Thyroid Hormones in Male Reproduction and Fertility

Rajender Singh¹, Alaa J Hamada² and Ashok Agarwal* ²

¹Central Drug Research Institute, Lucknow, India
²Center for Reproductive Medicine, Cleveland Clinic, Ohio, USA

Abstract: Thyroid hormones, previously thought not to affect spermatogenesis and male fertility, are now being recognized as having important role in spermatogenesis. The identification of thyroid hormone receptors on Sertoli cells, the nurturing cells for sperm in the testis, has embarked further research to investigate the role of thyroid hormones in male reproduction. Since spermatogenesis occurs in close contact with the Sertoli cells, the thyroid hormones must exert significant regulatory role in sperm production. Therefore, disturbances in the thyroid function could affect spermatogenesis and male fertility. Studies on human subjects and animals models are now revealing further insights into the effect of thyroid hormones on male fertility and infertility. The present review provides an update on the role of thyroid hormones in spermatogenesis and male fertility.

Keywords: Thyroid hormone, spermatogenesis, male fertility, male infertility.

INTRODUCTION

Endocrine system is the second key regulator of organ system functions after nervous system in human body. Hormones are actual messengers in endocrine signaling. Thyroid gland holds a critical place in controlling brain and somatic development in infants and metabolic activities in adults. Upon stimulation by thyroid stimulating hormone (TSH), thyroid gland secretes thyroid hormones: triiodothyronine (T3) and thyroxin (T4). Although thyroid hormones have a central role in controlling basal metabolic rate, growth, as well as the development and differentiation of many cells in the body [1], their effect on spermatogenesis is not fully understood. Until very recent thyroid was thought not to affect spermatogenesis; however, research is now actively being pursued to understand the primary effects of thyroid hormones on spermatogenesis.

Spermatogenesis is generally divided into three distinct stages: (i) mitosis of spermatogonia (ii) meiosis to make haploid germ cells (iii) maturation of spermatids to spermatozoa [2]. Disturbance at any step could affect the process of spermatogenesis and the spermatozoa may become defective [2]. Spermatogonia give rise to mature spermatozoa under hormonal control of the gonadotropins such as luteinizing hormone (LH) and follicle stimulating hormone (FSH). Recent identification of thyroid hormone receptors (TRs) directly on the testes and finding that thyroid hormone affects the growth and development of the male testes has accelerated research in this field [1, 3].

Specifically, TRs are located on the Sertoli cells in the seminiferous tubules, and it is believed that T3 binds directly to these receptors [3]. Sertoli cells are first somatic cells to differentiate in the testis and they support and nurture sperm during spermatogenesis [4]. TR on Sertoli cells can mediate possible role, if any, of thyroid hormones in sperm production [2]. More specifically, a particular interest has grown concerning the effects of thyroid disease such as hyperthyroidism and hypothyroidism on spermatogenesis and overall male fertility. This article aims at highlighting the current state of research relating thyroid to male reproduction and fertility.

THYROID HORMONE’S INTERACTION WITH GONADOTROPINS AND SEX STEROIDS

Thyroid is a part of the hypothalamus-pituitary-thyroid axis (HPT axis). Thyroid-stimulating hormone (TSH) is secreted by the anterior pituitary. Thyrotropin-releasing hormone (TRH) from the hypothalamus binds to its receptors at the pituitary to control release of TSH. TSH binds to the TSH receptor on thyroid epithelial cells to signal thyroid gland secrete T3 and T4. This is named as hypothalamus-pituitary-thyroid (HPT) axis.

LH and FSH are produced by the anterior pituitary. The production of these two hormones is stimulated by gonadotropin releasing hormone (GnRH) made by the hypothalamus. It is largely known how LH, FSH and testosterone regulate spermatogenesis. Testosterone is required for successful completion of the spermatogenesis process. Without it, conversion of round spermatids to spermatozoa during spermiogenesis is impaired [5]. It should be noted that follicle-stimulating hormone (FSH) plays important role in this conversion, as well as differentiation of spermatogonia into spermatocytes [6]. Since the germ cells have no receptors for testosterone and FSH, these hormones must act through the Sertoli cells, which are responsible for nurturing the germ cells. Testosterone is produced by the Leydig cells after receiving the signal from luteinizing hormone (LH) for its synthesis. This pathway is collectively known as the hypothalamus-pituitary-gonadal axis (HPG axis).
Variations in the HPT axis seem to affect HPG axis; however, the exact relationship between HPT and HPG axes remains somewhat unclear. In cases of thyroid dysfunction, no discernable changes were detected in basal serum gonadotropins (GN) in some studies while others discovered increment of GNs levels in thyrotoxicosis and its decline in hypothyroidism [7]. This decline is related to prolonged hypothyroidism induced pituitary hypogonadism [8, 9]. Hypersensitivity of GnRH induced secretion of gonado-tropins had been observed in thyrotropic male patients [7] while hyposensitivity of GnRH induced secretion of gonadotropines had been described in hypothyroidism [10]. Prolactin PRL hormone secreted from anterior pituitary, has detrimental effect on male fertility when it exceeds its physiological level. Hyperprolactinemia is well described in hypothyroidism [11] due to TRH stimulation. Incostistent results regarding prolactin levels were seen in thyrotropic male patients from different studies. Five studies found normal PRL [12-16] while others found elevated PRL [17, 18] and it was attributed to hyperestrogenic state in thyrotoxicosis which will be described later. It is well known that persistent hyperprolactinemia renders men presented with signs of hypogonadism, loss of libido, erectile dysfunction and rarely gynecomastia and galactorrhea. However, a direct inhibitory effect of Prolactin on the testis has not yet been demonstrated. All of the above hormonal changes in hypothyroidism are reversible when euthyroidism is achieved [8, 9].

Changes in sex steroid levels in men with thyroid disturbances have been the subject of many studies. In normal males, 2% of testosterone is free (unbound), and 44% is bound to a high-affinity sex hormone-binding globulin (SHBG), and the remainder is bound to albumin and other proteins. Free- and albumin-bound portions make up the measure known as bioavailable testosterone [19-21]. In hyperthyroidism, total testosterone and SHBG levels are increased [11, 22-28]. Free T is transiently reduced or normal [29] and mean basal bio-available T is decreased [30]. Androstenedione [24] and 17-hydroxyprogesterone [31] levels are also elevated. The etiology behind elevated total testosterone is still controversial. Elevated SHBG can explain this rise. However, direct stimulatory effect of thyroid hormone on Leydig cells has been proposed. Manna et al. conducted a study in which T3 appeared to increase LH receptors and steroidogenesis of Leydig cells [32]. T3 has also been seen to directly stimulate basal testosterone generation which could be the result of its action on Leydig cells [33]. By contrast other studies identified blunt testosterone response of testicular tissues to HCG stimulation [10, 27, 31, 34]. Some thyrotoxic men have elevated circulating estrogen level caused by enhanced production rate of the estrogen and increment of peripheral conversion of androgen to estrogen [35]. From the above mentioned information it can be concluded that despite increased total testosterone level, thyrotoxic men have relative androgen deficiency due to 1) reduced free and bioavailable testosterone, 2) relative estrogen rise and 3) if it is confirmed hyperprolactinemia. These changes can cause gynecomastia (24%) [16], decreased libido (70%) [31], erectile dysfunction (56%) [35], spider angiomas and spermatogenic dysfunction [16, 36] such as a reduced sperm count and/or motility.

In men with hypothyroidism total androgen level is reduced due to multiple factors such as decreased SHBG, hypothyroidism induced pituitary hypogonadism and hyperprolactinemia [8,9]. Men with post-pubertal hypothyroidism may experience a decreased libido, erectile dysfunction, and delayed ejaculation [37]. However, only few studies concerning the effects of post-pubertal hypothyroidism on human spermatogenesis are available [38]. Older studies failed to detect gross seminal fluid abnormalities in hypothyroid patients while few recent studies conclude detrimental effect of hypothyroidism on male fertility as will be described later.

**THYROID HORMONE RECEPTORS ON TESTICULAR CELLS**

The binding interaction between thyroid hormone and TR mediate the effects of T3. TR is encoded by two different genes C-erbAalpha and C-erbAbeta located in humans on chromosome 17 and 3, respectively. Since alternative splicing can result in more variants, many isoforms of TRs are present, including TRα1, TRα2, TRβ1, and TRβ2 [39]. The multiple subclasses of TRs may imply that they have different functions. They have different mechanisms of dimerization and DNA binding due to the different properties of each. In experiments on animal models, TR-beta expression has been detected in the testes [40]. There is controversy over the cell types in which TRs are expressed in the testis. The results of some studies show that TRs are localized to Sertoli cells [40, 41]. There are also data supporting the theory that TRα is exclusively expressed in the human testis [41].

Reports based on animal studies indicate that TRs in Sertoli cells undergo dynamic alterations throughout life. TRs are present in the postnatal and prepubertal periods at its highest concentrations in Sertoli cells. Thyroid hormone acts directly on Sertoli cells to inhibit proliferation while stimulating differentiation and maturation. After birth, the immature Sertoli cells continue to proliferate until the beginning of puberty when they stop dividing and start differentiating into their non-proliferative adult form. It is well established that there is close correlation between number of mature Sertoli cells present at puberty with both adult testicular size and sperm output [42]. It appears that triiodothyronine is the major hormone involved in determination of adult Sertoli cell population in collaboration with other factors. There is evidence backing the argument that other cell types in the testis have TRs [43,44]. Thyroid hormone plays important role in differentiation and maturation of Leydig cells. Although finding of TRs on Leydig cells is still under debate, it is hypothesized that Sertoli cell paracrine factors may explain the effect of T3 on Leydig cells [45-47].

**GESTATIONAL THYROID ACTIVITY, TESTICULAR DEVELOPMENT AND FERTILITY**

Gestational disturbance in thyroid function can affect not only testicular development of the upcoming generation but also its fertility potential in adulthood. Anbalagan et al., 2010, in a study on rats explored the mechanism underlying gestational onset hypothyroidism induced male infertility.
Pregnant rats were exposed to methimazole from embryonic days 9 to 14, 18, and 21, covering specific fetal periods of differentiation and development of male reproductive tract organs. Fertility of male rats was assessed by testing sperm count, forward motility, and in vivo fertilizing ability. Secretory activity of the epididymis was evaluated by quantifying sialic acid, carnitine, and glycercylphosphorylcholine. It was observed that gestational exposure to methimazole decreased sperm forward motility, in vivo fertilizing ability, bioavailability of androgens, AR status, and secretory activity of the epididymis in adult rats [48]. The authors concluded that transient gestational-onset hypothyroidism affects male fertility by impairing post-testicular sperm maturation process in the epididymis, owing to subnormal androgen(s) bioavailability, AR expression, and AR functional activity.

NEONATAL THYROID ACTIVITY, MALE REPRODUCTION AND FERTILITY

Thyroid hormone acts directly on Sertoli cells to inhibit proliferation while stimulating differentiation and maturation. After birth, the immature Sertoli cells continue to proliferate until the beginning of puberty when they stop dividing and start differentiating into their non-proliferative adult form. This makes the period up to puberty very critical for testis development. As it is true for adverse effects of disturbed thyroid function during gestational period, neonatal disturbance in thyroid function could also affect fertility in men. Auharek and de Franca (2010) investigated the effect of transient induction of neonatal hypo- and hyperthyroidism on post-natal testis development, Sertoli cell proliferation and different spermatogonial cell types [49]. Propylthiouracil (PTU) and tri-iodothyronine (T3) were given to mice to achieve neonatal hypo- and hyper-thyroidism, respectively. Although Sertoli cell maturation was accelerated or delayed, respectively, in T3- and PTU-treated mice, the pace of the germ cell maturation was only slightly altered before puberty and the period of Sertoli cell proliferation was apparently not affected by the treatments. However, compared with controls, the total number of Sertoli cells per testis from 10 days of age to adulthood was significantly increased and decreased in PTU- and T3-treated mice, respectively. In comparison to all other spermatogonia, type A2, was the largest cell in all ages and groups investigated. PTU-treated mice had a significantly increased total number of undifferentiated spermatogonia as well as volume and percentage of vessels/capillaries, probably due to the higher number of Sertoli cells, particularly at 10 days of age [49]. This shows significant impact of altered thyroid physiology on testis.

It is now widely accepted that congenital and early childhood hypothyroidism is an important reproductive health problem in men. Further research has now been undertaken to explore the exact mechanism of pre-pubertal thyroid hormone deficiency induced alteration of reproductive function in adults. Aruldhass et al., (2010) undertook a study on understanding the exact mechanism of hypothyroidism-induced changes in the prostate gland, an androgen-dependent organ, which contributes a significant portion of the seminal plasma [50]. Hypothyroidism was induced in pregnant and lactating rats by feeding 0.05% methimazole (MMI) through drinking water during fetal and neonatal milestones of testicular and prostatic development. Pregnant dams had MMI exposure from 9th day post-couitum (dpc) to 14 dpc (group II) or 21 dpc (group III). Lactating mothers had MMI exposure from day 1 post-partum (dpp) to 14 dpp (group IV) or up to 29 dpp (group V). Expression of androgen receptor (AR) in the dorsolateral and ventral prostate lobes (DLP and VP) of the pups was assessed by RT-PCR, western blot and radio receptor assay. The authors observed that AR mRNA expression consistently decreased in the DLP of all groups, whereas it increased in VP of group III and V rats. AR protein consistently decreased in both DLP and VP of all experimental rats. AR nuclear ligand-binding activity diminished in groups II and IV, whereas it increased in groups III and V. The authors concluded that an optimum thyroid activity during pre- and neonatal period determines AR status in the prostate glands at adulthood [50]. Compromise in the androgen receptor expression as a result of hypothyroidism could affect the physiology of prostate and hence male fertility.

THYROID FUNCTION AND OXIDATIVE STRESS

Oxidative stress is a consequence of an imbalance between production of reactive oxygen species (ROS) and the body’s antioxidant defense capacity [51, 52]. Oxidative stress has been identified as one of the very important factors that affect fertility status, and has been extensively studied in recent years. Sperm, like any other aerobic cells, are constantly facing the “oxygen-paradox”. Oxygen is essential to sustain life as physiological levels of ROS are necessary to maintain normal cell function and all that is true for sperm as well. However, excessive production of ROS (oxidative stress) is well known to be detrimental to sperm by adversely affecting the quality of sperm DNA. The main function of thyroid hormone within physiological ranges is to regulate and enhance metabolic reaction and oxygen consumption of different cells of the body. ROS which are the by-products of tissue metabolism are normally treated by physiological antioxidants. The role of thyroid in regulating oxidative stress in male reproductive organs is recently being explored. Previous reports showed that both hyper- and hypothyroidism are associated with increased oxidative stress in semen [53]. In testis there are two highly energy consuming physiological processes; spermatogenesis and steroidogenesis. In addition, testis is rich in polyunsaturated fatty acids (PUFA) which are liable to peroxidation by pro-oxidant agents. Testis on the other hand has enzymatic and non-enzymatic antioxidant defense systems with limited potentials [54]. In cases of thyrotoxicosis, part of sustained injury to various body tissues is attributed to oxidative damage [55]. Choudhury et al. conducted a study on rat testis after inducing hyperthyroidism and discovered that although there is positive regulatory effect on antioxidant enzyme catalase, there is negative effect on level of testicular glutathione peroxidase. In addition Choudhury et al. found decreased concentration of reduced glutathione GSH, ‘the important antioxidant molecule in Sertoli and spermatogenic cells’ [56]. Malgorzata et al. found that excess T3 and T4 induce DNA damage in human sperm which is then inhibited by addition of Catalase and two other flavonoid antioxidants such as quercetin and kaempferol [55]. The postulated
mechanisms of excess thyroxin provoking oxidative stress on sperm include hyperthyroidism associated hyperestrogenemia, enhanced nitric oxide synthase gene expression with nitric oxide overproduction, following increase of cytokines stimulating ROS generation, increased turnover of mitochondrial proteins, mitoptosis and increased rate of thyroid hormone induced lipolysis [57]. Hyperthyroidism has been associated with reduced circulating levels of alphatocopherol [58, 59] and coenzyme Q10 [59, 60]. Hypothyroidism on the other hand is also associated with excess seminal ROS stress.

Chattopadhyay et al., 2010 conducted a study to evaluate effects of altered thyroid hormone levels on regulation of mitochondrial glutathione redox status and its dependent antioxidant defense system in adult rat testis and their correlation with testicular function [61]. Adult male Wistar rats were rendered hypothyroid by administration of 6-n-propyl-2-thiouracil in drinking water for six weeks. At the end of treatment period, a subset of hypothyroid rats was treated with T3 (20 μg/100 g body weight/day for 3 days). Increased pro-oxidant level and reduced antioxidant capacity rendered the hypothyroid mitochondria susceptible to oxidative injury. The extent of damage was more evident in the membrane fraction. This was reflected in higher degree of oxidative damage inflicted upon membrane lipids and proteins. While membrane proteins were more susceptible to carbonylation, thiol residue damage was evident in matrix fraction. Reduced levels of glutathione and ascorbate further weakened the antioxidant defenses and impaired testicular function. Hypothyroid condition disturbed intra-mitochon- drial thiol redox status leading to testicular dysfunction. Hypothyroidism-induced oxidative stress condition could not be reversed with T3 treatment [61].

The authors concluded that mitochondrial thiol redox status in testis of hypothyroid rat is fundamental during spermatogenetic processes such as apoptosis, sperm function and sperm quality. Choudhury et al., found in their experiments on rat testis that hypothyroidism leads to a decrease in the activity of superoxide dismutase (SOD), a universal antioxidant enzyme, and the ratio of SOD/CAT + GPX decreased significantly [56]. In addition the authors noticed decrease in the ratio of reduced Glutathione to oxidized state of Glutathione (GSH/GSSG) following hypothyroid state, suggesting induction of oxidative stress in the testis [56].

A compromised antioxidant defense system during hypothyroidism might be the key factor in contributing towards oxidative stress in testicular mitochondria, reflected in higher levels of oxidatively damaged membrane lipids and proteins ultimately leading to tissue injury and dysfunction which cannot be alleviated by extraneous thyroid hormone treatment. This remains yet to be identified how far disturbed thyroid function in human subjects contributes to oxidative stress.

**THYROID DISEASE AND MALE FERTILITY**

The above referenced literature suggests significant impact of altered thyroid physiology on male reproduction and fertility. The two most common types of thyroid diseases are hypothyroidism and hyperthyroidism. The symptoms of hyperthyroidism often included fatigue, weight loss, irritability, muscle weakness and palpitations [62] while hypothyroidism may result in fatigue, palmar yellowing, dry skin, coarse hair, slurred speech, slowed mental activity, weight gain and an increased sensitivity to the cold [63].

Hypothyroidism may result in a decrease in the sex hormone binding globulin (SHBG) levels and a decrease in total serum testosterone (T) levels, as well as a decrease in the gonadotropins levels, specifically the luteinizing hormone (LH) and the follicle stimulating hormone (FSH) [36]. In cases of prolonged pre-pubertal hypothyroidism due to drop in LH and FSH levels, the Leydig and Sertoli cells, respectively are less stimulated to differentiate into mature cells, negatively affecting spermatogenesis. This increases the number of cells in the testes but decreases the number of mature cells. Thus, in patients with hypothyroidism, increased testicular size is observed along with a significant drop in mature germ cells within the seminiferous tubules [38, 64]. Fortunately, hypothyroidism is very rare in males with an occurrence rate of only 0.1% in the general population [36].

Studies assessing the role of hypo- and hyper-thyroidism have been conducted both on animal models and human subjects. Among the studies on human subjects, Corrales Hernandez et al., (1990) analyzed blood and semen samples of patients with primary hypothyroidism [65]. The study concluded that hypothyroidism adversely affected semen quality by compromising semen volume and progressive sperm motility. Krassas et al., (2008) conducted another study on human subjects with hypothyroidism [66]. The authors reported abnormal sperm morphology and decreased motility in the patients. At least two studies were conducted on animal models. As discussed above, Anbalagan et al., (2010) reported adverse effects of gestational hypothyroidism on fertility of the upcoming generation in Wistar rats [48]. In another similar study, Maran and Aruldhas, (2002) reported adverse effects of hypothyroidism on male reproductive organs and fertility [67]. It is therefore evident that hypothyroidism adversely affects male fertility.

Similarly, all the studies on hyperthyroidism also reported adverse effects on male reproductive organs and fertility. Clyde et al., by studying individual cases reported adverse effects of hyperthyroidism on semen quality [68]. Clyde looked at three individual case studies of men with hyperthyroidism and infertility. Hormone levels were measured and recorded, and the overall results indicated that all three patients had low sperm counts as well as decreased sperm motility. However, such abnormalities were corrected when the patients were treated for thyroid disease. Therefore, Clyde concluded that male infertility is more common than previously thought in males with hyperthyroidism, possibly in correlation with elevated levels of testosterone, LH and FSH. Hudson and Edwards (1992) after conducting study on human subjects stated adverse effects of hyperthyroidism on spermatogenesis by altering sex steroid levels [12]. Similarly, Krassas and Perros (2002) claimed adverse effects of hyperthyroidism on seminal parameters of human subjects [36]. Most of the studies concerning hyperthyroidism were conducted on human subjects with only one conducted on rats. Rijntjes et al., in their study on rats concluded that
hyperthyroidism delays Leydig cell development and adversely affects spermatogenesis [69].

CONCLUSION AND FUTURE DIRECTIONS

In the last two decades, increasing amounts of research efforts have been dedicated to looking into thyroid’s effect on male infertility. While it is clear that there is some definite connection between thyroid disease and abnormal spermatogenesis, much contradiction still surrounds the thyroid’s effects on the post-pubertal male. A lack of research exists in this area, further enhancing the contradictions that are present. All the studies on hypothyroidism and hyperthyroidism agree that abnormal thyroid profile is detrimental to spermatogenesis. Nevertheless, more studies need to be done concerning both hypo- and hyper-thyroidism, especially in animal models, to understand the mechanism by which thyroid affects male reproductive system and the effects of abnormal thyroid profile on spermatogenesis and male fertility.

The identification of the thyroid hormone receptors on the Sertoli cells could be path breaking for identifying the impact of thyroid hormones on adult testis. As discussed above, Sertoli cells play very important role in spermatogenesis by providing nutrition to the developing germ cells till formation of sperm. However, the field is open to further research as the cascade of events in regulation of spermatogenesis via thyroid receptors in not known. Further, several variants of thyroid receptors such as TRα1, TRα2, TRβ1, and TRβ2 are known. It is imperative to determine the types of the receptor expressed on the Sertoli cells. Further research could explore expression of thyroid receptors on other cell types in not only the testis but also other parts of male reproductive system such as epididymis. The identification of type of receptor could help establish the molecular events by which thyroid affects male reproductive function and fertility.

In conclusion, thyroid definitely impacts testis development, spermatogenesis and male fertility such that abnormal thyroid profile could affect semen quality and may lead to infertility. Thyroid function during pre-natal, neonatal and till puberty is particularly critical for fertility as adult. However, further research and testing is needed to understand how thyroid affects testicular development and spermatogenesis which could help uncover the connection between HPG and HPT axes, and thyroid and male infertility.

EXPERT COMMENTARY

Thyroid once thought not to affect adult testicular physiology and male fertility, is now increasingly being recognised as important for spermatogenesis. Alterations in the gonadotropins in response to change in the thyroid hormone levels indicate fine coordination between hypothalamus-pituitary-thyroid (HPT) and hypothalamus-pituitary-gonadal (HPG) axes. Both hypo- and hyper-thyroidism affect male fertility and prolonged exposure to altered thyroid physiology could lead to male infertility. Nevertheless, good news is that the effects of thyroid on testis are reversible and spermatogenic defects are taken care of once euthyroid state is achieved upon treatment. The field is open to further research particularly understanding the importance of thyroid physiology in post-pubertal male individuals.

FIVE YEAR REVIEW

Most of the early studies on the effect of thyroid on spermatogenesis and male fertility were conducted between the years 1970 and 2000. This included studies on human patients and were restricted to exploration of only the effect of natural hypo- and hyper-thyroidism on spermatogenesis. There has been relatively lesser numbers of studies between the years 2000 and 2006. Recently, a spurt in the number of studies exploring the effects of pre-natal and neo-natal onset of hypo- and hyper-thyroidism is seen. Most of the recent studies have been conducted on animal models. The availability of newer animal models and methods to induce hypo- and hyper-thyroidism has given a new direction to the research on the role of thyroid in spermatogenesis and male fertility.

KEY POINTS

• The evidence that thyroid affects male fertility comes from the studies on human subjects dating back a decade or more.
• Identification of thyroid hormone receptors on Sertoli cells in the testis indicates strong influence of thyroid hormones on spermatogenesis and male fertility.
• Alterations in pre-natal and neo-natal thyroid are most detrimental to not only testicular development but also to fertility as adult.
• Availability of animal models and methods to induce hypo- and hyper-thyroidism has now accelerated research in this field.
• More studies on animal models could help further understand the impact of altered thyroid physiology on male fertility.

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CONFLICT OF INTEREST

None Declared.

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