Central Asian Journal of Medical and Pharmaceutical Sciences Innovation **1**(1): 35-43 (2021)

REVIEW PAPER

The crucial role of estrogen/androgen hormones and their receptors in male infertility risk

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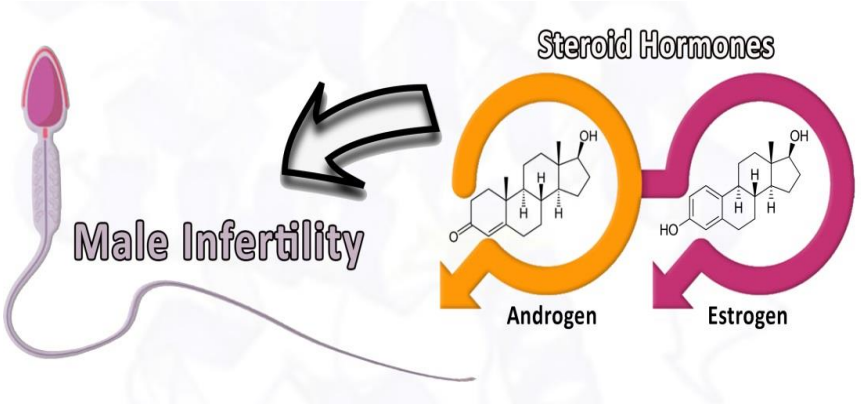
Highlights

- Male infertility as a universal problem could be affected by steroid hormones.
- Androgen and estrogen as steroid hormones control gene expression in reproductive organs.
- Variation in estrogen and progesterone receptors could alter the risk of male infertility.

Graphical Abstract



Article Info

Receive Date: 23 December 2020
Revise Date: 15 February 2021
Accept Date: 21 February 2021
Available online: 24 February 2021

Keywords:
Male infertility
Estrogen
Androgen
Hormone receptors

Abstract

Steroid hormones, including androgen and estrogen, regulate gene transcription in several tissues, especially in reproductive systems. It has been shown that the two these mentioned hormones are vital for the regulation of spermatozoa released from the epithelialum cells in of seminiferous tubes, a procedure which is characterized by endocytosis and broad regeneration of actin filaments. A subgroup of sterile men displayeds decreased levels of testosterone and elevated concentrations of estrogen., neverthelessNevertheless, it is undecided how increased levels of estrogen could promotes worsening ofdecrease male fertility potential. Though the molecular origin for estrogen-induced worseningdecreased male fertility levels of male fertility remains vague, estrogen receptors (ERs) have an essential role in facilitating this procedure. In addition, the androgen hormone plays an important role in the male reproductive system. They action act through their receptors, the androgen receptor (AR). It has been reported that AR mutations could result in idiopathic male infertility. In this review, the role of estrogen and androgen hormones and their receptors in male infertility, have beenwere discussed.

10.22034/CAJMPSI.2021.01.6 **E-ISSN: 2783-0993**

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Introduction

According to World Health Organization definition, infertility is defined as the inability of couples to conceive despite repeated sexual intercourse without prevention for a year or more (1). Infertility affects 10-15% of couples; about 50% of the causes of infertility are due to male factors such as insufficient sperm count, oligospermia, low sperm motility, asthenospermia, or abnormal sperm morphology, teratozoospermia (2, 3). In 70% of cases, there are specific causes for male infertility, including anatomical, immunological, physical or obstructive disorders, hormonal and environmental factors, but in the remaining 30%, there is no specific cause for infertility called idiopathic factors (4, 5). Infertility is divided into two categories: primary infertility and secondary infertility. Approximately 71-67% of patients have primary infertility and 33-39% has secondary infertility (6).

Spermatogenesis in the spermatogenic epithelium is regulated by the endocrine, autocrine, or paracrine glands (7, 8). Some hormones, such as gonadotropins and androgens, play a crucial role in the process of spermatogenesis. Spermatogenesis is a highly regulated process in which the spermatogenesis epithelium is controlled by other hormones (9), and estrogens are now recognized as potential regulators in various species, including humans (10). Animal models have been used to determine the importance of estrogens in male reproduction. Male rats deficient in aromatase (an enzyme that converts estrogen to testosterone) were able to grow naturallyfrom the age of 5 months onwards; they showed a defect in spermatogenesis all infertile by one year of age (11). The purpose of this review is to narrate the role of estrogen and androgen hormones and their receptors in male infertility.

Causes and types of male infertility

A suitable and essential initial step in the evaluation of infertile couples is semen analysis. When the quality of semen is normal, attention is paid to the female sexual partner. Known factors in male infertility include anatomical disorders such as varicocele, vesicular damage due to torsion and obstruction of the testicular sperm ducts, immunological, hormonal, genetic problems, ejaculatory defects, and environmental pressures (5, 12). On the other hand, as mentioned, there are unknown causes called idiopathic infertility that can affect men's fertility in some way (5).

In general, infertile men can be clinically divided into three categories: 1) men with incurable infertility, which accounts for 12% of infertile men. Approximately one-third of the causes of these diseases have been identified, which include Klinefelter syndrome, undescended testes, testicular contraction, testicular trauma, and exposure to toxic agents and radiotherapy that lead to testicular degeneration. 2) treatable patients and makeup 13% of infertile men. Potentially treatable conditions include genital obstruction, sperm autoimmunity, gonadotropin deficiency, sexually transmitted abnormalities, and reversible damage to semen quality. Incurable subfertile patients make up 75% of infertile men. These men are also oligospermia, meaning that their sperm count is less than 20 million sperm per milliliter or that they are asthenospermia with a large percentage of their sperm being immobile (13, 14). The main causes involved in male infertility are summarized in Figure 1.

Hormones and male infertility

Spermatogenesis is primarily controlled by gonadotropins (FSH and LH). LH indirectly affects spermatogenesis by stimulating testosterone production (15, 16). Sertoli cells have specific high-binding FSH receptors that carry intracellular androgens, act as an androgen reservoir within the spermatic tube, and transport testosterone from the testes into the epididymal tube (17). The physical proximity of Leydig cells to spermatozoa ducts maintains very high levels of androgen concentrations in the growing sperm medium (18). Hormonal needs to initiate and maintain spermatogenesis appear to be different. Maintenance immediately after the pituitary (removal of the pituitary gland) requires only testosterone (16, 19). Hormonal needs to initiate and maintain spermatogenesis appear to be different. Maintenance immediately after the pituitary (removal of the pituitary gland) requires only testosterone (16, 20). However, when the germinal epithelium is completely receded, both FSH and testosterone treatments are required (21). Qualitatively, testosterone promotes and

maintains spermatogenesis in humans, but quantitative restoration will not achieve (22). In humans, FSH is essential for maintaining normal sperm production (16, 24); and especially for initiating spermatogenesis in adult men and resuming spermatogenesis in men whose retinal epithelium has receded pituitary resection, is very important (18, 25). Quality sperm production is achieved by replacing FSH or LH alone. However, FSH and LH are essential for maintaining slightly normal spermatogenesis in humans (16, 18). The essential hormones involved in the male reproductive system are summarized in Figure 1.

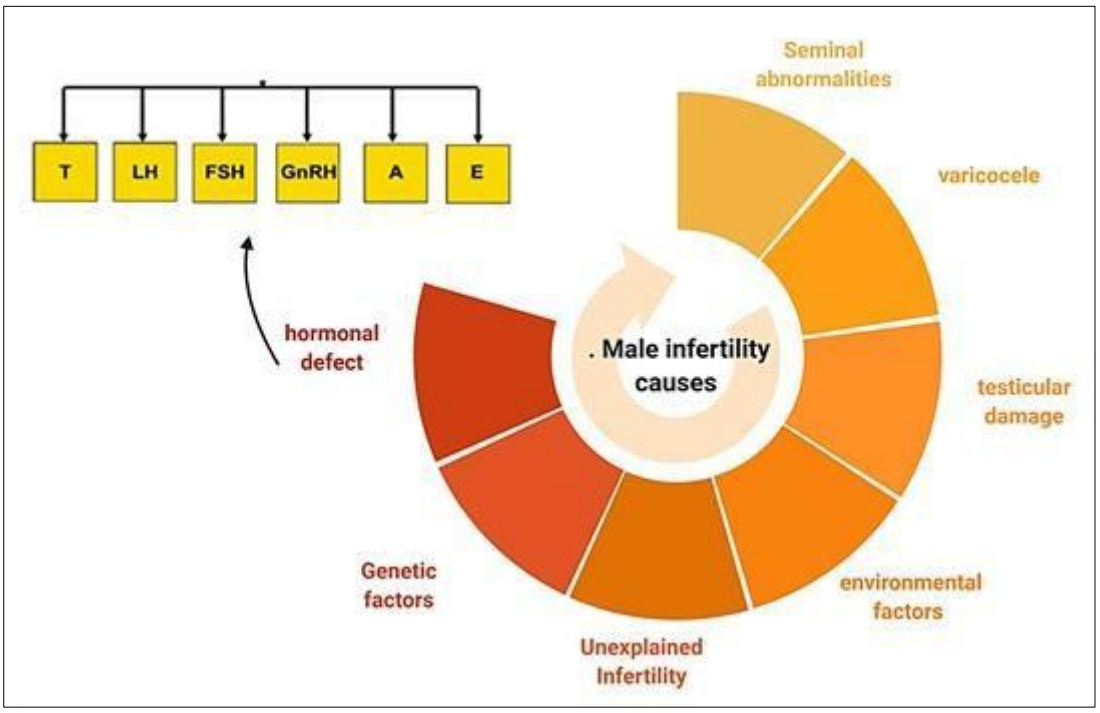

Figure 1. Male infertility causes and main hormones involved in male infertility. As depicted in this figure, hormonal defects, genetic factors, unexplained infertility, varicocele, seminal abnormalities, varicocele, testicular damage, and environmental factors are the main factors involved in male infertility. The main hormones in the male reproductive system are as follows: testosterone (T), luteinizing hormone (LH), follicle-stimulating hormone (FSH), gonadotropin-releasing hormone (GnRH), androgen (A), and estrogen (E).

Role of estrogen in the male reproductive system

In the past, estrogen was thought to be a female hormone, but now, it is found in both sexes and plays an essential role in the male reproductive system (26). Primary studies proposed that this hormone was harmful to the male reproductive system since exogenous therapeutic approaches stimulated the developmental process abnormalities. Though, presentations of estrogen synthesis in the testis proposed that this specific female hormone may play a central rolenormal male reproduction (27). Estrogen receptors and aromatase, and aromatase and aromatase, can be found in almost all stages of spermatogenesis in the testes (28). Estrogen is produced in Leydig cells, Sertoli cells, and even germ cells. In Leydig cells and helping spermatogonia grow, it modulates steroid hormones in the adult testis. In Sertoli cells, it modulates the cell population, establishes strong intercellular connections, and ultimately contributes to Acrosomal capacity and reactivity in germ cells. In addition to the areas involved in spermatogenesis, estrogen receptors can also be found in the preoptic region and the anterior part of the hypothalamus, which regulate libido by estrogen action on them or for erectile function in cavernous bodies in the penis (29).

The sperm release process (Spermiation) is essential for the male reproductive system's accuracy. Morphologically, it is defined by eliminati ng unusual adherens connections (ectoplasmic specializations), and creating brief endocytic plans (tubulobulbar complexes) needing remodeling of cytoskeleton and employment of protein molecules looked-for for endocytosis. Former administration of estrogen in rats (adult male) was observed to origin failure of spermiation because of interruption of tubulobulbar complexes. This process was

accompanied by a decrease in testosterone concentration in intratesticular space and rise in estrogen of intratesticular with dysregulation of gene expression involved in remodeling of the cytoskeleton (Arpc1b, Capg, and Evl) and endocytosis (Picalm, Stx5a, and Eea1) (30).

Types of estrogen receptors and their role in male infertility

or the steroid hormones to function physiologically in the reproductive system, the presence of a receptor for these molecules in the target cells is essential, for which they must bind to their specific receptor. These receptors are present as gene-regulating molecules in target cells and specifically bind to steroid hormones, and after binding to the complex by acting on gene-regulating sequences, they cause the expression of many genes (31, 32). Two primary receptors for estrogen are currently known: ER1 and ER2 (33). The first type, or alpha, is present in all estrogen-responsive tissues, but the second type, or beta receptor, is found in more limited tissues. The gene encoding ER1 is located on chromosome 6 (6q 24-26), and the gene encoding ER2 is located on chromosome 14 (14q 23.2) and has 18 exons (34, 35). The role of genetic variants of polymorphisms in these genes in male infertility is summarized in Table 1.

Table 1. Role of estrogen receptor varieties in male infertility.

Author, Year	Studied variations	Outcomes
Kukuvitis, 2002 (34)	PvuII, XbaI	They indicate that both ER-alpha plays the central role in male fertility.
Aschim, 2005 (35)	RsaI, AluI	They showed that genetic variations in ER-beta could have modulating influences on the spermatogenesis of humans.
Galan, 2005 (36)	PvuII, AluI	Their results showed a relevant role for the estrogenic pathway, particularly the ESR-alpha gene, in the male reproductive system's function.
Khattri, 2009 (37)	RsaI, AluI	Their findings propose that RsaI polymorphism in ER-beta is not correlated with male infertility in the Indian population.
Su, 2010 (38)	RsaI, AluI	They reported that variations of estrogen-related genes confer susceptibility to male infertility in the Taiwanese Han population.
Lazaros, 2010 (39)	PvuII, XbaI, RsaI, AluI	They reported that the polymorphisms in the ER-alpha gene might be associated with sperm defects in humans, especially in sperm motility and concentration.
Safarinejad, 2010 (40)	PvuII, XbaI, RsaI, AluI	They reported that a potential role of ESR-alpha and ER-beta polymorphisms on male infertility. Further studies are required to replicate their findings.
Agarwal, 2003 (41)	RsaI, AluI	They proposed that RsaI and AluI gene variation in ER are for human spermatogenesis and may play a main role in spermatogenesis.
Bianco, 2011 (42)	PvuII, XbaI, RsaI, AluI	They reported that combined genotypes of ER-beta and ER-alpha variations did not recognize a haplotype correlated with idiopathic male infertility. Therefore, in the Brazilian population, genetic polymorphisms in both ER-alpha (PvuII and XbaI) and ER-beta (AluI and RsaI) were not associated with idiopathic male infertility.
Ogata, 2012 (43)	RsaI	They reported that the RsaI polymorphism could be related to male infertility in some genetic models.
Zalata, 2013 (44)	PvuII, XbaI	They reported that estrogen is concerned in sperm maturation, ER-alpha gene variation may have a role in male infertility's pathophysiology.
Meng, 2013 (45)	PvuII, XbaI, RsaI, AluI	They revealed a potential role of ER-alpha in male infertility. So, Further studies are required to duplicate their findings and and clarify the biological mechanisms of the inflection of ER-alpha in human spermatogenesis.

The role of androgens in the male reproductive system

Androgens, including testosterone, function at receptor places in the substantial brain parts (46, 47). The principal act is gene expression regulation. After entering androgens into the cell, attach to the cytoplasmic AR, and stimulate a conformational alteration that results in the separation of heat shock proteins and

transportation of the receptor molecule from the cytoplasm the nucleus and lastly, receptor dimerization (48). The dimer of AR attaches to a special region of DNA, hormone response element, leading to down- or upregulation of gene expression (46). The androgen receptor is mostly transcripted as a single AR and contains a regulatory domain at the N-terminal, the domain of DNA-binding, a region of the small hinge, and a domain of ligand-binding (49). The domain of regulatory in the N-terminal facilitates most of the transcriptional activity of AR (50, 51). Androgens play an important role in the development of male reproductive organs, including the epididymis, vas deferens, seminal vesicles, prostate, and penis (52). Development of male male reproductive actions are dependent on the regular function of androgens, and a disturbed ratio of the active androgens may result in changing grades of functional and structural abnormalities in the reproductive system (53). It is essential for puberty, fertility and sexual function in men, as well as the normal production of sperm, and their reduction in the blood leads to defective spermatogenesis. Physiological androgens, namely testosterone and dihydrotestosterone, cause the growth of the internal and external genitalia of men (29). At puberty, an increase in androgens leads to the onset of spermatogenesis and the growth of associated sex organs, including the prostate gland. In Sertoli cells, testosterone selectively binds to the androgen receptor and activation of the receptor initiates and maintains the process of spermatogenesis and prevents germ cell apoptosis (54). The androgen receptor is found in all-male reproductive organs and can be stimulated by testosterone or its more potent metabolite, dihydrotestosterone. Severe androgen receptor defects may lead to abnormal sexual growth in men, and subtler changes can be a major cause of male infertility (55, 56).

Androgen receptor and male infertility

Androgen receptor is a ligand-dependent transcription factor that binds to androgens and plays an essential role in spermatogenesis, differentiation of secondary sexual traits, and maturity (56). The human AR gene is located on the X chromosome and contains eight exons. The androgen receptor has three major components: the N-terminal domain encoded by exon 1, the DNA binding domain associated with exons 2 and 3, and the ligand or androgen binding domain is encoded by exons 4 to 8. N-terminal mutations make up about one-third of the mutations in the AR gene (57). Defects in the structure and function of the androgen receptor lead to a wide range of diseases. Besides, mutations in the AR gene cause a variety of syndromes, including androgen sensitivity syndrome (AIS), spinal muscular atrophy (SBMA), and prostate cancer (57, 58). Genetic variants in the androgen receptor can alter the risk of infertility. A meta-analysis showed that increasing the CAG androgen receptor length could increase the risk of male infertility (59). Analysis of sequencing of the first exon region of AR showed c.1783C>T genetic mutation in the two azoospermic men (60). Recently, a network of genes related to male sexual dysfunction and the relationship between these genes has been proposed (61).

Conclusion

This review narrates two enzymes involving in the male reproductive system, estrogen and androgen. The optimal influences and function of estrogen depend on the cells in which it is made. The mixture of estrogen with some exogenous hormones such as anti-androgens or GnRH analogs might similarly have an inhibitory impact on the spermatogenesis process. Estrogen level could lastly raise the synthesis of collagen, and glycoproteins synthesis in Leydig and Sertoli cells results in reduced sperm concentration. Therefore, any changes in its receptor could result in male infertility. On the other hand, the androgen hormone has the central role in male fertility. Also, they are required for the growth of organs of the male reproductive system, including vas deferens, epididymis, prostate, seminal vesicle, and the penis. This hormone also carries out its impacts via androgen receptors that are vital for the spermatogenesis procedure.

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How to cite this paper:
A. Rivera Diaz P, Patricia Ortiz C, Delgado DR. The crucial role of estrogen/androgen hormones and their receptors in male infertility risk. Cent Asian J Med Pharm Sci Innov 2021; 1(1): 35-43.