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ASSOCIATION BETWEEN THYROID DYSFUNCTION AND MALE INFERTILITY

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***Abstract* – There is a high prevalence of thyroid disorder in the general population. Both hypo and hyperthyroidism have been attributed to male and female sexual dysfunction. The role of thyroid disorders in female infertility has been firmly established, while their role in male infertility is yet to be clearly defined. hyperthyroidism causes alterations in the sex steroid hormone metabolism as well as in spermatogenesis and fertility. Most of the studies conducted so far have shown that male patients with thyrotoxicosis have abnormalities in seminal parameters, mainly sperm motility. Severe, prolonged hypothyroidism, may impair reproductive function. Also, severe juvenile hypothyroidism may be associated with precocious puberty. There is paucity of researches studying the exact effect of thyroid disorders on male reproductive physiology. More researches are required to establish the relationship between thyroid dysfunction and male infertility.**

KEY WORDS: hypothyroidism, hyperthyroidism, spermatogenesis, testosterone, thyroid hormone, estradiol

I. INTRODUCTION

The association between thyroid disease and men's sexual functions, and thyroid disease as a cause of sexual problems in men is not as widely understood or known. Thyroid diseases are highly prevalent in the reproductive age group. The effects of thyroid hormone (TH) alterations on the reproductive system have been extensively studied in animals and have generally shown that changes from normal thyroid function result in decreased sexual activity and fertility.[1, 2]The effects of both hyperthyroidism and hypothyroidism on female gonadal function have been established clearly, but the impact of these thyroid disorders on male reproductive function remains unclear. [3, 4]There may be the following reasons for this:

1. In hyperthyroid males, fertility is usually not evaluated and the attention is generally given to other clinical manifestation of the disease.
2. Thyroid dysfunctions are seen less frequently in males as compared to females.
3. Animals experiment failed to show the effect of thyroid hormone on male reproductive system. [5]

There have not been enough clinical researches to study the effects of thyroid dysfunction on male reproductive function. While it is a well-known fact that thyroid diseases effect male reproduction system, the exact clinical features in thyroid disorder in males are not well defined.

II. THE MALE REPRODUCTIVE SYSTEM FROM FETAL TO ADULT LIFE

The gonadal differentiation of males starts at the seventh week of gestation, with the development of the gonadal blastemal into interstitium and germ cells containing testicular cords. The testes of the fetus grow to 800mg at birth from 20mg at 14th week of gestation. At around 5 to 6 months, they descend into the inguinal canal along with the ductus deferens and epididymis.[6] In the fetus, the secretion of testosterone (T) from testes reaches a peak late during the first trimester and then starts declining until parturition.[7] The fetal testes also produce anti mullerian hormone (AMH), which is responsible for dedifferentiation of the mullerian duct system present in the male fetus.[8] During the first year of life, there is an increase in T levels for a short period of time after which the testes stay relatively quiet till the onset of puberty. The pulsatile secretion of gonadotropins (Gns) is caused by the pulsatile secretion of gonadotropin releasing hormone (GnRH). In the fetus, the plasma levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) rise after the establishment of hypothalamic pituitary portal system until mid-gestation and then start decreasing as it goes towards term. As a result of the inhibitory control in male fetus, the mean level of the fetal plasma FSH become less in males as compared to females.[9] Up to two years after birth, the plasma levels of FSH and LH rise intermittently to adult values and sometimes rise to higher values and then remains low till the puberty. GnRH and Gns are secreted in discrete pulse in the adult males. The pulsatile secretion of LH occurs at a rate of 8-14 pulses/24 hour and varies in magnitude.[10] The pulsatile secretion of FSH is temporally coupled with that of LH but is lower in amplitude.[11] The LH secretion is controlled by the negative feedback action of gonadal steroids on the pituitary and the hypothalamus. Both testosterone (T) and estradiol (E2) can have an impact on this inhibition. In the brain and the pituitary, testosterone can be converted to E2. But most researches till now have shown that the two hormones act independently.[12] Leydig cells are stimulated by LH that result in the secretion of T, and, to a minor extent, E2.[13]LH also appears to cause testicular aromatization in Leydig cells. The high intra-testicular concentration of T could be crucial for the function of healthy

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sertoli's cells. It could also play a role in sperm transport or spermatogenesis.[14] In some tissues of the prostate, circulating T enter the cells and metabolize to more active products. DHT also metabolizes through the action of 5-α reductase II enzyme. 5-α reductase-I is the major isoenzyme in other tissues.[15] While in some areas, DHT is the active androgen, T is the active androgen in tissues like muscles, that lack the enzyme. The testicular functions decline with age.[16] The disease process and the life style of an individual may have a role in decline of testicular functions.[17] Although the testicular secretion is necessary for the production of E2 in males, the major source of the circulation hormone is from the aromatization of T present in the peripheral tissues along with skin, muscle and adipose tissues. There is also a little aromatization in the liver that contributes to the circulating hormone.[18]The hormone that is produced is further metabolized in the liver into estriol and catechol estrogens.[19]

III. HORMONAL CHANGES IN THYROTOXIC MALES

There is an increase in SHBG associated with thyrotoxicosis[20]that results in rise of total thyroxine(T4) levels in circulation and decrease in the metabolic clearance rate of testosterone (T).[21] The level of free T in plasma is maintained within the normal range.[22]However, in hyperthyroid males, bioavailable T was found subnormal.[23] The level of circulating E2 is elevated in many men with thyrotoxicosis.[24] Therefore the free T/free E2 ratio were found lower in hyperthyroid males as compared to normal men.[23] It is also observed that in some men with hyperthyroidism, there is an increase in rate of production of estrogen although it is not clear whether it is due to increase in production of adrenal androgen precursors or due to some other mechanism.[25]These changes can result in gynecomastia in up to 24% [23]decreased libido in up to 70% [26] and erectile dysfunction in up to 56%. [27] Researchers have found that LH and FSH responses to GnRH administration are exaggerated in males with hyperthyroidism. In contrast, the response of leydig cells to human chorionic gonadotropin (HCG) administration are blunted as assessed by serum testosterone responses. [26, 28, 29]Such abnormalities of hypothalamic-pituitary-gonadal axis is correlated significantly with the increased serum levels of T4. It is shown that it is entirely reversible once the euthyroid state is achieved. Hence, no specific treatment is required.

IV. HYPERTHYROIDISM AND INFERTILITY

The relationship between thyrotoxicosis and semen quality has been the subject of very few clinical studies. Clyde et al.[30] had investigated 3 hyperthyroid males and found that out of three patients, two had marked oligospermia along with decreased motility and in the third patient they found a borderline low sperm count along with decreased in sperm motility. Kidd et al.[22] had investigated five patients with hyperthyroidism and found that they all had low total sperm counts (less than 40 * 106/ml). In 1992, Hudson and Edward[31]studied the spermogram of 16 thyrotoxic males and found that their sperm density were lower as compared to the controls but was not statistically significant. In addition, they found that the sperm motility in these patients were significantly reduced as compared to the normal males. Abalovich et al.[23] studied the effect of hyperthyroidism on spermatogenesis in 21 patients with hyperthyroidism. Nine patients(43%) were found to had low total sperm count, 18 (86%) were found with lineal motility defects, and 13 (62%) were presented with progressive motility abnormalities. More recently, Krassas et al,[32] in a prospective study, investigated 23 males with hyperthyroidism along with 15 healthy controls. They performed a semen examination both before and after 5 months of restoration of euthyroidism that is achieved by treatment of methimazole (MMI) alone in 14 patients, or MMI plus radioiodine (R-I131) in 9 patients. In 16 out of 23 patients, total fructose, Mg and Zn concentrations were also measured in the seminal plasma. The result had indicated that the mean semen volume was within the normal range in patients but the mean sperm density was less when compared with controls, however the difference was not significant statically. A similar conclusion was made for the morphology of sperm, however in hyperthyroid males the mean sperm motility was found lower as compared to the males with controls. The morphology of the sperm did not change after the treatment for thyrotoxicosis. However, there is an improvement in sperm motility and the density. The type of drugs (methimazole alone or I-131 plus methimazole) that is administered for the control group of thyrotoxicosis did not showed any impact on the morphology or the number of sperms. The mean value for semen concentration of Zn, Mg and fructose were found same in both patients and controls, either before and after the euthyroid is achieved and values did not correlate with the sperm parameters or with the pre-treatment level of thyroid hormones.

Table 1. Hyperthyroidism and its effects on sperm quality.

AUTHORS	NUMBER OF PATIENTS	FINDINGS
Clyde et al. (1976)[30]	3	1.All the patients had decreased sperm motility. 2.Two out of three had severe and one had borderline oligospermia.
Kidd et al. (1979) [22]	5	All had sperm counts of less than 40 x 10^6 /ml
Hudson and Edwards (1992) [31]	16	1.Sperm densities were found to be low but not different from controls. 2. Sperm motility was significantly lower in hyperthyroid patients.
Abalovich et al. (1999)[23]	21	1.Nine patients had decreased sperm counts. 2. 18 patients had decreased sperm motility.
Krassas et al. (2002)[32]	23	1.Mean sperm densities were low but did not differ from controls. 2. Sperm motility significantly lower in hyperthyroid patients.

V. HORMONAL CHANGES IN THYROTOXIC MALES

Hypothyroidism is caused by decreased in serum total T.[33, 34]It is less prevalent in men as compared to women[35, 36] and it effect on the reproductive system is not clear.[28, 37] The response of LH to GnRH in hypothyroid males appears to be unclear.[26] SHBG and serum free testosterone are usually normal or low.[26, 33]In the serum of hypothyroid males the 5a:5b ratio of metabolites of the androstenedione and androsterone were markedly decreased.[38] In a prospective study the plasma T levels was increased after T4 therapy was started. The secretion of prolactin might be elevated, which is improves with sufficient T4 replacement therapy. [39]
Hypothyroidism is related with erectile dysfunction, delayed ejaculation and hypoactive sexual desire.[39]There are not many studies suggesting the effects of hypothyroidism on human fertility and spermatogenesis as the reports are less.[28] In the autopsy material the variations in histology and the size of testes have been noted.[40, 41] It has not been found to cause seminal alterations that are sufficient to impair infertility in men, but short term post pubertal hypothyroidism might decrease semen volume.[34, 42] Subclinical hypothyroidism does not have an impact on semen density, morphology and motility.[43]

VI. HYPOTHYROIDISM AND INFERTILITY

Hypothyroidism have an association with decreased libido.[44] There are not sufficient studies regarding the effects of hypothyroidism on male spermatogenesis and fertility. In a study Griboff [44] examined five patients aged between 30 and 64 years with primary hypothyroidism. In his investigation he had found that they all had normal sperm counts. The semen that is exposed to room air had revealed a rapid drying of material and the sperm motility was lost in two to five specimens. In a study De la Balze et al.[40] had investigated 6 males with hypothyroidism aged between 17 and 59 years. In five patients thyroid insufficiency occurred before the onset of puberty and in one patient thyroid insufficiency occurred in childhood. All the patients had shown the features of hypogonadotropic hypogonadism. Testicular biopsy of all patients had been done and it revealed that there were histological abnormalities in all the patients. It was concluded that severe and prolonged thyroid insufficiency occurring early in life resulted in moderate failure of pituitary Gn secretion and abnormal testicular biopsies. Wortsman et al.[33] had investigated 8 hypothyroid male patients aged between 37 and 77 years. All the patients had demonstrated hypogonadism, five were hypergonadotropic and the remaining three were hypogonadotropic. Seven patients out of eight had shown varying degrees of testicular atrophy but the sperm analysis were not performed. In four patients serum T and SHBG concentrations were found low. the authors had concluded that the abnormalities of gonadal function are common in men with primary hypothyroidism. Corrales Hernandez et al.[34] investigated spermatogenesis in ten patients who had a history of hypothyroidism that was treated with T4. In these patients, hypothyroidism was induced by stopping or by decreasing the dose of T4 over at least one spermatogenic cycle. It is observed that there was a decrease in seminal volume, progressive forward motility and cumulative percentage of mobile protozoans form compared to the controls. During euthyroid state, induction of hypothyroidism did not lead to seminal changes as compared with the same patients. Therefore, its appears, short-term post-pubertal hypothyroidism does not cause sufficient seminal alterations to impair male fertility. Jaya Kumar et al.[42] investigated the reproductive and endocrine functions of 8 male patients with primary hypothyroidism. They conducted the investigation during the hypothyroid state and after the euthyroid state was achieved with T4 substitution therapy. The authors found low serum testosterone, low SHBG, subnormal testosterone responses to HCG and high mean Gn levels. In 5 out of 8 patients, semen analysis was performed but these data were not reported. However, the authors claimed there was some improvement in sperm count and its motility. In a recent prospective controlled study Krassas et al.[45] investigated the effects of hypothyroidism on male spermatogenesis. During the investigation of semen analysis, teratozospermia index, fructose and acid phosphate measurements and acridine orange test determined both before 6 to 9 months and after treatment with T4 in 25 hypothyroid males and 15 normal individuals, they found that hypothyroidism had an adverse effect on male spermatogenesis, with sperm morphology was the only parameter that was affected significantly, motility was also affected but the differences were not significant statically.
Table 2. Hypothyroidism and its effects on sperm quality.

AUTHORS	NUMBER OF PATIENTS	FINDINGS
Griboff[44]	5	1.Sperm count was normal. 2. Exposure of semen to room air produced loss of sperm motility in two patients.
De la Balze[40]	6	Histological abnormalities were seen in all in testicular biopsies.
Wortsman[33]	8	Seven out of eight had varying degrees of testicular atrophy.
Corrales Hernandez[34]	10	No abnormalities were seen.
Jaya Kumar[42]	8	Five out of eight had sperm analysis done. No original data
Krassas[45]	25	1.Morphology was the only sperm parameter significantly affected. 2. Motility was also affected, but differences with samples from normal males were not statistically significant.

V. CONCLUSION

Both hyperthyroidism and hypothyroidism adversely affect the reproductive function in males and females. In males, hyperthyroidism causes alterations in the sex steroid hormone metabolism as well as in spermatogenesis and fertility. Most

of the studies conducted so far have shown that male patients with thyrotoxicosis have abnormalities in seminal parameters, mainly sperm motility. Severe, prolonged hypothyroidism, may impair reproductive function. Also, severe juvenile hypothyroidism may be associated with precocious puberty. More studies are required with a larger number of patients to define the effects of thyroid disorders on male reproductive function.

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