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REVIEW ARTICLE

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Thyroid impairment and male fertility: a narrative review of literature

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ABSTRACT

Purpose: To evaluate the effect of thyroid function on male fertility, focusing on hypo- and hyperthyroidism.

Methods: A PubMed/MEDLINE, Web of Science, and Scopus research was performed. Original studies in English published online up to 31 May 2023 were selected and reviewed. The final reference list was defined based on the relevance of each paper to the scope of this review.

Results: The available data in animals (31 studies) and human (26 studies) showed conflicting results. However, thyroid dysfunction altered erection and ejaculation both in animal models than in men.

Conclusion: Both hypothyroidism and hyperthyroidism seem to cause ejaculation and erectile dysfunction. Hence, Guidelines recommend against the systematic screening for thyroid disorders in the men in sub-fertile couples, but only in men with ejaculation and erectile dysfunction and/or altered semen parameters.

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Introduction

Infertility is defined as the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse, or due to an impairment of a person's capacity to reproduce, either as an individual or with his/her partner [1]. It is estimated to affect between 8% and 12% of reproductive-aged couples worldwide [2]. Males are found to be solely responsible for 20–30% of infertility cases but contribute to 50% of cases overall [3]. Multiple causes of male infertility have been identified; these include endocrine disorders (usually due to hypogonadism), sperm transportation disorders, primary testicular defects, and idiopathic causes [4].

Thyroid impairments are quite common. Subclinical and overt hypo- and hyperthyroidism have a prevalence ranging, respectively, from 0.1% to 12.4% and from 0.2% to 10% in adults [5–10]. Hashimoto's thyroiditis and Graves' disease are the two most frequent autoimmune thyroid diseases (AITD) inducing hypothyroidism and hyperthyroidism, respectively [11,12]. These conditions are often associated with other pathologies such as hematologic [13–15], cardiovascular [16,17], gastrointestinal [18,19], metabolic [20,21], and, last but not least, reproductive [22–64] abnormalities.

It is in fact well known that thyroid function has a close link and interplay with female fertility [65]. In milder hypothyroidism, infertility usually does not occur, but there is an increased risk of complications during pregnancy; on the other hand, severe hypothyroidism has a direct inhibitory effect on ovulation, also reducing ovarian reserve, and affects the pituitary-testicular axis, leading to infertility [66–68]. On the other hand, hyperthyroidism can also impair female fertility *via* multiple mechanisms [69].

The impact of thyroid function on male fertility is still matter of discussion and not fully understood, in particular subclinical dysthyroidism. The aim of the present review is to evaluate the effect of thyroid function on male fertility, focusing on hypo- and hyperthyroidism.

Methods

A PubMed/MEDLINE, Web of Science, and Scopus research was performed, for free-text words and terms

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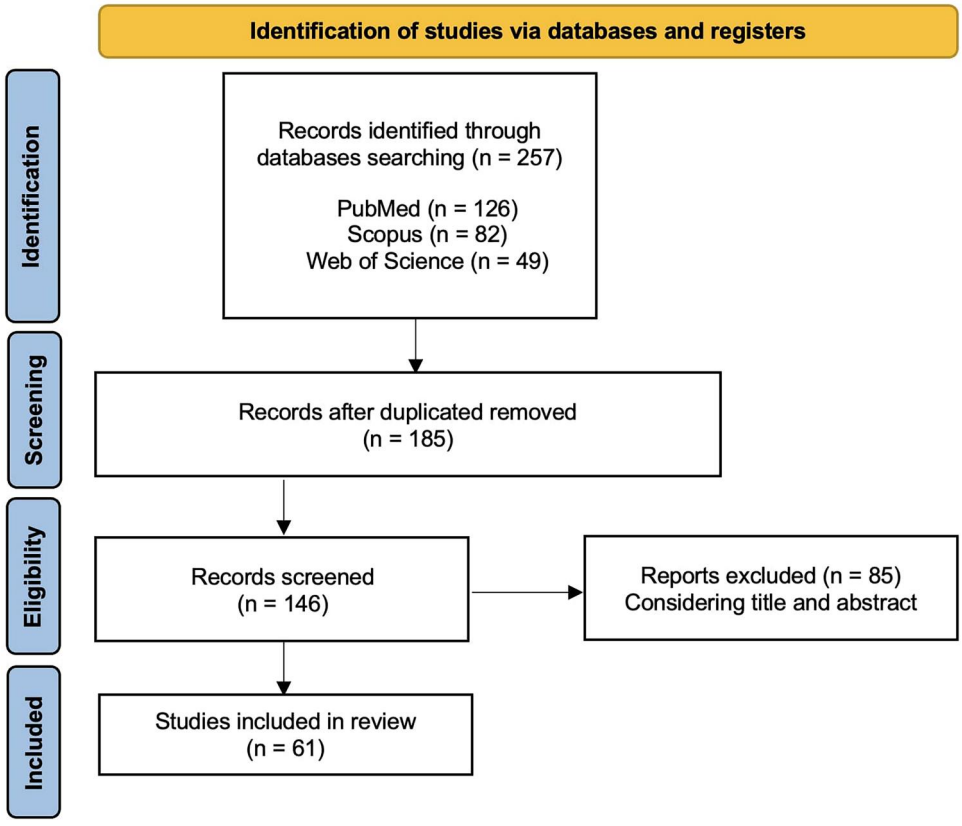

Figure 1. Diagram of the screening and selection process.

related to "fertility," "infertility," "male," "hypothyroidism," "hyperthyroidism," "subclinical," "sperm," "gonadal function," "thyroid," "TSH." Original studies in English published online up to 31 May 2023 were selected and reviewed. The final reference list was defined based on the relevance of each paper to the scope of this review.

Results

In the preliminary search, 257 studies were identified and 185 remained after removal of duplicates. A total of 146 articles were eligible for full-text screening and 61 full-text publications were included in the analysis. Specifically, 32 were performed in animal models; 29 were performed among human: 5 were case reports or case series, 2 were *in vitro* studies, and the remaining observational studies. The studies were published between 1962 and 2023. A flow diagram of the screening and selection process can be found in Figure 1.

Animal studies

A total of 32 studies were found and summarized in Table 1.

Many studies evaluated the effects of thyroid hormone impairment on hypothalamic–pituitary–gonadal axis. Bruni et al. showed that hypothyroidism reduced luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release in rats with intact gonads (controls *vs.* hypothyroid: LH (ng/mL) 24 ± 6 *vs.* 8 ± 3, $p < .005$; FSH (ng/mL) 301 ± 51 *vs.* 203 ± 9, respectively, $p < .005$) and caused an abnormal increase in castrated rats (controls *vs.* hypothyroid: LH (ng/mL) 1163 ± 17 *vs.* 1683 ± 129, $p < .001$; FSH (ng/mL) 1090 ± 65 *vs.*1882 ± 48, respectively, $p < .001$). Moreover, replacement levothyroxine (LT4) therapy restored a "normal" LH and FSH in both groups [22]. The same results were also reported by Valle et al. [23], and reinforced by other authors who, in addition, provided evidence of a restoration of testosterone levels by introducing LT4 therapy [24–26]. Moreover, Kala et al. showed a possible "double face" of hypothyroidism in terms of effect on the levels of testosterone in rats; persistent hypothyroidism diminished testosterone (4.2 ± 0.2 *vs.* 0.35 ± 0.02 ng/mL, $p < .005$), while transient hypothyroidism did not [27]. Romano et al. tried to explain these mechanisms by showing that hypothyroidism alters post-transcriptional cascades in LH synthesis with a reduction in serum testosterone level, and probably with a direct effect on testicular function [28].

Table 1. Summary of clinical studies and case reports about thyroid function and male fertility in animals *in vivo*.

Author, date	Study design	Animal model	Outcome
[40]	Case–control	Colony bred albino hypothyroid rats	Hypothyroidism did not evoke any significant change in testes weight, while the weights of seminal vesicle and ventral prostate were greater than controls. No alteration in spermatogenesis and no morphological changes of Leyding cells. Diminished libido was observed in hypothyroid rats and their fertility was reduced, with a diminished trend in litter size.
[70]	Observational	Long-Evans rats	Treatment with T3 led to no change in either serum LH or FSH levels
[71]	Case–control	10 hypothyroid Wistar rats	Hypothyroidism did not affect testicular function and weight of testicles, ventral prostate, and seminal vesicles.
[72]	Observational	Long-Evans rats	Treatment with T3 led to no change in either serum LH or FSH levels
[22]	Case–control	Sprague-Dawley male rats	Hypothyroidism results in decreased release of LH and FSH in rats with intact gonads, and in increased release of LH and FSH in castrate rats. Administration of a replacement dose of L-T4 can restore LH and FSH release to normal in rats with intact gonads, and to castration levels in castrate rats. Higher weight of seminal vesicles in hypothyroid rats.
[30]	Case–control	Hypothyroid Wistar rats	Reduced weight of seminal vesicles and ventral prostate and normal serum levels of testosterone, LH and FSH.
[43]	Case–control	Sprague-Dawley hyperthyroid rats	Hyperthyroidism leaded to a fall in FSH levels either *via* direct pituitary suppression or *via* accelerated FSH metabolism; no changes in E2 and testosterone, non-significant reduction of LH. *In vitro* studies showed an increased testicular testosterone synthesis and intratesticular stimulation of 17 beta-hydroxysteroid dehydrogenases.
[24]	Case–control	56 adult male hypothyroid Lewis rats (treated with PTU).	Pituitary concentrations of TSH, PRL and FSH were significantly reduced by the treatment with PTU. There was also a slight, but insignificant reduction of pituitary concentrations of LH. Those alterations were restored after treatment with thyroid hormones.
[73]	Case–control	Infertile and hypothyroid mice	Hypothyroidism was not associated with a reduction of spermatogenesis or testosterone secretion; etiology of infertility was unknown.
[25]	Case–control	54 hypothyroid Wistar rats	Reduced weight of seminal vesicles and ventral prostate and serum levels of testosterone, normalized after L-T4 replacement.
[74]	Case–control	90 hyperthyroid Wistar rats	Reduced serum levels of LH, FSH and testosterone in hyperthyroid rats.
[33]	Observational	Hypothyroid immature male rats	Thyroidectomy inhibited gametogenesis and development of the Leydig cell; however, the effects could be reversed by T4
[23]	Case–control	12 hypothyroid Wistar adult rats, among whom 6 T3 treated	Hypothyroidism decreases weight of testicles and sex accessory glands, serum levels of LH and testosterone. T3 replacement normalized serum hormonal levels but not the structural changes.
[75]	Case–control	13 hypothyroid rats	In hypothyroid rats seminiferous tubules were smaller in size and contained fewer spermatogonia, spermatocytes, spermatids and spermatozoa. T4 brought about an increase in cell counts of the seminiferous tubules and in sperm counts in both groups.
[76]	Case–control	15 hypothyroid rats	Hypothyroidism did not affect sexual behavior or cause infertility; hypothyroid rats initiated first pregnancy later than controls.
[77]	Case–control	18 hypothyroid Sprague-Dawley adult rats	Hypothyroidism did not affect testis weights, serum levels of testosterone, or the structure of seminiferous tubules.
[26]	Case–control	22 hypothyroid Wistar adult rats, among whom 11 T3 treated	Hypothyroidism decreases *in vitro* production on testosterone and its precursors but no signification variation in testis weight. T3 treatment partially restores *in vitro* testosterone production.
[78]	Case–control	Male Wistar rats	In the adult testis, both *in vivo* and *in vitro* treatments with thyroid hormone did not induce morphological modifications. A slight, but significative increase of FSH levels was found compared to controls in T3 treated animals
[35]	Case–control	60 infertile hypothyroid rdw rats	L-T4 treatment induced a partial reversion of the impaired sexual behavior and a complete reversion of fertility of epididymal sperm
[27]	Case–control	Rats with transient and persistent hypothyroidism	Persistent hypothyroidism diminishes the bioavailability of androgens and oestrogens, while transient hypothyroidism enhances it.
[32]	Case–control	Hypothyroid rats	Hypothyroidism resulted in a reduction in body weight, seminal vesicle and ventral prostate gland. A further decrease in the weight of seminal vesicle was recorded following administration of T3 to hypothyroid rats.
[31]	Case–control	Congenital hypothyroid mutant male rdw rats	Even low levels of circulating thyroid hormone stimulate the development of testes probably through Sertoli cells, resulting in the enlarged adult testes without fertility. Thyroid hormone plays a pivotal role in restoring mating activity, probably through FSH-mediated action towards adulthood.
[44]	Case–control	Male Wistar rats	In hyperthyroid rats, testes maturation and intense protein synthesis and processing were found. An increase in mitochondrial reactive oxygen species generation, underlying cellular oxidative damage, is a side effect of hyperthyroid-induced biochemical changes by which rat testis increase their metabolic capacity
[37]	Case–control	Hypothyroid adult male Wistar rats	Hypothyroid condition disturbed intra-mitochondrial thiol redox status leading to testicular dysfunction. Hypothyroidism-induced oxidative stress condition could not be reversed with T3 treatment.
[39]	Case–control	Hypothyroid male albino rats	Plasma total homocysteine, total NO metabolites, malondialdehyde and GSSG/GSH ratio quantified by HPLC increased in hypothyroid rats as compared to controls. These biochemical alterations at least in part disrupted spermatogenesis in these experimental models

(*continued*)

Table 1. Continued.

Author, date	Study design	Animal model	Outcome
[28]	Case–control	Hypothyroid rats	Hypothyroidism in adult male rats altered posttranscriptional mechanisms of LH synthesis and probably had a direct effect on testicular function.
[42]	Case–control	40 adult male Wistar rats rendered hyperthyroid with L-T4	Induction of hyperthyroidism cause a decrease in absolute genital sex organs weight, a significant decline in serum levels of LH, FSH and testosterone along with significant increase in serum estradiol level. Hypermetabolic state induced by excess level of thyroid hormones may be a causative factor for the impairment of testicular physiology as a consequence of oxidative stress
[29]	Case–control	20 hypothyroid (PTU treatment) Wistar adult rats, 20 hyperthyroid (L-T4 treatment) Wistar adult rats	Hypo- and hyperthyroidism lowered genital sex organs weight, sperm count and motility, serum levels of LH, FSH and testosterone; they increased serum E2 level, testicular oxidative stress, DNA damage and apoptotic markers. Data were backed by morphometric and histopathologic studies.
[36]	Case–control	10 hypothyroid Wistar rats, 10 hyperthyroid Wistar adult rats	Hypothyroidism decreased the total and daily sperm productions and increased the sperm transit time through the epididymis; the sperm functionality was reduced in both thyroid dysfunctions.
[34]	Case–control	12-15 male rats with hypothyroidism and 12-15 with hypothyroidism and diabetes	Diabetes combined with hypothyroidism inhibits spermatogenesis and decreased sperm motility. Hypothyroidism inhibited seminiferous tubules development in both immature and prepubertal mice.
[38]	Case–control	Euthyroid, hypothyroid, hyperthyroid Wistar rats	There is a correlation between thyroid disorders and impaired antioxidant defence mechanism, resulting in reproductive dysfunctions, as infertility, mainly observed in hypothyroidism.

T4: thyroxine; T3: thyronine; PTU: propylthiouracil; LH: luteinizing hormone; FSH: follicle stimulating hormone; E2: estradiol

El-Kashlan added that hormonal and testicular impairment was also caused by testicular oxidative stress, DNA damage, and apoptotic activity [29]. However, few authors showed normal serum levels of testosterone, LH and FSH in hypothyroid rats [30,73,77].

In terms of gonads, studies have shown a possible reduction in the volume of testicles, seminal vesicles, and ventral prostate in hypothyroid rats [23,25,28,30,75]. By contrast, larger seminal vesicles were observed by Bruni et al. [22], whereas Umezu et al. described enlarged adult testes probably through the hypertrophy of Sertoli cells [31]. On the other hand, some authors stated that hypothyroidism did not affect the weight of testicles, ventral prostate or seminal vesicles, or structure of seminiferous tubules [26,40,71,77]. Aruldhas et al. then reported volume normalization after LT4 replacement therapy [25], although Choudhury et al. on the contrary, described a further decrease in volume of seminal vescicle after the administration of triiodiotironine to hypothyroid rats [32]. Instead, Valle et al. reported no volume changes [23].

The direct effect of hypothyroidism on gametogenesis, seminiferous tubules, and Leydig cells development has been reported [33,34]. These findings were confirmed by other authors showing the complete reversion of fertility after levothyroxine treatment [29,33,35,36]. In particular, Romano et al. and El-Kashlan et al. well described a significant decrease in total and daily sperm production, increased sperm transit time through the epididymis and altered semen characteristics compromising the fertilization process [29,36]. Korejo et al. added that concomitant diabetes exacerbated the issue [34]. These data were confirmed by Chattopadhyay et al. adding that levothyroxine treatment is unable to restore normal fertility [daily testicular sperm production (No. $\times 10^6$/g tissue): Euthyroid* 10.65 ± 0.87 *vs.* hypothyroid* 3.99 ± 0.45 ($p < 0.05$)* *vs.* hypothyroid + T3 5.58 ± 0.61 ($p < 0.05$)*; Epididymal sperm count (No.10^4/ml): Euthyroid* 1121.40 ± 137.86 *vs.* hypothyroid* 553.80 ± 70.92 ($p < 0.05$)* *vs.* hypothyroid + T3 828.20 ± 56.73 ($p < 0.05$)*] [37]. On the contrary, a few authors saw no morphological changes in Leydig cells and reduction of fertility in hypothyroid mice [40,71,73]. These disorders seem mediated by impaired antioxidant defense mechanisms [29,38], as suggested by Ibrahim et al. [39].

Reduced libido in hypothyroid mice was first described by Karkun et al. [40], whereas Jiang et al. showed its partial reversion after the intrdocution of LT4 therapy [35]. These data were not supported by Chubb et al. [76].

In the same way, hyperthyroidism was associated with the reduction of LH (−45% *vs.* euthyroidism, $p < 0.001$), FSH (−33.3%, $p < 0.001$), and serum testosterone levels (−34.3%, $p < 0.001$) in rats [42,74]. Schneider et al. hypothysized that it was due to the concomitant pituitary suppression and accelerated FSH metabolism [43]. In addition, Asker et al. affirmed that thyrotoxicosis enhanced testicular oxidative stress (increase in malondialdehyde and nitric oxide concentrations by 19.0% and 44.4%, respectively, $p < 0.01$)

causing testicular physiological impairment [42]. Conversely, Jannini et al. showed a slight increase in FSH levels after inducing thyrotoxicosis by T3 therapy [78], whereas Howland showed normal serum LH and FSH levels [70,72]. Only one study evaluated the effect of thyrotoxicosis on testicular volume, reporting a significant reduction in weight (−17%, $p < 0.01$) [42]. Impaired sperm quality was reported by few authors (sperm count −40.4% and motility −37.7%, $p < 0.01$, by Asker et al.) [36,42]; low sperm count and motility could be due to the increase in testicular oxidative stress mediated by vimentin synthesis enhancement [29,44].

Human studies

A total of 29 studies were found and summarized in Table 2.

Few data on the effects of thyroid hormone impairment on the hypothalamic–pituitary–gonadal axis are reported. In hypothyroid patients, Wortsman et al. reported both hypergonadotropic and hypogonadotropic hypogonadism [45]. Serum FSH and LH levels were reported to rise after restoring euthyroidism by Jaya Kumar et al. in a small set of patients (LH (IU/l): hypothyroid 18.7 ± 7.3 *vs.* euthyroid 7.2 ± 2.0, $p < 0.001$; FSH (IU/l): hypothyroid 6.3 ± 2.0 *vs.* euthyroid 2.7 ± 0.9, $p < 0.001$) [46]. By contrast, Ambigapathy et al. found that hypogonadotropic hypogonadism was more common than hypergonadotropic hypogonadism, with serum LH normalization upon restoring euthyroidism [47]. In addition, in sub-fertile patients, Wortsman et al. reported that gonadal dysfunction preceded the development of hypothyroidism [45].

With reference to the gonads, De La Balze et al. showed that prepuberal onset of hypothyroidism was associated with delayed testicular maturation and involution of adult characteristics (tubular content, tubular wall and intertubular connective tissue), mediated by gonadotropin secretion failure due to prolonged thyroid insufficiency [49]. A positive correlation between fT3 level, seminal vesicle volume and inhomogeneous echotexture was reported by Lotti et al. [48].

On the other hand, but physiologically in line with that reported above, Rehman et al. showed a correlation between altered semen parameters and subclinical hypothyroidism [50]. In particular, the increase in thyroid stimulating hormone (TSH) levels was related to a significant reduction in normal morphology (% normal form: 5.79 ± 3.98 in euthyroid *vs.* 0.63 ± 0.92 in hypothyroid, $p < 0.05$), motility (% normal motility: 60.85 ± 21.00 in euthyroid *vs.* 20.18 ± 26.80 in hypothyroid, $p < 0.05$) and in sperm count (million sperm per mL: 88.85 ± 54.80 in euthyroid *vs.* 22.64 ± 31.39 in hypothyroid, $p < 0.05$) [50]. The first datum was subsequently confirmed by Nikoobakht et al. Krassas et al. and Griboff et al. [51,53,54], whereas impaired total and progressive sperm motility was confirmed by Ambigapathy et al. [47]. With the exception of spermatozoa morphology, these data were previously reported in the 1990s by Corrales Hernandez et al. [55]. Krassas et al. and Jaya Cumar et al. reported the normalization of morphology spermatozoa, improvement in sperm count and motility after LT4 therapy [46,53]. Mendeluk et al. conducted a semen analysis on spermatozoa incubated with LT4, finding a rapid and significant increase in the percentage of hyperactive sperm ($8.93 \times 10^6 \pm 9.52 \times 10^6$ in control *vs.* $17.20 \times 10^6 \pm 21.16 \times 10^6$ after procedure, $p < 0.03$) [56]. Condorelli et al. showed that it was due to the beneficial effect of L-T4 on sperm mitochondrial function, oxidative stress, and DNA integrity [57]. By contrast, Lotti et al. reported – in a cross-control study on 163 men in infertile couples – no association between hypothyroidism and semen parameters, as already reported by Trummer et al. [48,61].

In 5,401 infertile men, Zhao et al. found that serum TSH levels were positively associated with a DNA fragmentation index (DFI) over 25% [58].

Among 2511 infertile couples, Rao et al. found that paternal subclinical hypothyroidism was associated with a poorer clinical outcome in *in vitro* fertilization (IVF) and intracytoplasmatic sperm injection (ICSI), for couples over 35 years old (total pregnancy rate 42% in euthyroid subjects *vs.* 32% in cases of hypothyroidism, $p = 0.009$) [59].

Libido reduction and impaired erectile function was described in hypothyroid men [46,51]. In particular, Jaya Cumar et al. reported a prevalence of libido reduction in 37.5% of hypothyroid patients [46]. Ambigapathy et al. confirmed sexual dysfunction by Androgen Deficiency in the Aging Male (ADAM) score in 80% of men and in 72.72% by Arizona Sexual Experience Scale (ASEX) score [47]. Carani et al. showed hypoactive sexual desire, erectile dysfunction, and delayed ejaculation. Overall, ejaculation latency time declined significantly after L-T4 replacement therapy [60].

Trummer et al. found a prevalence of thyroid antibodies in 7.5% of infertile men and added that elevated TPO-Ab were strongly correlated with pathozoospermia and asthenozoospermia [61]. Instead, Poppe et al. and Binjandi et al. found no

Table 2. Summary of clinical studies and case reports about thyroid function and male fertility in human.

Author, date	Study design	Patients	Outcome
[49]	Case series	Six adult male patients with myxedema of severe degree and long duration	Prepuberal onset of hypothyroidism was associated with delayed testicular maturation and involution of adult characteristics
[54]	Case series	Five men with primary myxedema, 30–64 years old	Normal sperm in three patients, two showed losses in motility that in one patient improve after triiodothyronine administration
[63]	Case series	Three young men with hyperthyroidism	Two patients had marked oligospermia with decreased motility, and the third patient had a borderline low sperm count associated with decreased motility.
[79]	Observational study	Seven consecutive men with thyrotoxicosis due to Graves' disease	Men with hyperthyroidism have partial Leydig cell failure and impairment of spermatogenesis.
[45]	Observational retrospective	Eight men with primary hypothyroidism (five AITD related, and three amiodarone inducted), 37–77 years old	Hypergonadotropic state in five patients and hypogonadotropic hypogonadism in three patients, low testosterone levels in four patients
[64]	Observational prospective	8 hyperthyroid men given two identical intravenous GnRH tests	Chronic thyroid hormone excess makes the pituitary gonadotrophs "hypersensitive" to exogenous GnRH.
[55]	Observational prospective	Ten hypothyroid men who discontinued L-T4 therapy and 16 control fertile men	Decrease in seminal volume, progressive forward motility, and the cumulative percentage of mobile forms.
[46]	Observational prospective	Eight men with newly diagnosed primary hypothyroidism	Hypergonadotropism and low serum testosterone were observed during the hypothyroid phase and they restored with thyroxine substitution therapy.
[62]	Prospective observational	Nine men aged 17–35 years and seven men aged 36–46 years with Graves' disease	Hyperthyroid patients showed greater levels of testosterone, estradiol, LH, and FSH.
[80]	Prospective observational	25 male patients suffering from active Graves' disease	Hyperthyroidism causes marked alterations of the gonadotropic and PRL axis, asthenospermia, hypospermia, oligospermia, necrospermia, and teratospermia.
[61]	Prospective observational	305 men with idiopathic infertility	Latent thyroid dysfunction had no impact on semen parameters. Elevated TPO-Ab were significantly correlated with pathozoospermia and asthenozoospermia.
[52]	Observational prospective	Twenty-three thyrotoxic male patient	Hyperthyroidism is related to abnormalities in seminal parameters, mainly sperm motility, that improve or normalize when the patients become euthyroid.
[60]	Observational prospective	48 adult men, 34 with hyperthyroidism and 14 with hypothyroidism	Most patients with thyroid hormone disorders experience some sexual dysfunctions, particularly ejaculatory disorders, reversible by normalizing thyroid hormone levels.
[81]	Observational prospective	239 adult men of infertile couples, 39 with normal and 253 with abnormal semen characteristics	The prevalence of thyroid dysfunction and autoimmunity is comparable between men with normal and abnormal semen characteristics.
[82]	Case report	Man with new onset hypothyroidism and slow progressive motility	Three months after starting thyroxine his wife became pregnant
[53]	Observational prospective	Twenty-five hypothyroid men	Hypothyroidism has an adverse effect only on morphology,
[83]	Observational retrospective	298 men with early treated for congenital hypothyroidism	There is no evidence that fecundity is generally lower in young adults treated early for hypothyroidism than in the general population.
[84]	Case report	46 years old infertile man with primary myxedema	Decreased semen volume and severe oligozoospermia; only 2 spermatozoa, elevated levels of serum prolactin and decreased of serum testosterone. After restoration of euthyroidism parameters normalized.
[51]	Prospective cross sectional	66 euthyroid and 24 with hypothyroid men	Hypothyroidism adversely affects erectile function, sperm count, morphology, and motility.
[48]	Observational retrospective	145 euthyroid, 6 with subclinical hyperthyroidism and 12 with subclinical hypothyroidism men of infertile couples	Positive association between fT3 and ejaculate volume, seminal fructose levels, seminal vesicles volume, and testicular echo-texture inhomogeneity. Negative associations between fT4 levels and epididymal body and tail diameter.
[56]	*In vitro*	Semen samples of 40 euthyroid men with idiopathic infertility incubated with LT4	Addition of T4 to semen samples increased motility
[57]	*In vitro*	Spermatozoa of 15 euthyroid men with idiopathic infertility incubated with increasing concentrations of LT4	L-T4 significantly reduced sperm necrosis and lipid peroxidation ameliorating chromatin compactness, sperm mitochondrial function, oxidative stress and DNA integrity.

(*continued*)

Table 2. Continued.

Author, date	Study design	Patients	Outcome
[47]	Observational before-after	40 treatment-naïve patients diagnosed with primary hypothyroidism	Leydig cell function seemed more severely affected by hypothyroidism as compared to Sertoli cell function. Among sperm function parameters, motility was predominantly affected.
[50]	Cross sectional	376 male subjects, among how 160 with abnormal sperm parameters	Disturbance in thyroid hormones are related to alteration of sperm parameters and reproductive hormones.
[85]	Prospective cross sectional	1611 men	TPO-Ab positivity was not associated with infertility.
[59]	Retrospective cross sectional	2282 euthyroid men and 229 with SCH who underwent assisted procreation	SCH was associated with worse clinical outcomes after IVF/ICSI in men $\geq$35 years old.
[58]	Retrospective cross sectional	4983 euthyroid men and 418 with SCH who underwent IVF/ICSI	SCH was significantly associated with an increased risk of an abnormal DFI.

AITD: autoimmune thyroid disease; L-T4: levothyroxine; fT3: free triiodothyronine; fT4: free thyroxine; TPO-Ab: thyroid peroxidase antibodies; SCH: subclinical hypothyroidism; IVF: *in vitro* fertilization; ICSI: intracytoplasmic sperm injection; DFI: DNA fragmentation index

association between infertility and other thyroid function tests or TPOAb positivity [66,81,85].

Examining hyperthyroidism, Hudson et al. reported greater levels of testosterone (hyperthyroid 67 ± 19 *vs.* euthyroid 23 ± 3.1 (nmol/L), $p < 0.001$), estradiol (hyperthyroid 237 ± 63 *vs.* euthyroid 99 ± 11 (pmol/L), $p < 0.01$), LH (hyperthyroid 24 ± 6 *vs.* euthyroid 8.8 ± 2.3 (IU/L), $p < 0.001$], and FSH [hyperthyroid 18 ± 6.1 *vs.* euthyroid 6.8 ± 2.4 (IU/L), $p < 0.01$] in patients affected by Graves' disease [62]. Clyde et al. explained that this was due to the increased binding capacity and affinity of testosterone-estradiol binding globulin in hyperthyroid status, and added that hormone levels return to normal values upon restoring euthyroidism [63]. Röjdmark et al. found that pituitary gonadotrophs became "hypersensitive" to exogenous gonadotropin releasing hormone (GnRH) with LH and FSH response significantly higher in hyperthyroid patients because Leydig cells respond more powerfully to exogenous GnRH [64].

In the study of gonads, only Krassas et al. reported a reduction in volume; in particular, 30% of hyperthyroid patients showed reduced size, which was restored after treatment [52].

Clyde et al. and Krassas et al. reported oligospermia or borderline low count with decreased motility in thyrotoxicosis restored with medical therapy [52,63]. Similar results were found by Kidd et al. [79].

Finally, Carani et al. reported a high prevalence of delayed ejaculation in hyperthyroid men, which reduced after thyroid hormone normalization from 50% to 15% [60]. Krassas et al. reported sexual dysfunction associated with decreased libido in 56.5% of thyrotoxic patients, which improved after 6 months of treatment for hyperthyroidism [52].

Discussion

The most recent Guidelines on Thyroid Disorders prior to and during Assisted Reproduction by the European Thyroid Association was published in 2021 [86]. The present narrative review aims to apply the aforementioned Guidelines, adding the newest knowledge from 2021 to today.

It is well known that female fertility is impaired by thyroid disfunction, in particular by hypothyroidism; by contrast, we are still in the dark in terms of its effect on men, as the data available is less illuminating [86]. A possible relationship has been reported between thyroid hormone impairment and male fertility, both in animal models and in humans; however, the precise effect on the pituitary-testicular axis, gonad structure, function, and sexual behavior are not completely clear. In fact, as *Giano Bifronte* revealed, some authors have reported that thyroid hormones are irrelevant to the male reproductive sphere [23,26,30,40,48,61,70–73,76,77,85], whereas other authoritative sources argue that they affect male fertility [22–64]. This issue becomes more relevant for all sub-fertile couples, and particularly for those applying for Assisted Reproduction.

The available studies on animal models suggested an impaired "sexual" behavior from dysthyroidism. It has been widely demonstrated that hypothyroidism causes hypergonadotropic hypogonadism in rats, restored with the introduction of L-T4 therapy [22–26]. The most convincing explanation suggests that hormonal and testicular impairment is due to testicular oxidative stress, DNA damage and apoptotic activity [29]. In hypothyroid mice, reduced libido is observed along with a significant decrease of daily and total sperm production, as well as altered sperm characteristics compromising the

fertilization process [29,35–40]. These data were recently confirmed by Panahandeh et al. showing that hypothyroidism directly impairs semen parameters, whereas maternal hypothyroidism has no significant effect on gonad function in offspring [87]. Less evidence is available about the relationship between hyperthyroidism and fertility. In animal models, thyrotoxicosis seems associated with gonadotropin alterations and testicular oxidative stress, but the extent of its impact on fertility is yet to be demonstrated.

Referring to humans, the evidence on male subfertility and thyroid diseases is limited [86]. Nevertheless, there is a known, close correlation between radioactive iodine treatment for thyroid malignancy and sperm quality and fertility. For this reason, the recent guidelines suggest that sperm banking should be offered in cases involving multiple doses of radioactive iodine [86]. It is also conceivable that thyroid hormones may influence male fertility both prenatally and postnatally [88,89]. Indeed, it has been reported that hypothyroidism could lead to hypergonadotropic hypogonadism, which is in turn associated with testicular involution causing reduced sperm quality and alterations in normal morphology [45–47,50,51,53,54]. Nevertheless, how and to what extent this may impair fertility is yet to be proven. Evidence of altered semen parameters correlated with hypothyroidism has been presented in terms of sperm count, motility, and morphology [47,50,51,53,54,61].

However, it is important to underline that hypothyroidism can impair pulsatile secretion of GnRH by prolactin increase, leading hypogonadotropic hypogonadism [86,90]. Although it is known that long-standing hypothyroidism can cause pituitary hyperplasia reversible by L-T4 treatment [91], males with primary hypothyroidism seldom exhibit elevated serum prolactin concentrations [90]. Anyway, prolactin levels should be always assessed in all hypothyroid patients to exclude a secondary hypogonadotropic hypogonadism [86].

By referring to autoimmunity, few data are available. Trummer et al. reported that elevated thyroid peroxidase antibodies were significantly correlated with pathozoospermia and asthenozoospermia [61]. Instead, Poppe et al. and Binjandi et al. found no association between infertility and other thyroid function tests or TPOAb positivity [66,81,85]. Moreover, only Poppe et al. showed that the prevalence of thyroid autoimmunity is comparable between men with normal and abnormal semen characteristics [81]. In light of this, Guidelines do not recommend screening for thyroid autoimmunity in men of subfertile couples [86].

For these reasons, the Guidelines on Thyroid Disorders prior to and during Assisted Reproduction by the European Thyroid Association clearly suggests "*screening for thyroid dysfunction (TSH) in men with ejaculation and erectile dysfunction and or altered semen parameters*" [86]. This suggestion is confirmed in the articles published after Guidelines by Zhao et al. and Rao et al. confirming higher DFI and poorer clinical outcome in assisted reproduction with an increase in TSH [58,59]. On the contrary, hyperthyroidism seems to be associated with higher levels of testosterone due to an increase in sex hormone binding globulin [62,63], but few data are reported on sperm impairment and no conclusions can be drawn.

In conclusion, hypothyroidism and hyperthyroidism could cause ejaculation and erectile dysfunction, but with little clinical impact. Guidelines recommend screening for thyroid disorders only in men with ejaculation and erectile dysfunction or with altered semen parameters, but not in the men in sub-fertile couples.

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