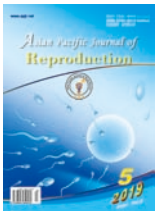

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Male reproductive hormones and semen quality

Sulagna Dutta[1]✉, Pallav Sengupta[2], Suriyani Muhamad[3]

[1]*Department of Oral Biology and Biomedical Sciences, Faculty of Dentistry, MAHSA University, Malaysia*

[2]*Department of Physiology, Faculty of Medicine and Biomedical Sciences, MAHSA University, Malaysia*

[3]*School of Social and Economic Development, Universiti Malaysia Terengganu, Malaysia*

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ABSTRACT

Male reproductive functions are mediated by different hormones whose orchestrations remain a major research interest. The 'master' regulator hormonal axis is the hypothalamo-pituitary-gonadal/testicular axis which is led by the pulsatile release of hypothalamic gonadotropin-releasing hormone. This, in turn, stimulates the anterior pituitary trophic hormones, the luteinizing hormone and follicle-stimulating hormone. Luteinizing hormone and follicle-stimulating hormone act upon the testicular cells, the Leydig cells for steroidogenesis and Sertoli cells to aid spermatogenesis, respectively. This primary axis is influenced by an array of other testicular hormones, metabolic hormones, and different regulatory factors. These hormonal crosstalks influence the intricate testicular functions, sexual behavior and semen quality in men. Given the growing concern in the last few decades over the increasing prevalence of male subfertility and/or infertility mostly in terms of deteriorating semen quality, it is required to find its underlying mechanisms. In this regard, the endocrine regulation of testicular functions is of prime importance in the determination of semen quality and sperm functions. This review article aims to present a concise updated overview on the mechanism by which the key hormones integrate the male reproductive functions and maintain the semen quality.

1. Introduction

Semen quality and male reproductive functions are coordinated by actions of accurate hormonal crosstalks[1−8]. The declining trend of semen quality over the last few decades[9−13] is a major global concern and it is crucial to explore its underlying mechanisms[14,15]. Impairments in endocrine regulations of male reproductive functions perhaps are the key players in altering semen quality. The hypothalamo-pituitary-gonadal (HPG) axis holds the prime control over the process of spermatogenesis. The hypothalamus triggers the anterior pituitary gonadotropins secretion by the pulsatile release of gonadotropin-releasing hormone (GnRH)[3,16]. Uninterrupted proper spermatogenesis is maintained through steady high intratesticular testosterone. Testosterone production is mediated by the Leydig cells on stimulation of the gonadotropin, luteinizing hormone (LH). Testosterone is the prime circulating androgen. It may be converted to 5α-dihydrotestosterone, and 44% of its circulated form remains bound to sex-hormone-binding globulin[17]. Testosterone crosses the tubular basement membrane and diffuses into the Sertoli cells to bind with androgen-binding-protein (ABP)[18,19]. Sertoli cells also possess receptors for follicle-stimulating hormone (FSH) that

✉Corresponding author: Sulagna Dutta, Ph.D., Department of Oral Biology and Biomedical Sciences, Faculty of Dentistry, MAHSA University, Malaysia.
Tel: +60142377866
E-mail: sulagna_dutta11@yahoo.com

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probably is required for the initiation of spermatogenesis[20,21]. Sertoli cells also produce glycoprotein hormones such as inhibins, activins and follistatins that mediate feedback regulations of the principal hormones. Apart from the classical hormones, there are several metabolic hormones, growth factors as well as paracrine factors that influence spermatogenesis either *via* their direct effect upon the testicular cells or by affecting the hormonal crosstalks [1,7,8,22]. Hormonal regulations are vital from the time of development and differentiation of the male genital organs, testicular descent, growth of the accessory glands and initiation of spermatogenesis[23].

Spermatogenesis, the process to produce spermatozoa, occurs within the seminiferous tubule of testis under strict endocrine regulation. It commences at the pubertal phase of man's life, as the seminiferous tubules remain quiescent in the childhood phase. The onset of spermatogenesis is induced by the elevated levels of gonadotropins and testosterone, which persists throughout life, slightly declining in old age. It takes about 65-70 days to produce mature spermatozoa from the very first stage of spermatogonia[24]. The intricate hormonal regulations of spermatogenesis are crucial for robust production of functional sperms and thereby are the major determinants of semen quality.

The present article is a concise update on the mechanism by which the prime hormones integrate the male reproductive functions and maintain the semen quality.

2. Hypothalamic hormones in regulation of semen quality

Semen quality relies upon proper spermatogenesis, sperm maturation, and seminal fluid composition, mediated by undisputed hormonal regulations. The hypothalamic-pituitary-testicular axis acts *via* both positive and negative feedback loops, as per the endogenous and exogenous cues, to regulate testicular functions. Hypothalamus, *via* pulsatile secretion of GnRH, trigger anterior pituitary gonadotropins, lutropin or LH, and follitropin or FSH. The gonadotropins, in turn, mediate the vital testicular functions, steroidogenesis and spermatogenesis. LH operates *via* receptors located on the interstitially placed Leydig cells to stimulate the synthesis of testosterone and other androgens[25,26]. Testosterone is a key player in several male reproductive functions, including extragonadal actions for sexual (libido) and anabolic (muscle strength, bone density) functions, besides the core intratesticular paracrine regulation of spermatogenesis. FSH is another essential pituitary gonadotropin that acts upon the Sertoli cells to stimulate spermatogenesis. Sertoli cells secrete some key hormones, inhibin (inhibitory) and activin (stimulatory) and other paracrine factors which along with testosterone mediate the feedback loops to influence the actions HPG axis in the regulation of spermatogenesis (Figure 1). The feedback mechanisms include both regulation of the hypothalamic GnRH and the subsequent pituitary gonadotropins secretions[25,26].

Recent advents in the concepts in male reproductive physiology introduced several other regulatory factors. These essentially include gonadotropin inhibiting hormone and other peptides, which are small RF-amide peptides consisting of *C*-terminal Arg-Phe-NH2 motif[25]. Yet another vital regulatory peptide that finds immense relevance is Kisspeptin (with 54-amino-acids), encoded by the *KiSS-1* gene. It has been suggested that Kisspepetin acts upon the hypothalamus *via* G protein-coupled receptor 54 and is a key peptide in mediating the onset of puberty. It has also been put forth that Kisspeptin may play a crucial role in precious puberty in male[27].

3. Gonadotropins in regulation of semen quality

3.1. FSH

FSH is one of the anterior pituitary gonadotropins that is triggered by low-frequency hypothalamic GnRH pulses. FSH in synergism with testosterone acts to stimulate all the spermatogenic steps.

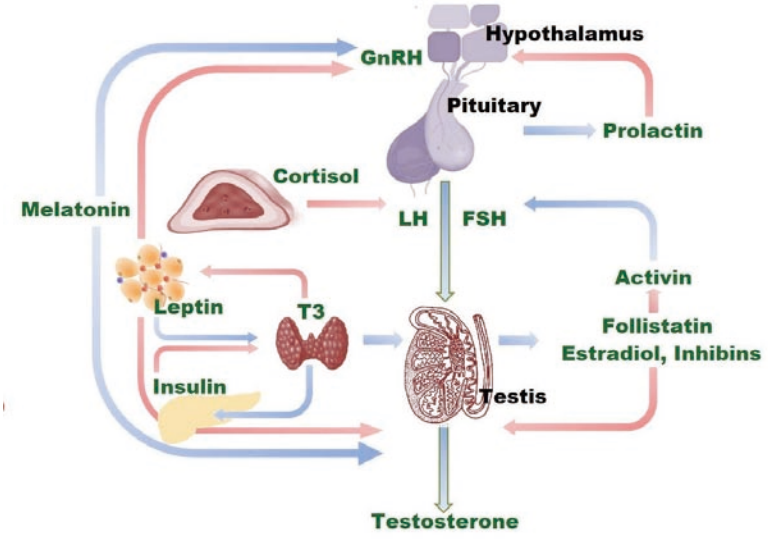

Figure 1. Hypothalamo-pituitary-testicular axis and its crosstalk with other hormones in the regulation of male reproductive functions. GnRH: gonadotropin-releasing hormone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; T3: triiodothyronine.

However, the distinct individual role of FSH on testicular functions are yet to be fully understood. Research has thrown lights in its role in determining Sertoli cell numbers alongside the maintenance of sperm production[21].

The effects of FSH upon the developing spermatogonial cells are mediated by their actions upon FSH receptors on Sertoli cells. The FSH receptors are activated through dissociation of α-subunit–linked Gs protein. This is followed by activation of adenylyl cyclase and increase in intracellular cyclic adenosine monophosphate (cAMP)[18]. cAMP mediates the release of the catalytic subunit of protein kinase, which leads to a phosphorylation cascade of several intracellular proteins. These include the transcription factors and cAMP response element-binding protein among others. There are several other hypotheses regarding the mechanism of action of FSH but not yet completely explained for *in vivo* conditions[28].

FSH stimulates the Sertoli cells to produce ABP. It also essentially contributes to the formation of blood-testis barrier. ABP functions to concentrate the testicular testosterone in sufficient levels (about 50–200 times that in blood) for consistency and accuracy in the process of spermatogenesis and hence to maintain robust semen quality[29]. Following initiation of spermatogenesis by FSH triggering the signal to set the pace of the process above basal level, testosterone supposedly is solely responsible for its continuation. However, increased FSH levels have been associated with increased spermatozoa production through inhibition of type A spermatogonia[30].

Although, as per the conventional consensus, FSH secretion is triggered by pulsatile GnRH release, it has been shown that it is overly sensitive to hypothalamic frequency modulations. The secretion of FSH is tightly regulated *via* negative feedback loop operated mainly by Sertoli cell peptides, inhibin B, and by antagonizing the activin stimulation of *FSH β* gene expression[18].

3.2. LH

LH (lutropin or lutrophin[31]), is secreted by the anterior pituitary gonadotropic cells[32]. In males, LH can also be referred to as the interstitial cell-stimulating hormone owing to its action upon the interstitial Leydig cell to aid steroidogenesis and production of testosterone. Its actions are in synergism with actions of FSH on the Sertoli cells[32] and thereby it indirectly participates in the immaculate regulation of spermatogenesis and consistency in semen quality.

LH acts on its receptors on the plasma membrane of the Leydig cells. There are almost 15 000 LH receptors on the Leydig cells[33]. It has been stipulated that five percent or less receptor occupancy is enough for LH mediated testicular functions[34]. LH receptor is a glycoprotein (93-kDa) comprising of three functional domains, such as an LH-binding extracellular glycosylated domain, a seven-looped transmembrane domain and an intracellular signal transduction domain[33]. The LH receptors are Gs-protein coupled receptors that act *via* adenylyl cyclase activation. The downstream signaling involves increased intracellular cAMP production and activation of protein kinase. This is followed by phosphorylation of cholesterol esterase for cholesterol release from intracellular stores, and/or activation of cytochrome P450 11A1, for triggering steroidogenesis. Moreover, LH mediated expression of 17β-hydroxysteroid dehydrogenase leads to conversion of testicular androstenedione to testosterone[35].

LH secretion from anterior pituitary is suggested to be induced by high-frequency hypothalamic GnRH pulses. When plasma testosterone level is low, hypothalamic GnRH induces pituitary LH secretion, and when the level of testosterone is adequate, it operates negative feedback inhibition of GnRH and LH release. Testosterone may also get aromatized to estradiol and thereby inhibit LH secretion since estradiol downregulates hypothalamic GnRH pulse amplitude as well as the responsiveness of anterior pituitary to GnRH[36].

4. Prolactin and semen quality

Prolactin or luteotropin, an anterior pituitary protein hormone, self-regulates its release *via* a short feedback loop. This feedback mechanism relies upon the activation of its specific hypothalamic auto-receptors, specifically placed on the tuberoinfundibular dopaminergic neurons. Upon stimulation, these neurons release dopamine which is carried by long portal vessels to the adenohypophysis. Dopamine, through its action *via* its cognate dopamine-2 dopaminergic receptors on the lactotrophs, inhibits further prolactin release[37]. Thus, the effect of prolactin on male reproductive functions and regulation of semen quality may be independent of the influence of gonadal hormones over prolactin release. However, on certain occasions, testicular steroids have also shown to regulate prolactin release, such that high estrogen levels influence dopaminergic neurons and disrupt the auto-feedback loop of prolactin inhibition[38]. Prolactin may increase testosterone synthesis by stimulating the LH receptors on Leydig cells and also upregulate spermatogenesis, posing ameliorative effects upon semen quality[39,40].

5. Testosterone and semen quality

Along with the HPG hormones, androgenic sex steroids are imperative for the continuation of normal spermatogenic cycles. Steroidogenesis in the Leydig cells stimulated by LH produce androgens, which in turn can modulate the LH release by negative feedback loop and thus regulate their own production. The most biologically active androgens are the testosterone and its 5α-reduced derivative, dihydrotestosterone.

After its production in the Leydig cells, testosterone, just like a paracrine hormone, diffuses in the seminiferous compartments and acts on its receptor on Sertoli cells. The androgen receptor mediating the functions of testosterone is a 110 KD receptor (androgen receptor or NR3C4) in the cytoplasm and nucleus of the cells. Its prime function is to support spermatogenesis. The germ cells themselves are devoid of any functional androgen receptor, while they are found

in the Sertoli cells, and in other testicular cells such as the Leydig cells, peritubular myoid cells, arteriole smooth muscle and vascular endothelial cells. Binding of testosterone on its androgen receptor in the cytoplasm is followed by its translocation to the nucleus where it regulates gene transcription *via* acting upon specific gene promoter regions[41]. Besides this classical mode of testosterone actions, its nonclassical pathway marks its binding to androgen receptor to activate Src (proto-oncogene c-Src) kinase followed by induction of epidermal growth factor receptor, activation of mitogen-activated protein kinase cascade kinases including rapidly accelerated fibrosarcoma, mitogen-activated protein kinase kinase, and extracellular-signal-regulated kinase, leading to transcriptional regulations[20,42].

Testicular testosterone and the expressions of androgen receptor in Leydig and peritubular cells, are maintained almost at constant levels. This suggests that there exists a constitutively activated testosterone signal in these cells. However, in the Sertoli cells, the androgen receptor expressions undergo cyclical alterations as per with the stages of the seminiferous epithelial cycle and their highest expressions are found in stage three of the six stages of the seminiferous cycle[42]. Almost two-thirds of the testicular testosterone is bioavailable either in free form or weakly bound to albumen, while one-third remains tightly associated with ABP or the sex hormone-binding globulin. Bioavailable testosterone exceeds the level required for saturating the expressed androgen receptor.

Testosterone is essential to support and maintain the consistency of spermatogenesis especially in the four critical processes. Firstly, it maintains the dynamic blood-testis barrier by participating in the reassembly of its machinery on the basal side of spermatocyte after dismantling of the earlier old blood-testis barrier[43]. Secondly, testosterone signaling disruption leads to spermatogenesis halts during the stage of meiosis resulting in just a few spermatogonia to develop up to the stage of haploid spermatid and elongated spermatid production is inhibited, thereby affecting the sperm count and semen quality. The interruption in spermatogenesis may due to cellular stresses, unfolded protein responses, generation of reactive oxygen and nitrogen species and oxidative damage, DNA damage and alterations of regulatory proteins vital for RNA splicing, post-translational modifications, and other functions for meiotic divisions that are dependent upon testosterone signaling. Thirdly, impaired testosterone signaling leads to premature release of round spermatid from the Sertoli cells as the attachment between the Sertoli cell with elongated spermatid falls apart. Finally, even if the matured sperms are released normally during stage Ⅷ, in case of inadequate testosterone, they are retained followed by phagocytosis by the Sertoli cells[43]. Src, which associate with the proteins at the ectoplasmic specialization, mediates activation the sperm release. Src phosphorylates and activates the *N*-cadherin and β-catenin proteins in Sertoli cells developing ectoplasmic specialization adhesion sites with maturing elongated spermatids. As the β-catenin and *N*-cadherin are activated, they diffuse away from each other breaking the cell linkage and thereby releasing the matured sperm. Suppression of FSH and testosterone have demonstrated that Sertoli cells gene expressions are associated with adhesion of sperm with ectoplasmic specialization[43]. Reports have shown that *in vivo* maturation arrest can be overcome, in some cases, by incubation of partially disintegrated testicular tissue in media containing FSH and testosterone[44]. Thereby, the above discussion suggests that testosterone is essential in the maintenance of semen quality by playing imperative roles in spermatogenesis, sperm maturation and sperm release.

6. Other testicular hormones and semen quality

6.1. Inhibin, activin and follistatin

Sertoli cells secrete several essential regulatory glycoproteins or hormones that greatly influence the key male reproductive hormones, to modulate testicular functions and semen quality. The main Sertoli cell peptides are the inhibins, activins, and follistatins. Inhibins may exist in two known forms, inhibin A and inhibin B[45], both of which may inhibit FSH secretion from pituitary without affecting LH secretion[45]. Activins are reportedly stimulatory to HPG axis inducing FSH secretion. Activins may have three functional forms, activin A, activin B and activin AB[46] and are the disulphide-linked dimers of inhibin b-subunits. They are suggested to belong to the protein superfamily of transforming growth factor-β[46]. Another key peptide that binds to activin with strong affinity and neutralizes activin mediated FSH stimulation is follistatin[47]. All these peptides influence the precise operation of the HPG over testicular steroidogenesis and spermatogenesis to ensure semen quality both form qualitative and quantitative aspects.

6.2. Estrogen and progesterone

Estrogen highly influences testicular functions and semen quality *via* both hormonal crosstalks and *via* acting directly on testicular cells. Testicular biosynthesis of estrogen is catalyzed by aromatase and estrogen receptors on the testicular cells are also evident. It has been suggested that since the prenatal period, testicular cells synthesize estrogen that continues throughout adulthood[48]. It is reported that estrogen receptors (ER α and β) are present in the testis of all age[48]. Certain cells, like Leydig cells, have both ER α and β, whereas seminiferous epithelial cells possess just the ER β[48,49]. Estrogen may influence spermatogenesis and semen quality by its role in testosterone mediated negative feedback regulation of pituitary gonadotropins.

Estrogen also has a physiological role in sperm functions, as sperm possess both ERs and aromatase. Estrogen may have an intracrine mode of action in the sperm to play an essential role in sperm viability/apoptosis and in acrosome reactions. Furthermore, various nongenomic actions of estrogen in regulating sperms functions are surfacing with the advent in research in this arena[48].

Another vital sex hormone in determining the testicular functions and semen quality is the cholesterol derived progesterone, a natural

progestin. It is an established concept that progesterone acts by antagonizing the effects of testosterone in order to strongly inhibit hypothalamic and pituitary secretions[50]. The progesterone-operated feedback loop decreases plasma LH and testosterone levels and thus impedes the process of spermatogenesis. High levels of progesterone lay deleterious effects on male reproductive functions, may lead to atrophy of male accessory sex glands and deteriorate semen quality[51].

7. Role of hormones in spermiogenesis, spermiation and sperm maturation

A major determinant of male fecundity is the semen quality, which is ascertained by adequate numbers of functional spermatozoa in the seminal fluid. To attain utmost functionality of spermatozoa, every developmental phase of spermatozoa must be immaculately regulated. Spermiogenesis is the most critical post-meiotic spermatid developmental phase and is presumably the concluding step of spermatogenesis. This phase is characterized by the production of mature spermatozoa from the haploid spermatids, *via* an array of molecular and morphological alterations. The mature spermatozoa are to be released from the Sertoli cells into tubular lumen by the process of spermiation[33]. During this phase, excess cytoplasm and unnecessary organelles are removed from the maturing spermatozoa to render them highly motile. Proper hydration of the testes and hormonal regulations coordinate these phases of sperm maturation. LH induced steroidogenesis in Leydig cells is suggested to be increased during this phase, stimulating the Sertoli cells to trigger spermiation response. While spermiation process initiates, there is low seminal sperm count and high gonadotropins levels, while in the next few weeks the sperm production greatly increases with the reduction of gonadotropins levels[24,52].

Sperms undergo post-testicular maturation in the epididymis. The epididymal intraluminal environment is ideal for sperm maturation and sperm storage in proximal and distal ductal parts, respectively. Androgens are responsible for the regulation of epididymal metabolism, its absorptive and secretory activities, as well as the production of some of its major secretory proteins. Sperm maturation in the epididymis is influenced by both androgens and other local testicular factors[53].

8. Conclusions

The concept of hormonal regulations of semen quality is complex and still under rigorous research. The hormonal crosstalks are monitored primarily by the hormones of the HPG axis while under the influence and feedback mechanisms of an array of other hormones and factors. The principal hormones that regulate male reproductive functions are GnRH, gonadotropins (LH and FSH) that act on testicular cells Leydig cells and Sertoli cells to mediate steroidogenesis and spermatogenesis. The androgens, most importantly testosterone, sustain the functions of testis and male accessory sex organs. The review also explains the role of other reproductive hormones such as prolactin in the induction of testosterone synthesis and estrogen in the negative feedback loop of the HPG axis. The role of Sertoli cell hormones, such as inhibin, follistatin, and activin in the endocrine and paracrine regulation of testicular functions have also been concisely presented. The present review article thus discussed the updated mechanism of actions of the key regulatory male reproductive hormones in determining semen quality. But, there is a need for further research in this arena to reveal the unexplored issues.

Conflict of interest statement

The authors declare that there is no conflict of interest.

References

[1] Sengupta P, Arafa M. Hormonal regulation of spermatogenesis. In: Singh R. (ed.). *Molecular signaling in spermatogenesis and male infertility*. London: CRC Press; 2019.

[2] Alahmar A, Sengupta P, Dutta S. Thyroid hormones in male reproduction and infertility. *Asian Pac J Reprod* 2019; **8**(5): 203-210.

[3] Darbandi M, Darbandi S, Agarwal A, Sengupta P, Durairajanayagam D, Henkel R, et al. Reactive oxygen species and male reproductive hormones. *Reprod Biol Endocrinol* 2018; **16**(1): 87.

[4] Bhattacharya K, Sengupta P, Dutta S. Role of melatonin in male reproduction. *Asian Pac J Reprod* 2019; **8**(5): 211-219.

[5] Krajewska-Kulak E, Sengupta P. Thyroid function in male infertility. *Front Endocrinol* 2013; **4**: 174.

[6] Sengupta P, Dutta S. Thyroid disorders and semen quality. *Biomed Pharmacol J* 2018; **11**(1): 1-10.

[7] Sengupta P, Bhattacharya K, Dutta S. Leptin and male reproduction. *Asian Pac J Reprod* 2019; **8**(5): 220-226.

[8] Sengupta P, Dutta S, Tusimin M, Karkada I. Orexins and male reproduction. *Asian Pac J Reprod* 2019; **8**(5): 233-238.

[9] Sengupta P, Dutta S, Krajewska-Kulak E. The disappearing sperms: Analysis of reports published between 1980 and 2015. *Am J Men's Health* 2017; **11**(4): 1279-1304.

[10]Sengupta P, Borges Jr E, Dutta S, Krajewska-Kulak E. Decline in sperm count in European men during the past 50 years. *Hum Exp Toxicol* 2018; **37**(3): 247-255.

[11]Sengupta P, Nwagha U, Dutta S, Krajewska-Kulak E, Izuka E. Evidence for decreasing sperm count in African population from 1965 to 2015. *Afr Health Sci* 2017; **17**(2): 418-427.

[12]Sengupta P, Dutta S, Tusimin MB, Irez T, Krajewska-Kulak E. Sperm counts in Asian men: Reviewing the trend of past 50 years. *Asian Pac J Reprod* 2018; **7**(2): 87-92.

[13]Sengupta P. Reviewing reports of semen volume and male aging of last 33 years: From 1980 through 2013. *Asian Pac J Reprod* 2015; **4**(3): 242-246.

[14]Sengupta P. Recent trends in male reproductive health problems. *Asian J Pharm Clin Res* 2014; **7**(2): 1-5.

[15]Sengupta P. Current trends of male reproductive health disorders and the changing semen quality. *Int J Prev Med* 2014; **5**(1): 1.

[16]Holdcraft RW, Braun RE. Hormonal regulation of spermatogenesis. *Int J Androl* 2004; **27**(6): 335-342.

[17]De Ronde W, Van Der Schouw YT, Pierik FH, Pols HA, Muller M, Grobbee DE, et al. Serum levels of sex hormone-binding globulin (SHBG) are not associated with lower levels of non-SHBG-bound testosterone in male newborns and healthy adult men. *Clin Endocrinol* 2005; **62**(4): 498-503.

[18]Plant TM, Marshall GR. The functional significance of FSH in spermatogenesis and the control of its secretion in male primates. *Endocr Rev* 2001; **22**(6): 764-786.

[19]Ramaswamy S, Weinbauer GF. Endocrine control of spermatogenesis: Role of FSH and LH/testosterone. *Spermatogenesis* 2014; **4**(2): e996025.

[20]Shupe J, Cheng J, Puri P, Kostereva N, Walker WH. Regulation of Sertoli-germ cell adhesion and sperm release by FSH and nonclassical testosterone signaling. *Mol Endocrinol* 2011; **25**(2): 238-252.

[21]Simoni M, Weinbauer G, Gromoll J, Nieschlag E. Role of FSH in male gonadal function. *Ann Endocrinol* 1999; **60**(2): 102.

[22]Skinner MK, Norton JN, Mullaney BP, Rosselli M, Whaley PD, Anthony CT. Cell-cell interactions and the regulation of testis function. *Ann NY Acad Sci* 1991; **637**(1): 354-363.

[23]Plant TM, Zeleznik AJ. (eds). *Knobil and Neill's physiology of reproduction*. Cambridge: Academic Press; 2014.

[24]O'Shaughnessy PJ. Hormonal control of germ cell development and spermatogenesis. *Semin Cell Dev Biol* 2014; **29**: 55-65

[25]Asimakopoulos B. Hypothalamus-PituitaryGonadal axis: It is time for revision. *Hum Genet Embryol* 2012; **2**: 1000-1106.

[26]Corradi PF, Corradi RB, Greene LW. Physiology of the hypothalamic pituitary gonadal axis in the male. *Urol Clin* 2016; 43(2): 151-162.

[27]Dhillo WS, Chaudhri OB, Patterson M, Thompson EL, Murphy KG, Badman MK, et al. Kisspeptin-54 stimulates the hypothalamic-pituitary gonadal axis in human males. *J Clin Endocrinol Metab* 2005; **90**(12): 6609-6015.

[28]Simoni M, Gromoll Jr, Nieschlag E. The follicle-stimulating hormone receptor: Biochemistry, molecular biology, physiology, and pathophysiology. *Endocr Rev* 1997; **18**(6): 739-773.

[29]Nieschlag E, Behre HM, Nieschlag S. *Testosterone: Action, deficiency, substitution*. Cambridge: Cambridge University Press; 2012.

[30]Kraemer WJ, Rogol AD. *The endocrine system in sports and exercise*. Malden, Massachusetts: Blackwell Publishing; 2005.

[31]Ujihara M, Yamamoto K, Nomura K, Toyoshima S, Demura H, Nakamura Y, et al. Subunit-specific sulphation of oligosaccharides relating to chargeheterogeneity in porcine lutrophin isoforms. *Glycobiology* 1992; **2**(3): 225-231.

[32]Czieselsky K, Prescott M, Porteous R, Campos P, Clarkson J, Steyn FJ, et al. Pulse and surge profiles of luteinizing hormone secretion in the mouse. *Endocrinology* 2016; **157**(12): 4794-4802.

[33]Rhoades RA, Bell DR. *Medical phisiology: Principles for clinical medicine*. Philadelphia: Lippincott Williams & Wilkins; 2012.

[34]Casarini L, Santi D, Simoni M, Potì F. 'Spare'luteinizing hormone receptors: Facts and fiction. *Trends Endocrinol Metab* 2018; **29**(4): 208-217.

[35]Strauss JF, Barbieri RL. *Yen & Jaffe's reproductive endocrinology e–book: Physiology, pathophysiology, and clinical management*. Philadelphia: Elsevier Health Sciences; 2013.

[36]Pitteloud N, Dwyer AA, DeCruz S, Lee H, Boepple PA, Crowley Jr WF, et al. Inhibition of luteinizing hormone secretion by testosterone in men requires aromatization for its pituitary but not its hypothalamic effects: Evidence from the tandem study of normal and gonadotropin-releasing hormone-deficient men. *J Clin Endocrinol Meta*b 2008; **93**(3): 784-791.

[37]Anderson ST, Barclay JL, Fanning KJ, Kusters DH, Waters MJ, Curlewis JD. Mechanisms underlying the diminished sensitivity to prolactin negative feedback during lactation: Reduced STAT5 signaling and up-regulation of cytokine-inducible SH2 domain-containing protein (CIS) expression in tuberoinfundibular dopaminergic neurons. *Endocrinology* 2006; **147**(3): 1195-1202.

[38]Voogt JL, Lee Y, Yang S, Arbogast L. Regulation of prolactin secretion during pregnancy and lactation. Progress in brain research. *Prog Brain Res* 2001; **133**: 173-185.

[39]Bachelot A, Binart N. Reproductive role of prolactin. *Reproduction* 2007; **133**(2): 361-369.

[40]Gill-Sharma MK. Prolactin and male fertility: The long and short feedback regulation. *Int J Endocrinol* 2009; **2009**: 1-13.

[41]Tsai M, O'Malley BW. Molecular mechanisms of action of steroid/thyroid receptor superfamily members. *Ann Rev Biochem*1994; **63**(1): 451-486.

[42]Fix C, Jordan C, Cano P, Walker WH. Testosterone activates mitogen-activated protein kinase and the cAMP response element binding protein transcription factor in Sertoli cells. *Proc Natl Acad Sci* 2004;**101**(30): 10919-10924.

[43]Smith LB, Walker WH. The regulation of spermatogenesis by androgens. *Semin Cell Dev Biol* 2014; 3**0**: 2-13.

[44]Tesarik J, Bahceci M. Restoration of fertility by *in–vitr*o spermatogenesis. *Lancet* 1999; **353**(9152): 555-556.

[45]Luisi S, Florio P, Reis FM, Petraglia F. Inhibins in female and male reproductive physiology: Role in gametogenesis, conception, implantation and early pregnancy. *Hum Reprod Update* 2005; **11**(2): 123-135.

[46]Kingsley DM. The TGF-beta superfamily: New members, new receptors, and new genetic tests of function in different organisms. *Genes Dev* 1994; **8**(2): 133-146.

[47]De Kretser D, Hedger M, Loveland K, Phillips D. Inhibins, activins and follistatin in reproduction. *Hum Reprod Update* 2002; **8**(6): 529-541.

[48]O'donnell L, Robertson KM, Jones ME, Simpson ER. Estrogen and spermatogenesis. *Endocr Rev* 2001; **22**(3): 289-318.

[49]Carreau S. Estrogens and male reproduction. *Folia Histochem Cytobiol* 2000; **38**(2): 47-52.

[50]Andersen ML, Tufik S. Does male sexual behavior require progesterone? *Brain Res Rev* 2006; **51**(1): 136-143.

[51]Abid S, Gokral J, Maitra A, Meherji P, Kadam S, Pires E, et al. Altered expression of progesterone receptors in testis of infertile men. *Reprod Biomed Online* 2008; **17**(2): 175-184.

[52]Sofikitis N, Giotitsas N, Tsounapi P, Baltogiannis D, Giannakis D, Pardalidis N. Hormonal regulation of spermatogenesis and spermiogenesis. *J Ster Biochem Mol Biol* 2008; **109**(3-5): 323-330.

[53]Sullivan R, Mieusset R. The human epididymis: Its function in sperm maturation. *Hum Reprod Update* 2016; **22**(5): 574-587.