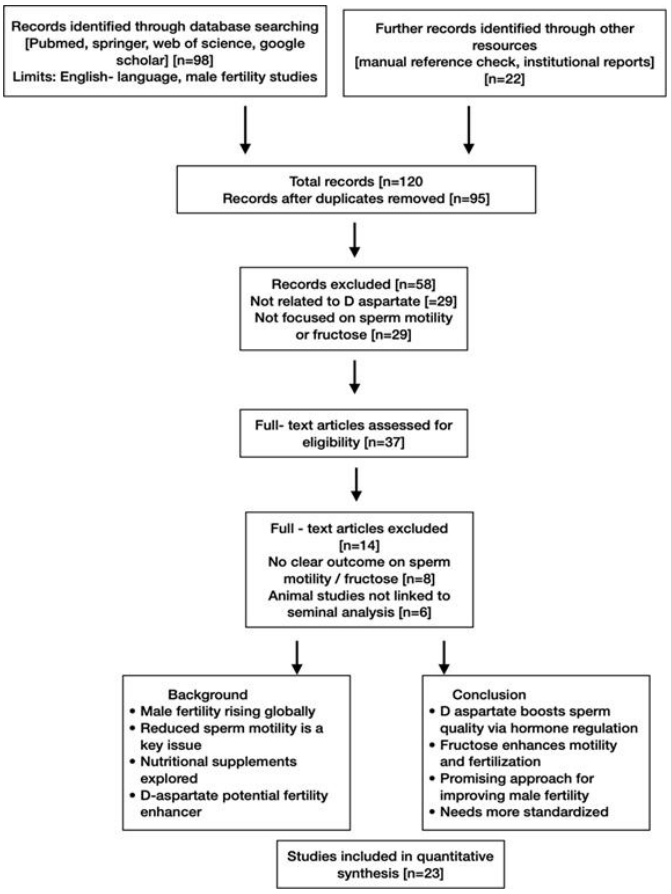
Inclusion criteria

- Human studies evaluating male infertility.
- Studies assessing LH, FSH, testosterone levels, or feedback loop integrity.
- Research on genetic mutations affecting LHCGR, FSHR, or gonadotropin signaling.
- Clinical studies with hormonal, semen, or fertility outcomes.
- Molecular studies linking HPG axis disruption to spermatogenic failure.
- Studies published in English.

Exclusion criteria

- Animal or non-human experimental studies not linked to seminal analysis.
- Studies without clear outcomes on LH/FSH or testosterone balance.
- Non-English publications.
- Articles focusing on unrelated endocrine disorders.
- Conference abstracts, editorials, and letters without primary data.
- Studies solely on exogenous hormone therapy without assessing feedback mechanisms.

III. Studysearch Diagram



R. Purushothaman, K. Lokesh, P. Kamali Paul, and M. Gayathri, "Feedback Disruption in Infertile Men: Howaltered LH/FSH Testosterone Loops Contribute to Dysfunction," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 8, Issue 6, pp. 63-71, 2025.

IV. DISCUSSION

Principles and Regulations of Spermatogenesis

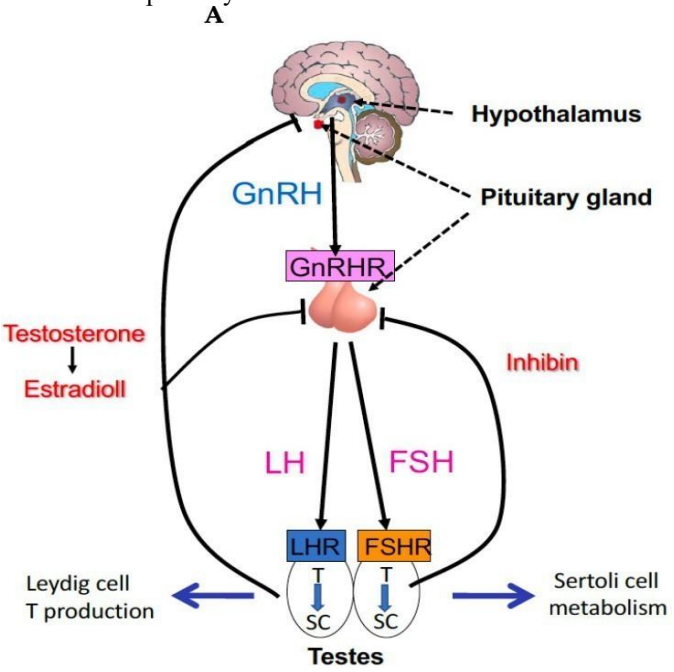
Aseries of biological processes known as spermatogenesis aid in the maturation of germ cells in the testicular seminiferous tubules [8,9]. Through cellular mechanisms of mitotic development, meiotic recombination of genetic materials, and morphological sperm maturation, the process takes place step-by- step and involves the interaction of multiple autocrine, paracrine, and other hormonal stimuli and nutrients that support the development of the germ cells [10,11]. The anterior pituitary gland's secretion of LH and FSH in response to the hypothalamic gonadotropin-releasing hormone (GnRH) is essential for the formation and maintenance of both qualitative and quantitative spermatogenesis. To regulate the growth, maturation, and function of the gonads, GnRH causes the anterior pituitary's gonadotrope cells to produce and secrete gonadotropin in distinct pulses into the bloodstream. The anterior pituitary gland's secretion of LH and FSH in response to the hypothalamic gonadotropin-releasing hormone (GnRH) is essential for the formation and maintenance of both qualitative and quantitative spermatogenesis. In order to regulate the gonads' development, maturation, and function, GnRH causes the anterior pituitary's gonadotrope cells to synthesize and secrete gonadotropin in distinct pulses into the bloodstream [12].LH promotes the synthesis of T, which is thought to be essential for successful spermatogenesis, secondary sexual traits and functions, and anabolic and psychological effects [4,5,13]. On the other side, FSH maintains the Sertoli cells' supportive role in spermatogenesis, which increases T action. The interplay among these hormones is essential for the adult testis's twin roles of virility and fertility [5,14].FSH is known to influence the number and quality of sperm, even though T is regarded as the master switch of spermatogenesis. The feedback regulation of GnRH and gonadotropin secretion in the preservation of the HPG axis' homeostasis depends on the interaction of the various elements and the ensuing direct negative feedback effects of T and inhibin B, which are generated by the Sertoli cells [14–16].

Specific G protein-coupled membrane receptors (GPCR), FSHR [17] and LHR (LHCGR in humans) [18– 20], which are expressed in the testes' Sertoli cells and granulosa cells or in the testes' Leydig cells and thecal and luteal cells of the ovaries [5,21–24], are responsible for the direct action of FSH and LH at the testicular level.Through theAR expressed in Sertoli cells, T, which is produced by Leydig cells, triggers the functional responses required for spermatogenesis [7]. The chromosomal location of FSHR and LHR on chromosome 2p21 is remarkably similar [25,26], indicating evolutionary duplication of a common ancestral gene. On the other hand, the analogous thyroid-stimulating hormone receptor (TSHR) spread throughout the genome as it evolved to 14q31 [25–27].

Eleven exons make up the LHR gene [19], while ten exons make up the FSHR gene [17,28,29]. The largest exons, 11 and 10, respectively, encode the receptor's whole transmembrane region. Unlike other genes that encode G protein-coupled receptors, this gene has short extracellular domains that are intron-free. A gene producing leucin rich repeats (found in the extracellular domain) and a protoreceptor gene without introns that encodes a GPCR may have recombined to produce the gonadotropin receptor genes during evolution [27,30,31].

Control of spermatogenesis.

A. Hormonal control. The hypothalamus releases GnRH, which acts on the pituitary gland, it secretes LH and FSH. LH stimulates Leydig cells in the testes to make testosterone. FSH acts on Sertoli cells to support sperm development. Testosterone and inhibin provide negative feedback to the brain and pituitary to balance hormone levels. The hypothalamus releases GnRH, which acts on the pituitary gland. The pituitary secretes LH and FSH.LH stimulates Leydig cells in the testes to make testosterone. FSH acts on Sertoli cells to support sperm development. Testosterone and inhibin provide negative feedback to the brain and pituitary to balance hormone levels.



Genetic Defects of the Gonadal Axis and their Contribution to Understanding Human Reproduction

The primary function of LH is to stimulate testosterone (T) production by binding to LHR (LHCGR in humans) on Leydig cells, with high intratesticular T required for spermatogenesis and maturation [32,33]. Mutations in LHβ and LHCGR cause disorders of sexual development and reproductive dysfunction [34,35]. Studies of patients with genetic gonadotropin abnormalities help elucidate human gonadal physiology, with mutations in LHR, FSHR, and their ligands revealing syndromes and hormone actions on target organs [36,37]. Complete inactivating LHβ mutations in five males resulted in masculinization at birth but absent pubertal development, absence or immature Leydig cells, blocked germ cell maturation, and lack of spermatogenesis [38–41]. LH is not required for fetal masculinization, which is mediated by placental hCG acting on LHCGR, but postnatal LH is essential for Leydig cell proliferation, maturation, T secretion, and

R. Purushothaman, K. Lokesh, P. Kamali Paul, and M. Gayathri, "Feedback Disruption in Infertile Men: Howaltered LH/FSH Testosterone Loops Contribute to Dysfunction," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 8, Issue 6, pp. 63-71, 2025.

initiation of spermatogenesis. In some LH-deficient men, even prolonged high-dose hCG treatment failed to restore spermatogenesis due to a missed critical "window of testicular susceptibility" [42], though fertility was restored in two patients with timely hCG therapy [43,44].

Proliferation of Testosterone-Producing Leydig Cells in Different Waves

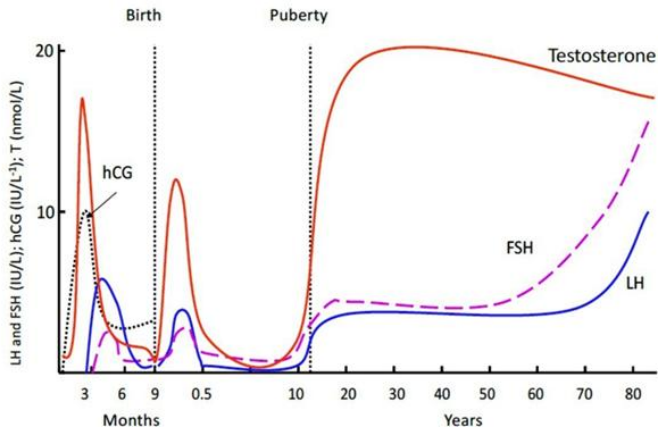
The three waves of Leydig cell proliferation in humans, each producing testosterone (T), are shown in Figure 1B [7,13]. The first, antenatal wave occurs after 10 weeks of fetal life, is hCG-dependent, and peaks at 14–15 weeks, driving internal genital differentiation and external masculinization [45]. The second, postnatal wave occurs at the end of the second month during transient HPG axis activation ("mini-puberty"), when increased LH and FSH stimulate Leydig cell development and a T peak; the testes then become quiescent by the end of the first year. The third wave at puberty reactivates the HPG axis, triggering T secretion, virilization, and spermatogenesis via T and FSH. Adult treatment of inactivating LHβ mutations is largely ineffective, reflecting limited understanding of the hormonal thresholds necessary to initiate and maintain spermatogenesis in men.

Disruption of Feedback Loops in Male Infertility Content:

Impaired feedback between testosterone, LH, and FSH leads to distinct hormonal patterns in infertile men:

- Primary testicular failure: High LH/FSH, low testosterone.
- Secondary hypogonadism: Low LH/FSH, low testosterone.
- Compensated hypogonadism: Normal testosterone but elevated LH. Such imbalances reflect defective negative feedback in the HPG axis [3-7]

B



B. The three waves of Leydig cell proliferation in humans. Each of them is characterized by the production of T. The first wave is antenatal, occurring after 10 weeks of fetal life and is hCG- dependent. Fetal T secretion peaks at 14–15 weeks, and induces the differentiation of the internal genitalia and masculinization of the external genitalia. The other two waves of Leydig cell proliferation are postnatal, regulated by pituitary LH.At the end of the second month of life, in the postnatal period, the HPG axis is transiently activated. The increased secretion of LH and FSH causes the development of a second wave of Leydig cells, and the appearance of a peak of T at levels close in magnitude to those observed at puberty. This event, called "mini-puberty", is short- lived, and its role is poorly understood. The third wave starts at puberty and lasts for the rest of a man's life.

Waves of Leydig Cell Proliferation and Hormonal Regulation

Leydig cells proliferate in three distinct waves, each associated with testosterone production [7,13,45]:

1. Fetal phase (hCG-dependent): Testosterone peaks at 14–15 weeks of gestation, inducing masculinization of genitalia.
2. Mini-puberty (postnatal): Transient LH/FSH activation at ~2 months of age leads to temporary testosterone rise, important for testicular priming.
3. Puberty onward: Reactivation of the HPG axis sustains testosterone production and full spermatogenesis.

Failure of mini-puberty activation can permanently affect Leydig cell development, leading to adult infertility despite hormonal replacement [42–44].

Feedback Disruption in LH–TestosteroneAxis

Mutations in LHβ or LHCGR genes result in defective testosterone synthesis and disrupted spermatogenesis [34,35]. Inactivating LHβ mutations in men cause absent puberty, undetectable LH, low testosterone, and azoospermia, with few or no Leydig cells present [38–41].

However, a case of partial LHβ defect revealed normal spermatogenesis despite very low serum testosterone (0.4 ng/mL) and ITT levels only 5% of normal [46].

This suggests that minimal LH stimulation and low ITT can sustain spermatogenesis, although insufficient for systemic virilization.

These findings challenge the classical view that high intratesticular testosterone is essential for sperm production and highlight a "critical window" for LH exposure—especially around mini- puberty—for normal testicular maturation [42,46].

LHβ and LHCGR Mutations

Mutations in the LHβ subunit gene or LH/choriogonadotropin receptor (LHCGR) lead to Leydig cell hypoplasia or insensitivity to LH.

- Affected males present with low serum testosterone, underdeveloped Leydig cells, and infertility, but often normal male genitalia at birth due to placental hCG activity during fetal life.
- These cases demonstrate that LH is indispensable for pubertal testosterone production and spermatogenesis, but not for fetal masculinization.
- Partial mutations may allow limited testosterone production and partial spermatogenesis, highlighting a dose-dependent LH–testosterone relationship [5–7].

R. Purushothaman, K. Lokesh, P. Kamali Paul, and M. Gayathri, "Feedback Disruption in Infertile Men: Howaltered LH/FSH Testosterone Loops Contribute to Dysfunction," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 8, Issue 6, pp. 63-71, 2025.

FSHβ and FSHR Mutations

Mutations in the FSHβ gene (ligand deficiency) or FSHR gene (receptor defect) reveal that FSH is quantitatively important in spermatogenesis.

- FSHβ mutations cause azoospermia, low testicular volume, and infertility due to absent FSH stimulation of Sertoli cells.
- FSHR mutations, however, show variable phenotypes—some men maintain partial spermatogenesis and fertility, indicating that FSH enhances sperm production but is not absolutely required when intratesticular testosterone is sufficient.
- These findings establish FSH as a modulator of spermatogenic efficiency rather than an initiator [12-14].

Alterations in FSH–Sertoli Cell Function

FSH stimulates Sertoli cell proliferation prenatally and during puberty, determining adult testis size and sperm production capacity [47-48,54-55].

Complete or partial loss of FSHβ or FSHR function in men reveals variable effects:

- Inactivating FSHβ mutations cause azoospermia and infertility [37,53].
- FSHR mutations result in reduced sperm counts or oligozoospermia, though some men remain fertile, likely due to residual receptor activity [49,51,52].

Elevated FSH levels in these cases reflect feedback resistance from dysfunctional Sertoli cells, a hallmark of primary testicular failure.

Interplay Between LH, FSH, and Testosterone

FSH and LH operate synergistically to sustain spermatogenesis. LH-induced testosterone acts on Sertoli cells to promote spermatid differentiation, while FSH maintains Sertoli cell metabolism and germ cell support [5,14,47-50].

Disruptions in their balance can produce:

- High FSH, low T: primary testicular failure.
- Low FSH/LH, low T: secondary (hypogonadotropic) failure.Hence, evaluating LH, FSH, T, and inhibin B levels helps differentiate central versus testicular causes of infertility.

Clinical Implications of Feedback Disruption

Hormonal therapies targeting feedback imbalance may restore fertility if initiated early.

- hCG therapy (LH analog) can induce Leydig cell maturation when administered during critical developmental windows [43,44].
- Combined FSH and LH (or hCG) therapy supports both Sertoli and Leydig functions in hypogonadotropic men [53].

However, postpubertal initiation often fails due to irreversible Leydig cell underdevelopment, confirming that early hormonal feedback integrity is vital for fertility restoration.

Insights from Combined Gonadotropin Deficiencies

Rare cases of combined LH and FSH deficiency (due to pituitary or GnRH gene defects) demonstrate that both hormones are crucial for testicular growth and sperm maturation.

- Men with congenital hypogonadotropic hypogonadism fail to undergo normal puberty and show small testes, low testosterone, and azoospermia.
- Administration of recombinant FSH and hCG (LH analog) can restore spermatogenesis, proving the essential role of both gonadotropins in human fertility [6-11].

Clinical and Therapeutic Implications

- Genetic findings guide personalized hormonal therapy in infertility:
  - FSH supplementation improves sperm output in men with low FSH.
  - hCG or recombinant LH restores testosterone in LH-deficient hypogonadism.
- Genetic screening can identify receptor or subunit mutations, enabling early diagnosis and management [14].

Hormone comparison between subgroups: Table 1 compares the serum levels of FSH, LH, DHEA, and testosterone in normozoospermic fertile men and infertile men in the following subgroups: oligozoospermic, asthenozoospermic, and azoospermic men.

A- comparison of the serum FSH levels in the subgroups of infertile men and fertile men (normozoospermic): Table (1) and Figure (1) show that the mean and standard error of FSH in azoospermic men (30.47 ± 9.70) were significantly ($p<0.001$) higher than those of oligozoospermic men (18.00 ± 7.51), asthenozoospermic men (6.96 ± 1.46), and normozoospermic fertile men (4.92 ± 0.51).

B - Serum LH levels in the normozoospermic (fertile men) and infertile men subgroups are compared: Compared to oligozoospermic men (9.05 ± 2.52), asthenozoospermic men (6.00 ± 1.04), and normozoospermic fertile men (7.72 ± 1.29), the mean and standard error of LH in azoospermic men were substantially ($p<0.001$) higher at 14.35 ± 4.63.

C- Serum DHEAlevels in the normozoospermic (fertile men) and infertile men subgroups are compared: According to table (1) and figure (3), the mean and standard error of DHEAin oligozoospermic men (7.26 ± 2.35) was significantly ($P<0.05$) higher than that of azoospermic men (6.80 ± 1.80), significantly ($P<0.05$) higher than that of asthenozoospermic men (6.17 ± 0.85), and significantly ($P<0.05$) higher than that of normozoospermic fertile men (4.67 ± 0.52).

D-Serum testosterone levels in the normozoospermic (fertile men) and infertile men subgroups are compared: In comparison to normozoospermic fertile men (2.73 ± 0.36), asthenozoospermic men (2.77 ± 0.50), and azoospermic men (2.40 ± 0.41), the mean and standard error of testosterone in oligozoospermic men (3.03 ± 0.57) were considerably ($P<0.05$) greater.

R. Purushothaman, K. Lokesh, P. Kamali Paul, and M. Gayathri, "Feedback Disruption in Infertile Men: Howaltered LH/FSH Testosterone Loops Contribute to Dysfunction," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 8, Issue 6, pp. 63-71, 2025.

International Research Journal of Pharmacy and Medical Sciences
ISSN (Online): 2581-3277

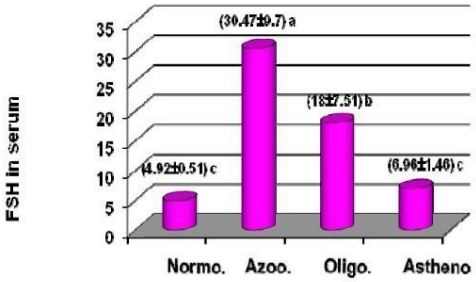


Figure (1): Comparison of serum FSH levels between fertile men group (normozoospermic) and infertile men subgroups

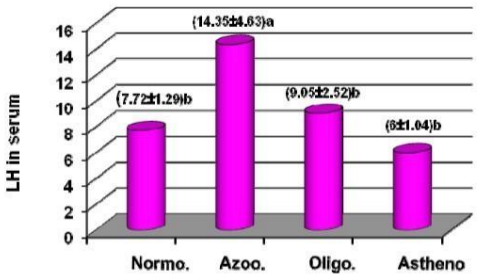


Figure (2): Comparison of serum LH levels between fertile men group (normozoospermic) and infertile men subgroups

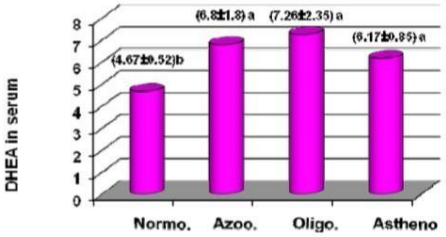


Figure (3): Comparison of serum DHEA levels between fertile men group (normozoospermic) and infertile men subgroups.

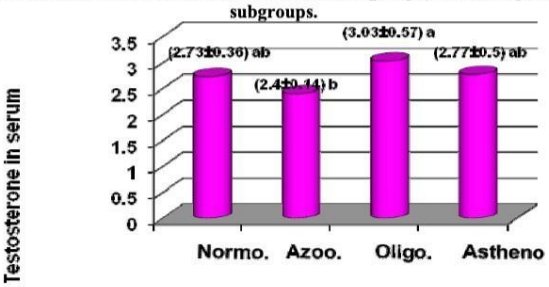


Figure (4): Comparison of serum Testosterone levels between fertile men group (normozoospermic) and infertile men subgroups.

Table 1: Comparison of serum FSH, LH, DHEA and Testosterone levels between fertile men group(normozoospermic) and infertile men subgroups.

The group	Mean ± SE			
	FSH	LH	DHEA	Testosterone
Normo.	4.92 ± 0.51 c	7.72 ± 1.29 b	4.67 ± 0.52 b	2.73 ± 0.36 ab
Azoo.	30.47 ± 9.70 a	14.35 ±4.63a	6.80 ± 1.80 a	2.40 ± 0.41 b
Oligo.	18.00 ± 7.51 b	9.05 ± 2.52 b	7.26 ± 2.35 a	3.03 ± 0.57 a
Astheno	6.96 ± 1.46 c	6.00 ± 1.04 b	6.17 ± 0.85 a	2.77 ± 0.50 ab
LSD value	8.943 **	4.012 **	1.273 *	0.549 *
P-value	0.0021	0.0037	0.0463	0.0318

* (P<0.05), ** (P<0.001).
Means having different letters in same column differ significantly. M±SE = Mean ± Standard Error

R. Purushothaman, K. Lokesh, P. Kamali Paul, and M. Gayathri, "Feedback Disruption in Infertile Men: Howaltered LH/FSH Testosterone Loops Contribute to Dysfunction," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 8, Issue 6, pp. 63-71, 2025.

Table (2): Comparison of hormones between fertile and infertile (main group).

The group	Mean ± SE of hormones			
	Testosterone	DHEA	LH	FSH
Fertile men	2.73 ± 0.36	4.67 ± 0.52	7.72 ± 1.29	4.92 ± 0.51
Infertile men	2.71 ± 0.28	6.71 ± 0.96	9.85 ± 1.88	18.50 ± 4.33
T-Test value	0.531 NS	1.855 *	3.924 NS	5.659 *
* (P<0.05), NS: Non-Significant				

Table (3): Correlations between hormones in serum seminal fluid functional parameters

Hormones in serum	Correlation coefficient-r		
	Concentration	Motility	MNS
Testosterone	0.04 NS	0.28 *	0.28 *
DHEA	0.08 NS	-0.03 NS	0.33 *
LH	-0.21 NS	-0.29 *	0.02 NS
FSH	-0.29 *	-0.34 *	0.08 NS
* (P<0.05), NS: Non-Significant.			

Hormone comparison between the major group of infertile and fertile individuals: According to table (2), the mean and standard error of testosterone in fertile men (2.73 ± 0.36) were not significantly different from those of testosterone in infertile men (2.71 ± 0.28).According to table (2), the DHEAmean and standard error in the infertile group (6.71 ± 0.96) was substantially (P<0.05) greater than that of the fertile men (4.67 ± 0.52).According to table (2), the mean and standard error of LH in males in the infertile group (9.85 ± 1.88), when compared to those of LH in men who were fertile (7.72 ± 1.29), were not significant (p>0.05). Table (2) indicates that the FSH mean and standard error in infertile men (18.50 ± 4.33) was substantially (P<0.05) greater than that in fertile men (4.92 ± 0.51).

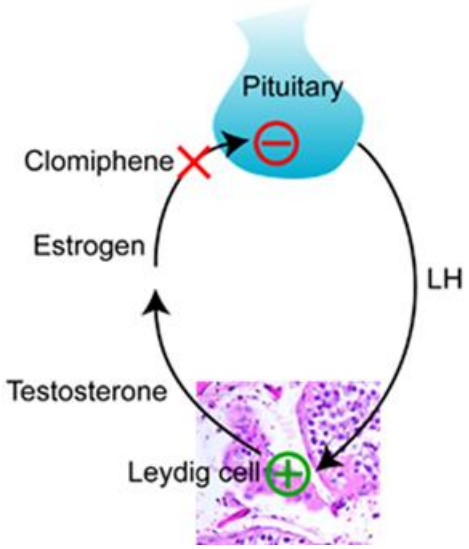
Infertile Men's Sperm ParametersAre Improved by Clomiphene Citrate

The pituitary regulates the production of testosterone in the testis in order to comprehend how clomiphene functions. Leydig cells in the testis produce testosterone. Luteinizing hormone ("LH"), which is released by the pituitary, causes the Leydig cells to produce more testosterone. The female hormone estrogen is produced from testosterone and instructs the pituitary to cease producing additional LH. Hormone function is a classic example of a negative feedback mechanism. It functions similarly to a heater and thermostat. The thermostat reduces the amount of electricity sent to the heater as the room warms up. The thermostat increases the amount of electricity sent to the heater when the room becomes colder.

Clomiphene functions by preventing the pituitary from producing estrogen. The pituitary produces more LH and perceives less estrogen. The testis's Leydig cells produce more testosterone when there is more LH present.

Giving a male testosterone has the exact opposite effect. LH decreases because the pituitary believes that the testis is producing an abundance of testosterone. As a result, the testis stops producing testosterone, which causes the blood's typically high levels of testosterone to drop.

Thus, clomiphene is a means of simultaneously raising blood and testicular testosterone levels. It raises blood testosterone levels while maintaining testis size and function.



The FDAhas not approved the use of clomiphene in males. The pharmaceutical firm that first applied for FDAapproval did so for women, just like the majority of the drugs we use to treat male fertility. Compared to the majority of prescription testosterone forms, this drug is reasonably priced. Because it is "off label," the FDA has not approved its use in males.

Men typically tolerate clomiphene well as a medicine. The majority of people have no symptoms as their testosterone levels increase. Those who do see an increase in muscular growth, sex drive, and energy, particularly if they exercise. Patients hardly ever say they feel overly furious or violent.

Patients have reported visual alterations only twice in the past 20 years.Because the pituitary is located close to the brain's optic nerve, alterations in vision could indicate that the pituitary is growing or shrinking. It is concerning if anything in the brain changes in size because the skull is a closed space. Patients who used clomiphene and experienced breast growth, or "gynecomastia," throughout the past 20 years. It goes without saying that clomiphene is stopped if any of these negative side effects occur.

R. Purushothaman, K. Lokesh, P. Kamali Paul, and M. Gayathri, “Feedback Disruption in Infertile Men: Howaltered LH/FSH Testosterone Loops Contribute to Dysfunction,” *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 8, Issue 6, pp. 63-71, 2025.

Males who have low testosterone levels or infertility can utilize clomiphene. The medication is a prescription off-label. It is effective, and men who take it typically tolerate it well [2].

V. Conclusion

Disruption of the LH/FSH–testosterone feedback loop plays a central role in male infertility. Reduced LH activity impairs Leydig cell testosterone production, while defective FSH signaling compromises Sertoli cell support, resulting in impaired spermatogenesis despite normal testicular structure. Human studies demonstrate that even low intratesticular testosterone (≈5–10% of normal) can sustain spermatogenesis locally, yet adequate FSH signaling is indispensable for maintaining sperm quantity. Early disturbances in LH/FSH–testosterone feedback, especially during fetal development, mini- puberty, or puberty, can prevent full testicular maturation and cause lifelong fertility issues.

Therapeutic interventions aimed at restoring proper LH and FSH activity can improve fertility potential. Clomiphene citrate, a selective estrogen receptor modulator, exemplifies this approach by blocking estrogen- mediated negative feedback at the pituitary. This increases gonadotropin secretion, stimulating Leydig cells to produce testosterone while preserving testicular size and function. By enhancing both serum and intratesticular testosterone levels, clomiphene supports spermatogenesis without suppressing endogenous hormone production, unlike direct testosterone therapy.

Furthermore, clomiphene is generally well-tolerated, with minimal adverse effects reported over decades of clinical use. Its action underscores the importance of preserving the integrity of endocrine feedback loops in men with infertility. Male infertility should therefore be understood not merely as a deficiency of hormones, but as a breakdown in feedback regulation within the hypothalamic– pituitary–gonadal axis. Restoring the timing, amplitude, and coordination of LH and FSH secretion is critical for optimal spermatogenesis, hormonal balance, and fertility outcomes. Pharmacological strategies like clomiphene demonstrate that targeted correction of feedback disruption can effectively improve reproductive function and maintain long-term testicular health.

Reference

1. Oduwole, O.O.; Vydra, N.; Wood, N.E.M.; Samanta, L.; Owen, L.; Keevil, B.; Donaldson, M.; Naresh, K.; Huhtaniemi, I.T. Overlapping Dose Responses of Spermatogenic and Extragonadal Testosterone Actions Jeopardize the Principle of Hormonal Male Contraception. *FASEB J.* 2014, *28*, 2566–2576.
2. Male Health, "How Clomid Works in Men," *Male Health*, April 28, 2010, https:// www.maledoc.com/blog/2010/04/28/how-clomid-works-in-men/
3. Levine, H.; Jørgensen, N.; Martino-Andrade,A.; Mendiola, J.; Weksler-Derri, D.; Mindlis, I.;Pinotti, R.; Swan, S.H. Temporal Trends in Sperm Count: ASystematic Review and Meta- Regression Analysis. *Hum. Reprod. Update* 2017, *23*, 646–659. [CrossRef][PubMed]
4. Anderson, R.A.; Baird, D.T. Male Contraception. *Endocr. Rev.* 2002, *23*, 735–762. [CrossRef]
5. McLachlan, R.I.; O'Donnell, L.; Meachem, S.J.; Stanton, P.G.; de Kretser, D.M.; Pratis, K.; Robertson, D.M. Identification of Specific Sites of Hormonal Regulation in Spermatogenesis in Rats, Monkeys, and Man. *Recent Prog. Horm. Res.* 2002, *57*, 149–179. [CrossRef]
6. Smith, L.; Walker, W. Hormonal signaling in the testis. In *Knobil and Neill's Physiology of Reproduction*; Plant, T.M., Zeleznik,A.J., Eds.;Academic Press: Waltham, MA, USA, 2015; pp. 637–675.Saez, J.M. Leydig Cells: Endocrine, Paracrine, andAutocrine Regulation. *Endocr.Rev.* 1994, *15*, 574–626. [CrossRef]
7. Mruk, D.D.; Cheng, C.Y. The Mammalian Blood-Testis Barrier: Its Biology and Regulation.*Endocr. Rev.* 2015, *36*, 564–591. [CrossRef]
8. Steinberger, E.; Steinberger, A. Spermatogenic function of the testis. In *Handbook of Physiology*; Greep, R.O., Hamilton, D.W., Eds.;American Physiological Society: Washington, DC, USA, 1975; pp. 1–10.
9. Ehmcke, J.; Schlatt, S.ARevised Model for Spermatogonial Expansion in Man: Lessons from Non-Human Primates. *Reproduction* 2006, *132*, 673–680. [CrossRef]
10. Dubé, E.; Cyr, D.G. The Blood-Epididymis Barrier and Human Male Fertility. *Adv. Exp. Med. Biol.* 2012, *763*, 218–236. [CrossRef]
11. Ramaswamy, S.; Weinbauer, G.F. Endocrine Control of Spermatogenesis: Role of FSH and LH/ Testosterone. *Spermatogenesis* 2014, *4*, e996025. [CrossRef]
12. Huhtaniemi, I. Mechanisms in Endocrinology: Hormonal Regulation of Spermatogenesis: Mutant Mice Challenging Old Paradigms. *Eur. J. Endocrinol.* 2018, *179*, R143–R150. [CrossRef]
13. Oduwole, O.O.; Huhtaniemi, I.T. Feasibility of Male Hormonal Contraception: Lessons from Clinical Trials andAnimal Experiments. *Curr. Mol. Pharmacol.* 2014, *7*, 109–118. [CrossRef]
14. Hayes, F.J.; DeCruz, S.; Seminara, S.B.; Boepple, P.A.; Crowley, W.F. Differential Regulation of Gonadotropin Secretion by Testosterone in the Human Male: Absence of a Negative Feedback Effect of Testosterone on Follicle-Stimulating Hormone Secretion. *J. Clin. Endocrinol. Metab.* 2001, *86*, 53–58. [CrossRef]
15. Manetti, G.J.; Honig, S.C. Update on Male Hormonal Contraception: Is the Vasectomy in Jeopardy? *Int. J. Impot. Res.* 2010, *22*, 159–170. [CrossRef]
16. Sprengel, R.; Braun, T.; Nikolics, K.; Segaloff, D.L.; Seeburg, P.H. The Testicular Receptor for Follicle Stimulating Hormone: Structure and Functional Expression of Cloned CDNA. *Mol. Endocrinol.* 1990, *4*, 525–530. [CrossRef]
17. Loosfelt, H.; Misrahi, M.; Atger, M.; Salesse, R.; Vu Hai-Luu Thi, M.T.; Jolivet, A.; Guiochon- Mantel, A.; Sar, S.; Jallal, B.; Garnier, J. Cloning and Sequencing of Porcine LH- HCG Receptor CDNA: Variants Lacking Transmembrane Domain. *Science* 1989, *245*, 525–528. [CrossRef]
18. Atger, M.; Misrahi, M.; Sar, S.; Le Flem, L.; Dessen, P.; Milgrom, E. Structure of the Human Luteinizing Hormone- Choriogonadotropin Receptor Gene: Unusual Promoter and 5′ Non-Coding Regions. *Mol. Cell. Endocrinol.* 1995, *111*, 113–123. [CrossRef]
19. McFarland, K.C.; Sprengel, R.; Phillips, H.S.; Köhler, M.; Rosemblit, N.; Nikolics, K.; Segaloff, D.L.; Seeburg, P.H. Lutropin-Choriogonadotropin Receptor:An Unusual Member of the G Protein-Coupled Receptor Family. *Science* 1989, *245*, 494–499. [CrossRef]
20. Orth, J.; Christensen,A.K. Localization of 125I-Labeled FSH in the Testes of Hypophy- Sectomized Rats by Autoradiography at the Light and Electron Microscope Levels. *Endocrinology* 1977, *101*, 262–278. [CrossRef]
21. Kangasniemi, M.; Kaipia,A.; Toppari, J.; Perheentupa,A.; Huhtaniemi, I.; Parvinen, M. Cellular Regulation of Follicle-Stimulating Hormone (FSH) Binding in Rat Seminiferous Tubules. *J. Androl.* 1990, *11*, 336–343.
22. Simoni, M.; Gromoll, J.; Nieschlag, E. The Follicle-Stimulating Hormone Receptor: Biochemistry, Molecular Biology, Physiology, and Pathophysiology. *Endocr. Rev.* 1997, *18*, 739– 773. [CrossRef]
23. Welsh, M.; Saunders, P.T.K.; Atanassova, N.; Sharpe, R.M.; Smith, L.B. Androgen Action via Testicular Peritubular Myoid Cells Is Essential for Male Fertility. *FASEB J.* 2009, *23*, 4218– 4230. [CrossRef]
24. Rousseau-Merck, M.F.;Atger, M.; Loosfelt, H.; Milgrom, E.; Berger, R. The Chromosomal Localization of the Human Follicle- Stimulating Hormone Receptor Gene (FSHR) on 2p21- P16 Is Similar to That of the Luteinizing Hormone Receptor Gene. *Genomics* 1993, *15*, 222–224. [CrossRef]
25. Rousseau-Merck, M.F.; Misrahi, M.; Loosfelt, H.; Atger, M.; Milgrom, E.; Berger, R. Assignment of the Human Thyroid Stimulating Hormone Receptor (TSHR) Gene to Chromosome 14q31. *Genomics* 1990, *8*, 233–236. [CrossRef]
26. Gross, B.; Misrahi, M.; Sar, S.; Milgrom, E. Composite Structure of the

Human Thyrotropin Receptor Gene. *Biochem. Biophys. Res. Commun.* 1991, *177*, 679–687. [CrossRef]
27. Heckert, L.L.; Daley, I.J.; Griswold, M.D. Structural Organization of the Follicle- Stimulating Hormone Receptor Gene. *Mol. Endocrinol.* 1992, *6*, 70–80. [CrossRef]
28. Aittomäki, K.; Lucena, J.L.; Pakarinen, P.; Sistonen, P.; Tapanainen, J.; Gromoll, J.; Kaskikari, R.; Sankila, E.M.; Lehväslaiho, H.; Engel,A.R.; et al. Mutation in the Follicle- Stimulating Hormone Receptor Gene Causes Hereditary Hypergonadotropic Ovarian Failure. *Cell* 1995, *82*, 959–968. [CrossRef]
29. Gross, B.; Misrahi, M.; Loosfelt, H.; Vu Hai Luu Thi, M.;Atger, M.; Meduri, G.; Pichon, C.; Jolivet, A.; Milgrom, E. Receptors for Pituitary Glycoprotein Hormones. *C R Acad. Sci. III* 1992, *314*, 21–22. [PubMed]
30. Misrahi, M.; Beau, I.; Meduri, G.; Bouvattier, C.; Atger, M.; Loosfelt, H.; Ghinea, N.; Hai, M.V.; Bougnères, P.F.; Milgrom, E. Gonadotropin Receptors and the Control of Gonadal Steroidogenesis: Physiology and Pathology. *Baillieres Clin. Endocrinol. Metab.* 1998, *12*, 35–66. [CrossRef]
31. Kato, Y.; Shiraishi, K.; Matsuyama, H. Expression of Testicular Androgen Receptor in Non- Obstructive Azoospermia and Its Change after Hormonal Therapy. *Andrology* 2014, *2*, 734– 740. [CrossRef] [PubMed]
32. O'Hara, L.; Smith, L.B. Androgen Receptor Roles in Spermatogenesis and Infertility. *Best Pract. Res. Clin. Endocrinol. Metab.* 2015, *29*, 595–605. [CrossRef]
33. Themmen, A.P.N.; Huhtaniemi, I.T. Mutations of Gonadotropins and Gonadotropin Receptors: Elucidating the Physiology and Pathophysiology of Pituitary-Gonadal Function. *Endocr. Rev.* 2000, *21*, 551–583. [CrossRef]
34. Themmen,A.P.N.An Update of the Pathophysiology of Human Gonadotrophin Subunit and Receptor Gene Mutations and Polymorphisms. *Reproduction* 2005, *130*, 263–274. [CrossRef]
35. Meduri, G.; Bachelot,A.; Cocca, M.P.; Vasseur, C.; Rodien, P.; Kuttenn, F.; Touraine, P.; Misrahi, M. Molecular Pathology of the FSH Receptor: New Insights into FSH Physiology. *Mol. Cell. Endocrinol.* 2008, *282*, 130–142. [CrossRef]
36. Huhtaniemi, I.T.; Themmen, A.P.N. Mutations in Human Gonadotropin and Gonadotropin- Receptor Genes. *Endocrine* 2005, *26*, 207–217. [CrossRef]
37. Weiss, J.; Axelrod, L.; Whitcomb, R.W.; Harris, P.E.; Crowley, W.F.; Jameson, J.L. Hypogonadism Caused by a Single Amino Acid Substitution in the Beta Subunit of Luteinizing Hormone. *N. Engl. J. Med.* 1992, *326*, 179–183. [CrossRef]
38. Axelrod, L.; Neer, R.M.; Kliman, B. Hypogonadism in a Male with Immunologically Active, Biologically Inactive Luteinizing Hormone:An Exception to a Venerable Rule. *J. Clin. Endocrinol. Metab.* 1979, *48*, 279–287. [CrossRef]
39. Valdes-Socin, H.; Salvi, R.; Daly,A.F.; Gaillard, R.C.; Quatresooz, P.; Tebeu, P.-M.; Pralong, F.P.; Beckers,A. Hypogonadism in a Patient with a Mutation in the Luteinizing Hormone Beta-Subunit Gene. *N. Engl. J. Med.* 2004, *351*, 2619–2625. [CrossRef]
40. Lofrano-Porto, A.; Barra, G.B.; Giacomini, L.A.; Nascimento, P.P.; Latronico, A.C.; Casulari, L.A.; da Rocha Neves, F.D.A. Luteinizing Hormone Beta Mutation and Hypogonadism in Men and Women. *N. Engl. J. Med.* 2007, *357*, 897–904. [CrossRef]
41. Grumbach, M.M. AWindow of Opportunity: The Diagnosis of Gonadotropin Deficiency in the Male Infant. J. Clin. Endocrinol. *Metab.* 2005, *90*, 3122–3127. [CrossRef]
42. Valdes-Socin, H.; Salvi, R.; Thiry,A.; Daly,A.F.; Pralong, F.P.; Gaillard, R.; Beckers,A. Testicular Effects of Isolated Luteinizing Hormone Deficiency and Reversal by Long-Term Human Chorionic Gonadotropin Treatment. *J. Clin. Endocrinol. Metab.* 2009, *94*, 3–4. [CrossRef] [PubMed]
43. Yang, X.; Ochin, H.; Shu, L.; Liu, J.; Shen, J.; Liu, J.; Lin, C.; Cui, Y. Homozygous Nonsense Mutation Trp28X in the LHB Gene Causes Male Hypogonadism. *J. Assist. Reprod. Genet.* 2018, *35*, 913–919. [CrossRef] [PubMed]
44. Tapanainen, J.; Kellokumpu-Lehtinen, P.; Pelliniemi, L.; Huhtaniemi, I. Age-Related Changes in Endogenous Steroids of Human Fetal Testis during Early and Midpregnancy. *J. Clin. Endocrinol. Metab.* 1981, *52*, 98–102. [CrossRef] [PubMed]
45. Achard, C.; Courtillot, C.; Lahuna, O.; Méduri, G.; Soufir, J.-C.; Lière, P.; Bachelot,A.; Benyounes, H.; Schumacher, M.; Kuttenn, F.; et al. Normal Spermatogenesis in a Man with Mutant Luteinizing Hormone. *N. Engl. J. Med.* 2009, *361*, 1856–1863. [CrossRef] [PubMed]
46. Sharpe, R.M.; McKinnell, C.; Kivlin, C.; Fisher, J.S. Proliferation and Functional Maturation of Sertoli Cells, and Their Relevance to Disorders of Testis Function in Adulthood. *Reproduction* 2003, *125*, 769–784. [CrossRef]
47. Orth, J.M. The Role of Follicle-Stimulating Hormone in Controlling Sertoli Cell Proliferation in Testes of Fetal Rats. *Endocrinology* 1984, *115*, 1248–1255. [CrossRef]
48. Tapanainen, J.S.; Aittomäki, K.; Min, J.; Vaskivuo, T.; Huhtaniemi, I.T. Men Homozygous for an Inactivating Mutation of the Follicle-Stimulating Hormone (FSH) Receptor Gene Present Variable Suppression of Spermatogenesis and Fertility. *Nat. Genet.* 1997, *15*, 205–206. [CrossRef]
49. 84 Nieschlag, E.; Simoni, M.; Gromoll, J.; Weinbauer, G.F. Role of FSH in the Regulation of Spermatogenesis: ClinicalAspects. *Clin. Endocrinol.* 1999, *51*, 139–146. [CrossRef]
50. Rannikko,A.;Pakarinen,P.;Manna,P.R.;Beau,I.;Misrahi,M.;Aittomäki,K.;Huhtaniemi,I.Functi on alCharacterizationofthe Human FSH Receptor with an Inactivating Ala189Val Mutation. *Mol. Hum. Reprod.* 2002, *8*, 311–317. [CrossRef]
51. Tranchant,T.;Durand,G.;Gauthier,C.;Crépieux,P.;UlloaAguirre,A.;Royère,D.;Reiter,E.Preferen t alβ-ArrestinSignalling at Low Receptor Density Revealed by Functional Characterization of the Human FSH ReceptorA189 V Mutation. *Mol. Cell. Endocrinol.* 2011, *331*, 109–118. [CrossRef] [PubMed]
52. Zheng,J.;Mao,J.;Cui,M.;Liu,Z.;Wang,X.;Xiong,S.;Nie,M.;Wu,X.NovelFSHβMutationinaMa leP atientwithIsolatedFSH Deficiency and Infertility. *Eur. J. Med. Genet.* 2017, *60*, 335–339. [CrossRef]
53. Huhtaniemi, I.T.; Yamamoto, M.; Ranta, T.; Jalkanen, J.; Jaffe, R.B. Follicle-Stimulating Hormone ReceptorsAppear Earlier in the Primate Fetal Testis than in the Ovary. *J. Clin. Endocrinol. Metab.* 1987, *65*, 1210–1214. [CrossRef]
54. Warren, D.W.; Huhtaniemi, I.T.; Tapanainen, J.; Dufau, M.L.; Catt, K.J. Ontogeny of Gonadotropin Receptors in the Fetal and Neonatal Rat Testis. *Endocrinology* **1984**, *114*, 470–476. [CrossRef]