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REVIEW ARTICLE

The impact of thyroid diseases starting from birth on reproductive function

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Abstract

The aim of this review is to provide relevant information regarding the impact of thyroid disease, starting from birth and mainly concerning hyperthyroidism and hypothyroidism, on reproduction. Hyperthyroidism occurs much less commonly in children than hypothyroidism, with Graves' disease (GD) being the most common cause of thyrotoxicosis in children. Children born with neonatal GD have no defects in the reproductive system that could be related to hyperthyroidism. Current treatment options include antithyroid drugs (ATD), surgery, and radioactive iodine (RAI). In males, normal thyroid function seems important, at least in some parameters, for maintenance of semen quality via genomic or non-genomic mechanisms, either by locally acting on Sertoli cells, Leydig cells, or germ cells, or by affecting crosstalk between the HPT axis and the HPG axis. Sexual behavior may also be affected in thyroxic men, although many of these patients may have normal free testosterone levels. In women, menstrual irregularities are the most common reproduction-related symptoms in thyrotoxicosis, while this disorder is also associated with reduced fertility, although most women remain ovulatory. An increase in sex hormone-binding globulin (SHBG) and androgens, thyroid autoimmunity, and an impact on uterine oxidative stress are the main pathophysiological mechanisms which may influence female fertility. Thyroid hormones are responsible for normal growth and development during pre- and postnatal life, congenital hypothyroidism (CH) being the most common cause of neonatal thyroid disorders, affecting about one newborn infant in 3500. The reproductive tract appears to develop normally in cretins. Today, CH-screening programs allow for early identification and treatment, and, as a result, affected children now achieve normal or near-normal development. Hypothyroidism in males is associated with decreased libido or impotence. Although little is currently known about the effects of hypothyroidism on spermatogenesis and fertility, it has been established that sperm morphology and motility are mainly affected. In women of reproductive age, hypothyroidism results in changes in cycle length and amount of bleeding. Moreover, a negative effect on fertility and higher miscarriage rates has also been described.

Keywords Thyroid disease · Menstrual disturbances · Hyperthyroidism · Hypothyroidism · Pediatric thyroid disease

Introduction

Although it was long thought that the gonads were unresponsive to thyroid hormones (THs), in the 1990s, TH receptors were detected in human and rat testis throughout the lifespan [1], and, over the past few decades, it has been established that, through these receptors, THs regulate the maturation and growth of the testes and control Sertoli cell and Leydig cell proliferation and differentiation during testicular development [2]. Moreover, studies have shown that thyroid dysfunction results in altered sex hormone levels, impaired testicular function, and eventually infertility [3–5].

The aim of this review is to discuss relevant information regarding the impact of thyroid disease, starting from birth and concerning mainly hyperthyroidism and hypothyroidism, on reproduction. In order to collect all relevant information, an extensive search in the PubMed and SCOPE databases was conducted for pertinent publications in the English language of the last 30 years.

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Thyrotoxicosis

Childhood hyperthyroidism

Hyperthyroidism occurs much less commonly in children than hypothyroidism. In children, the most common cause of thyrotoxicosis is Graves' disease (GD), which is characterized by diffuse goiter, hyperthyroidism, and, occasionally, ophthalmopathy [6, 7]. Other causes of childhood thyrotoxicosis include toxic nodules, toxic multinodular goiters, acute and subacute thyroiditis, and the ingestion of thyroid hormone [6, 7]. Hyperthyroidism is associated with excessive activity, tremor, tachycardia, weight loss, accelerated linear growth and advanced puberty, impaired skeletal mineralization, and menstrual disturbances, these being mainly amenorrhea and polymenorrhea [6, 7]. Current treatment options include antithyroid drugs (ATD), surgery, and radioactive iodine (RAI).

Thyrotoxicosis in males and reproduction

Hormonal changes

Thyroid hormone regulates the synthesis of two sex hormone-binding (SHB) proteins [8], namely, sex hormone-binding globulin (SHBG), a glycoprotein synthesized by hepatocytes, and androgen-binding protein(ABP), synthesized by the Sertoli cell [9]. ABP maintains the necessary levels of intratesticular androgen for germ cell maturation and differentiation. In rats and in humans, SHBG and ABP have the same amino acid sequence, as they are encoded by the same SHBG gene, though they differ in carbohydrate content and structure (glycosylation) [9–11].

An increase in SHBG has been a feature consistently associated with thyrotoxicosis, which state leads to increased circulating levels of total testosterone (T) and a reduction in the metabolic clearance rate of T [12, 13]. By contrast, free T concentrations usually remain normal, although bioavailable T was found to be subnormal in hyperthyroid males in one study [14]. Total and free estradiol (E_2) concentrations may be elevated and, consequently, the free T/free E_2 ratio can be lower in hyperthyroid males compared to normal individuals [14–18]. Relative free E_2 elevation may contribute to the higher incidence of gynecomastia and decreased libido observed in hyperthyroid males [19, 20]. Another consistent finding has been that luteinizing hormone (LH) and follicle-stimulating hormone (FSH) responses to gonadotropin-releasing hormone (GnRH) administration are exaggerated in hyperthyroid males, contrasting with a blunted response of Leydig cells to human chorionic gonadotropin (hCG) administration, as assessed by serum T responses [16–18]. Such abnormalities of the hypothalamic-pituitary-gonadal (HPG) axis are significantly correlated with increased serum thyroxine (T_4) levels. They are reversible with restoration of the euthyroid status, so that no treatment of these TH-induced abnormalities is required (Table 1). The role of THs in testicular development and spermatogenesis and the possible interaction between HPG and the hypothalamic-pituitary-thyroid (HPT) axis are depicted in Fig. 1.

Spermatogenesis and fertility in thyrotoxicosis

It is believed that thyroid hyperfunction may affect male reproductive function.

Effects of thyrotoxicosis on semen quality have been the subject of only a few studies, with oligospermia, decreased motility, and low sperm density being the main findings in older studies [14, 21–23]. In a more recent, controlled, prospective study [19], 23 thyrotoxic males and 15 healthy controls were investigated via semen analysis both before and 5 months after restoration of euthyroidism by methimazole (MMZ) treatment only (in 14 patients) or MMZ plus ^{131}I (in 9 patients). Total fructose, zinc (Zn), and magnesium (Mg) concentrations were also measured in seminal plasma in 16 of the 23 patients. The results indicated that mean semen volume was within the normal range in thyrotoxic patients, but mean sperm density was lower, though this was not statistically significant when compared to controls. A similar trend was found on analysis of sperm morphology, namely, mean sperm motility was lower in thyrotoxic males when compared to controls. After treatment of thyrotoxicosis, both sperm density and motility improved, although sperm morphology did not change. The type of treatment employed (MMZ alone or MMZ plus ^{131}I) had no impact on sperm count or morphology. Mean values for seminal plasma fructose, Zn, and Mg concentrations did not differ between controls and patients, before and after restoration of euthyroidism, and the values did not correlate with sperm parameters or with TH levels measured while the patients had thyrotoxicosis [19].

Mendeluk et al. [24] confirmed Romano's results [25] in humans. They showed that the addition of T_4 (0.002 μg/mL) to sperm preparation rapidly (after 20′) and significantly improved sperm motility, while also increasing the number of spermatozoa recovered by the "swim-up" technique. The authors hypothesized that T_4 acts directly on calcium channels, increasing calcium intake and cyclic adenosine monophosphate (cAMP) synthesis and leading to protein kinase A activation, which, in turn, causes vigorous flagellar movements resulting in so-called "hyperactivation". Overall, T_4 seemed to improve sperm motility more effectively than pentoxifylline, a traditionally used substance to increase sperm motility in asthenozoospermic samples. They concluded that T_4 appears to regulate positively sperm motility and hypothesize a non-genomic action of T_4 on spermogenesis.

The pathophysiological mechanism underlying testicular dysfunction resulting from thyroid disorders has not as yet been elucidated [26]. However, observations from several

reports, mainly in animals, suggest oxidative stress, lipid peroxidation [4, 20], and cellular apoptosis [27, 28] as major culprits. THs modulate oxidative stress as they significantly promote mitochondrial oxygen consumption [29]. Furthermore, because the testes are rich in polyunsaturated fatty acids and poor in antioxidant defense, they are more vulnerable to peroxidation injury than other tissues [30, 31].

Normal thyroid function seems important, at least in some parameters, for maintenance of semen quality via genomic or non-genomic mechanisms, either locally acting on Sertoli cells, Leyding cells, or germ cells, or by affecting crosstalk between the HPT axis and the HPG axis (Fig. 1).

An important question is whether male patients with infertility are affected by thyroid dysfunction more often than euthyroid males. Three studies utilizing patients from infertility clinics have examined this question. Lotti et al. [32] investigated a cohort of 163 men free of genetic abnormalities who were seeking medical care at an andrology clinic for couple infertility. All subjects underwent a complete andrological and physical examination, biochemical and hormonal assessment, scrotal and transrectal color-doppler ultrasound (CDUS), and semen analysis including seminal interleukin 8 (sIL-8) levels. Among the patients studied, 145 (88.9%) were euthyroid, 6 (3.7%) had subclinical hyperthyroidism, and 12 (7.4%) had subclinical hypothyroidism. No patient had overt hyper- or hypothyroidism. In univariate analysis, no associations between thyroid-stimulating hormone (TSH) or TH levels and sperm parameters were detected. Conversely, they observed positive associations among free triidothyronine (FT_3) and free T_4(FT_4) levels, ejaculate volume, and seminal fructose levels. In a multivariate model, after adjusting for confounders such as age, body mass index (BMI), smoking habits, sexual abstinence, calculated FT_4, prolactin (PRL), and sIL-8 levels, only the associations found for FT_3 levels were confirmed. When CDUS features were investigated, using the same multivariate model, they found positive associations between FT_3 levels and seminal vesicle (SV) volume, both before and after ejaculation. In addition, after adjusting for confounders, negative associations between FT_4 levels and epididymal body and tail diameters were found. No significant associations between TSH or TH levels and CDUS features of other organs of the male genital tract, including testis and prostate, were observed. Finally and most importantly, when the features of subjects with euthyroidism, subclinical hypo- and hyperthyroidism were compared, no significant differences in seminal or hormonal parameters were noted. Conversely, evaluating CDUS parameters, subjects with subclinical hyperthyroidism showed a higher difference between the SV longitudinal diameters measured before and after ejaculation when compared with subclinical hypothyroid men, even after adjusting for confounders ($p < 0.007$). All other male genital tract CDUS characteristics did not differ among

Table 1 Summary of hormonal changes in male and female patients with thyrotoxicosis

	Thyrotoxicosis Males	Thyrotoxicosis Females
SHBG	↑	↑
E_2	N or ↑	↑
Estrone	—	↑
Production rate of estrogens	—	→
Metabolic clearance rate of estrogens or androgens	↓	↓
Free E_2	↑	→
Testosterone	↑	↑
Δ4-androstendione	—	↑
DHEA	↑	↑
Free testosterone	→	—
Bioavailable testosterone	↑	—
Convertion of testosterone to Δ4-androstendione	↑	→ or ↑
Androgen conversion to estrone	↑	↑
Progesterone	↑	↓ or →
LH	↑ or →	↑ or →
FSH	↑ or →	↑ or →
After GnRH	↑	↑
LH	↑	↑
FSH		

SHBG sex hormone-binding globulin, *E_2* estradiol, *DHEA* dehydroepiandrosterone, ↑ increase, ↓ decrease, → no change, *N* normal, — not available, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *GnRH* gonadotropin-releasing hormone

groups [32]. These data support a positive effect of TH on SV size and a permissive role in SV volume before and after ejaculation, likely through an action on SV and epididymal contractility. This study has major limitations. First, the number of patients with subclinical diseases was small. Second, it concerned only patients from a region of Italy, and, third, it was a cross-sectional analysis. Thus, the above results do not comprise a systematic evaluation of thyroid function in males of infertile couples.

Vaghela et al. [33] investigated whether hyper- and hypothyroidism exerted an impact on human semen quality and reproductive function, as well as reproductive hormone levels. A total of 351 subjects attending an infertility clinic were recruited. THs, reproductive hormones, and semen quality were measured. The subjects were grouped on the basis of TH profile as hyper-, hypo-, and normal thyroid function with respect to semen quality and reproductive hormone levels. Of the total, 45 subjects (12.82%) were hypothyroid, 39 (11.11%) were hyperthyroid, and the remaining 267 (76.05%) had normal thyroid function. Mean sperm count was lower in hyper- and hypothyroid subjects in comparison to controls. Fast and total progressive motility was significantly decreased and nonmotile sperm was significantly higher in the hyper- and hypothyroid groups. Sperm morphology did not differ between the groups, although the normal percentage was slightly higher in the euthyroid group. They concluded that THs do play a role in male reproduction.

However, it is of note that in the study by Lotti et al. [32], patients with thyroid dysfunction had mild disease, i.e., all were subclinical, while in that of Vaghela et al. [33], the patients had overt disease, this possibly explaining the difference between their study results.

Trummer et al. [34] investigated 305 men with idiopathic infertility. They measured TSH, FT_4, FT_3, antithyroid peroxidase (antiTPO) and antithyroglobulin (antiTG) antibodies, and antiTSH receptor antibodies (TRAK). They reported the prevalence of thyroid disease as well as the correlation with gonadal hormones and the results of semen analyses. Subclinical thyroid dysfunction (abnormal basal TSH, FT_4, or FT_3) was diagnosed in 11.5%, while 10 patients (3.3%) had pathologic TSH (nine had elevated TSH and one decreased TSH). No correlation between thyroid dysfunction and semen parameters was detected. TSH correlated significantly with PRL ($p < 0.001$). Antithyroid antibodies were elevated in 7.5% of patients. Elevated antiTPO antibodies were weakly correlated with pathozoospermia ($p = 0.036$) and asthenozoospermia ($p = 0.049$). They concluded that subclinical thyroid dysfunction had no impact on semen parameters, but that underlying autoimmunity might play a role. In patients with elevated antiTPO antibodies, sperm abnormalities should be considered. Antisperm antibodies were not measured in this study [34].

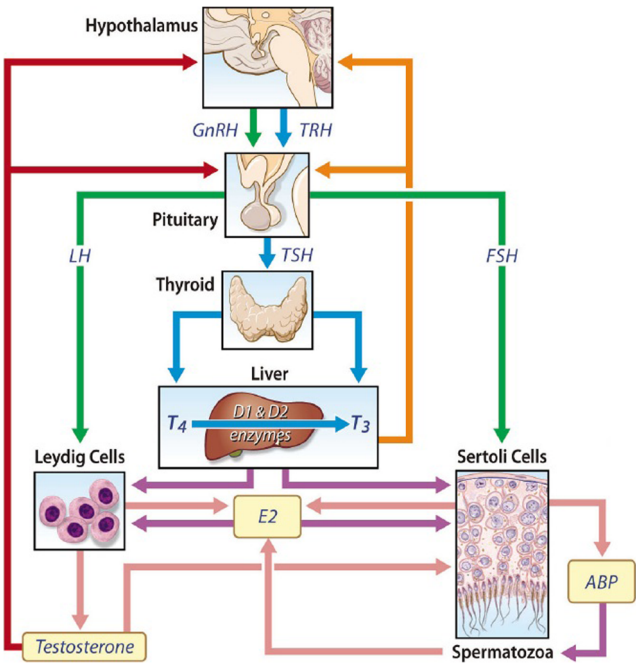

Fig. 1 Summary of the role of the thyroid in testicular development and spermatogenesis and possible interaction between the hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-thyroid (HPT) axes: all arrows denote the production of a molecule or an action on a specific tissue/organ. The HPG axis is coded with green (stimulatory) and red (inhibitory) arrows. From Rajender S. et al. 2011 [142], with permission

Sexual behavior and thyrotoxicosis

Sexual behavior may also be affected in thyrotoxic men, although many of these patients may have normal free T levels. Despite elevated total T and usually normal basal FT_4 concentrations in hyperthyroid men, anecdotal reports suggest that erectile dysfunction (ED) is observed frequently, with prevalence rates reaching 70% [35]. Carani et al. [36] investigated 34 adult men with hyperthyroidism in a prospective study. The patients were screened for hypoactive sexual desire (HSD), ED, premature ejaculation (PE), and delayed ejaculation (DE) at presentation and again 8 to 16 weeks after restoration of the euthyroid state. It was observed that hyperthyroidism was associated with a marked increase in the prevalence of HSD, DE, PE, and ED, which tended to resolve after restoration of euthyroidism. The most striking effect was the marked decrease in PE from 50 to 15%, the latter being the rate found in the general population.

Using the Sexual Health Inventory for Males (SHIM), the impact of thyrotoxicosis on male sexual health was evaluated in 27 hyperthyroid male patients (and 71 controls) who participated in a prospective, controlled study [37]. The patients were asked to respond to the SHIM five-item questionnaire before and 1 year after initiation of treatment. A global score between 25 and 22 was considered normal, between 21 and

11, it was indicative of mild to moderately severe ED, and 10 or less was diagnostic of severe ED. The results showed that 70% of hyperthyroid patients had a SHIM score of 21 or less, compared with only 34% in control individuals completing the questionnaire ($p < 0.0001$). There was a positive correlation between serum FT_4 levels and SHIM scores ($p = 0.005$). Significant increases in SHIM scores occurred following the restoration of euthyroidism, suggesting that specific treatment for ED can be deferred in some hyperthyroid men.

Corona et al. [38] and the EMAS (European Male Ageing Study) group investigated the association between thyroid and erectile function in two different cohorts of subjects. The first was derived from the EMAS study, a multicenter survey performed on a sample of 3369 community-dwelling men aged 40–79 years (mean 60 ± 11 years). The second cohort was a consecutive series of 3203 heterosexual male patients (mean age 51.8 ± 13.0 years) attending the Andrology Clinic of the University of Florence (UNIFI) study. In the EMAS study, all subjects were tested for TSH and FT_4. TSH levels were checked in all patients in the UNIFI study and FT_4 only when TSH was outside the normal range. Overt thyrotoxicosis was found in 0.3 and 0.2% of the EMAS and the UNIFI study, respectively. In all patients of both studies, suppressed TSH levels were associated with ED. Overt hyperthyroidism was associated with an increased risk of severe ED (hazard ratio = 14 and 16 in the EMAS and UNIFI study, respectively; both $p < 0.005$ after adjusting for confounding factors). We recommend, as the above researchers also suggest, that the possibility of ED should be evaluated in all individuals with hyperthyroidism, though assessment of thyroid function cannot be recommended as routine practice in all patients with ED [38].

Finally, in a recent investigation [39], two separate patient samples with benign thyroid diseases were investigated. One, a cross-sectional sample, consisted of 754 women and 118 men, and the other, a longitudinal sample, consisted of 358 women and 74 men. For further details, please see reference [39].

Treatment of thyrotoxicosis with radioactive iodine in male adults

I^{131} is widely used in the treatment of hyperthyroidism [40]. Because of potential mutagenic effects of radiation on the gonads, there is legitimate concern regarding possible side effects of I^{131} administration on reproductive function in young men. Reassuringly, several studies have reported normal reproductive performance in men with thyrotoxicosis after I^{131} therapy. I^{131} therapy is therefore justifiably used by clinicians in the treatment for thyrotoxicosis in adults of all ages [41–44].

Ceccarelli et al. [45] evaluated a series of 15 thyrotoxic male patients before and at different times after I^{131} therapy. Patients received I^{131} activity in doses from 370 to 851 MBq according to the formula: estimated mass of the whole thyroid or the nodule by ultrasound (g) × 7.4 MBq/radioactive iodine uptake. Mean basal FSH concentrations were within normal limits and did not change after therapy, although two patients showed substantial FSH increases lasting for 1 year (albeit one was already mildly hypogonadal before treatment). Asthenospermia was observed before I^{131} treatment in ten of the 15 patients and sperm quality was significantly improved in five of these ten patients within 1 year after therapy. Sperm morphology did not show any significant modification. LH was normal and did not change after I^{131} therapy, whereas T levels were reduced 45 days after I^{131} therapy and returned to basal values 1 year later. The total radiation dose to the testes was 39 ± 14 microGy/MBq (range 27–86 microGy/MBq) and may result in small and transient damage to both to the germinal epithelium and Leydig cells.

Thyrotoxicosis in females and reproduction

In 1905, Kendle [46] for the first time reported the development of precocious puberty in a young girl with severe hypothyroidism. It has since been largely confirmed that significant associations also exist between thyroid disorders and abnormalities of the female reproductive system. Specifically, thyrotoxicosis in females has been well documented to produce variable degrees of gonadal dysfunction [14, 15, 47–50].

Hormonal changes

As in men, thyrotoxicosis results in increased serum levels of SHBG. Furthermore, total estrogen levels may be 2- to 3-fold higher in hyperthyroid women (compared to normal women) during all phases of the menstrual cycle [51]. Whether the increased estrogen levels are entirely attributable to increases in SHBG or whether there is an actual increase in free E_2 levels (as is the case in hyperthyroid males) remains to be determined.

Changes also occur in androgen metabolism in hyperthyroid women. Mean plasma levels of T and androstenedione increase, and the production rate of T and androstenedione is significantly elevated among women with hyperthyroidism, while the conversion ratio of androstenedione to estrone, as well as of T to E_2, is increased in this population group [2, 52, 53].

Akande and Hockaday [54] and Pontikides et al. [55] found that mean LH levels in both the follicular and luteal phases of the menstrual cycle are significantly higher in hyperthyroid women than in normal women. Table 1 summarizes the hormonal changes seen in females with thyrotoxicosis.

Zähringer et al. [18] studied seven women with GD and six controls, sampling blood every 10 min for an 8-h period during the early follicular phase of the menstrual cycle. LH secretion was increased, whereas the pulsatile characteristics of LH and FSH secretion did not differ in patients when

compared to controls. However, LH peaks may be absent in patients with severe menstrual disturbances, such as amenorrhea.

Serum LH levels decrease to normal after a few weeks of treatment with ATD [56]. Baseline FSH levels may be increased or normal, although data are limited [55, 57, 58]. The mechanism underlying the increase in serum LH and FSH in hyperthyroid women is as yet unclear. The same authors [57, 58] reported that hyperthyroxinemia results in an augmented gonadotropin response to GnRH.

Menstrual disturbances in thyrotoxicosis

Menstrual irregularities are the most common reproduction-related symptoms in women with thyrotoxicosis. Children born with neonatal GD have no defects in the reproductive system that could be related to hyperthyroidism [59]. Hyperthyroidism occurring before puberty was reported to delay sexual maturation and the onset of menses. In contrast, the mean age at menarche was reported to be slightly advanced in hyperthyroid girls compared to their healthy controls [60].

Much confusion still exists among physicians as concerns the definition of the different terms used to characterize menstrual abnormalities. Nevertheless, the following terms continue to be accepted and in general use. Oligomenorrhea, polymenorrhea, and amenorrhea define the duration of the menstrual cycle, whereas hypomenorrhea, hypermenorrhea, and menorrhagia define the amount of menstrual flow. Thus, oligomenorrhea was identified [61] when the interval between two periods was more than 35 days, polymenorrhea less than 21 days, and amenorrhea in women with previously normal periods when there was no menstruation for more than 3 months [61, 62]. Hypomenorrhea was arbitrarily defined as more than a 20% decrease in menstrual flow, hypermenorrhea as more than a 20% increase in menstrual flow in comparison with the previous periods, and menorrhagia as heavy menstrual bleeding [49].

Amenorrhea is one of the earliest known clinical changes associated with hyperthyroidism and was reported by von Basedow in 1840 [63]. Since then, amenorrhea and a number of other menstrual cycle changes, including oligomenorrhea, hypomenorrhea, and anovulation, have been observed. Biochemical and hormonal abnormalities, nutritional disturbances, and emotional upheavals that are commonly associated with hyperthyroidism may, individually or in combination, be the cause of these menstrual disturbances [2].

The frequency of menstrual abnormalities differs in more recent studies compared with earlier reports. Oligomenorrhea, polymenorrhea, and amenorrhea are the most frequent symptoms (60% in total) in old studies [58, 64–66], while a more recent, prospective, controlled study found abnormalities in only 21.5%. None of the patients had amenorrhea. In a similar number of normal controls, 18 (8.4%) had irregular periods and of these 12 had oligomenorrhea [48].

Although these findings indicate that menstrual disturbances are 2.5-fold more frequent in thyrotoxicosis than in the normal population, they are still lower than previously described, and they support the current notion that, due to better medical care and public awareness, thyroid disturbances are likely diagnosed much earlier than in the past, when the symptoms are still mild. It has also been observed that smoking aggravates the development of menstrual disturbances in thyrotoxicosis, as it does in GO [67]. Fifty percent of thyrotoxic patients with abnormal menstruation were smokers, compared to only 19% of thyrotoxic patients with normal periods [48]. Moreover, patients with menstrual disturbances had higher total T_4 levels, which was also observed in smokers with abnormal periods. Thus, total T_4 levels appeared to be an important factor related to the development of menstrual abnormalities in thyrotoxicosis, while no difference regarding T_4 levels was found between smokers and non-smokers, this being in contrast to total T_3, for which no such correlation was found [48].

In a study from Japan, Kakuno et al. [68] investigated 586 patients with GD, all of reproductive age. They found 107 patients (18.3%) with menstrual disturbances, the prevalence being statistically insignificant compared to healthy controls [25 out of 105 (23.8%)]. However, when they subdivided the patients into four groups on the basis of serum levels of FT_4 (NR = 0.7–1.6 ng/dL, less than 4, 4 and higher, and controls) and FT_3 (NR = 1.7–3.7 pg/mL, less than 30, 30 and higher, and controls), they found significant differences between the two FT_3 subgroups (less than 30, and 30 and higher) as regards secondary amenorrhea [1 out of 424 (0.2%) vs. 4 out of 162 (2.5%)] and the total number of menstrual disturbances [69 (16.3%) vs. 38 (23.5), $p < 0.05$]. Additionally, the prevalence of hypomenorrhea (3.7%) in the more toxic group was significantly higher in comparison to healthy controls (0%). They concluded that their data are similar to those of the earlier report by Krassas et al. [48].

Fertility in subclinical and overt hyperthyroidism

Infertility is the inability to conceive after 1 year of regular intercourse without contraception [69, 70]. This definition was based on the study of 5574 women engaging in unprotected intercourse who ultimately conceived (1946–1956). Among these women, 50% conceived within 3 months, 72% within 6 months, and 85% within 12 months [71]. Two more recent prospective, population-based studies have shown that 50% of healthy women became clinically pregnant during the first two cycles and 80 to 90% during the first 6 months [72, 73]. The prevalence of infertility was estimated to range between 10 and 15% and has remained stable over recent decades [71]. Thirty-five percent of couples' inability to

conceive is related to female causes, 30% to a male factor, 20% to both causes, and the remaining 15% is considered to be idiopathic, when the spermogram and female work-up are both normal [74, 75].

Thyrotoxicosis in women has been associated with reduced fertility, although most thyrotoxic women remain ovulatory, as determined by endometrial biopsies [65]. Joshi et al. [66] reported that three of 53 thyrotoxic women (5.8%) had primary or secondary infertility.

The prevalence of hyperthyroidism in infertile women was studied prospectively by Poppe et al. [76]. An early publication reported that the prevalence of suppressed serum TSH (a symptom of both subclinical hyperthyroidism and overt hyperthyroidism) was 2.1% (nine of 438 women of infertile couples), comparable with a prevalence of 1.5% of women in the general population [77]. Poppe et al. found that subclinical hyperthyroidism was present in seven out of the nine patients, and two had overt hyperthyroidism. Four of these nine patients with suppressed serum TSH had positive thyroid antiTPO antibodies. Thyroid-stimulating immunoglobulins were not measured. When antiTPO antibodies were positive, suppressed serum TSH was more frequent in all infertile women compared to women in the same groups without positive antiTPO antibodies (7 vs. 1%; $p < 0.05$), which means that patients with autoimmune thyroid disease are more prone to become thyrotoxic [76].

Quinto-Moro et al. [78] examined infertility in a cross-sectional study of 193 women aged 18–50 years with GD. The infertility was defined as 12 months of unprotected sexual intercourse without conception. They found that the prevalence of infertility was 52.3% in GD. Mean age at diagnosis of GD was 36.5 years. The mean number of pregnancies was lower in women who were 35 years old or younger at diagnosis and was always lower following diagnosis of the disease, irrespective of age.

Regarding pathophysiological mechanisms and infertility, one important factor which affects female fertility is a significant increase in serum SHBG, which in turn increases androgens, their conversion rates, and E_2 (Table 1). Moreover, thyroid hormones have a direct effect on the reproductive system.

A second mechanism that could account for infertility in GD is through thyroid autoimmunity, with autoimmune processes causing subfertility or pregnancy loss [79]. Notably, it was also proposed that while thyroid antibodies merely reflect a different level of autoimmunity, other autoimmune processes cause subfertility or pregnancy loss [79].

Apart from these theories, thyroid autoimmunity has been directly linked with other causes of infertility, such as endometriosis, ovarian failure, and polycystic ovary syndrome [80, 81]. Thyroid antibodies are present in follicular fluid [79] and may have cytotoxic effects, damaging the oocyte and thus leading to poorer oocyte quality, a possibility which still lacks direct evidence [79]. It has also been suggested that excessive levels of THs may have an impact on uterine oxidative stress, thereby influencing fertility [82].

Radioiodine therapy for hyperthyroidism and reproduction

I^{131} is widely used for the treatment of hyperthyroidism and differentiated thyroid cancer. In hyperthyroidism, the average administered activity of I^{131} is approximately 10 mCi (370 MBq), whereas for cancer, the doses given are 10 to 20 times higher, exposing the gonads to a higher radiation dosage. In thyrotoxic women treated with 10 mCi of I^{131}, the genetic risk is negligible and the reproductive health of treated women and the health of their progeny appear to be normal [42]. Therefore, the use of I^{131} for treatment of hyperthyroidism does not have a detrimental effect on the gonads, although, to be on the safe side, it is advisable to avoid conception for approximately 6 months after the administration of I^{131}[49]. This is in accordance with the current American Thyroid Association guidelines.

Hypothyroidism

Congenital hypothyroidism and neonatal thyroid screening

Thyroid hormones are responsible for normal growth and development during pre- and postnatal life. They are also essential for normal brain development. Congenital hypothyroidism (CH), the most common endocrine neonatal disorder, is caused by a defect in thyroid structure or hormonogenesis. It affects about one newborn infant in 3500, though in some countries, higher incidences have been reported. CH, if not treated immediately after birth, causes lifelong cognitive motor and somatic deficits. Thanks to CH-screening programs, initiated in the 1970s to ensure early identification and treatment in order to prevent mental retardation, affected children now show normal or near-normal physical, neurological, and psychological development. With screening, the developmental prognosis is considerably improved, though follow-up studies still report developmental delay compared to controls [83].

There are limited data available showing the long-term effects of early treatment of CH on social, emotional, and behavioral outcomes. However, in cases in which treatment is delayed, among other symptoms, menstrual irregularities, obesity, and psychological disturbances have been reported as consequences in later life.

Effects of hypothyroidism in early life in males

Congenital hypothyroidism is not associated with abnormal development of the male reproductive tract [84]. This is not

surprising given that small but adequate amounts of maternal THs cross the placenta to satisfy fetal demands [85]. When adequately treated with levothyroxine (LT_4), boys with CH progress through puberty normally and at the appropriate time [86, 87]. Untreated hypothyroidism in early childhood can result in delay in sexual maturation and delayed puberty, which can be reversed by TH therapy [88]. However, in rare cases, severe juvenile hypothyroidism may be associated with precocious pseudopuberty [46, 84]. External genitalia develop early, but without axillary or pubic hair, and there is often macro-orchidism [89]. The serum gonadotropins are usually normal, and serum T is in the pre-pubertal range. It is proposed that cross-reactivity of very elevated TSH serum levels with the FSH receptor may be responsible for this rare phenomenon [90].

Chronic lymphocytic thyroiditis [Hashimoto's thyroiditis (HT)] is the most common cause of acquired hypothyroidism in children and adolescents. It is an autoimmune disease closely related to GD. Some children present with an asymptomatic goiter, whereas others may present with mild tenderness or a sensation of fullness in the anterior neck. Short stature and alterations in GH secretion and action [91], bone age delay, myopathy, dry and cold skin, and delay in sexual maturation are some of the main symptoms of the disease.

GD occurs in 1% of the pediatric population, with the disease having a predilection for females (at a rate of 4 to 7 times), while a family history of the disease is present in 30–40% of patients [92]. Prevalence increases with age, and patients may be euthyroid, hypo-, or hyperthyroid. Ophthalmopathy may occur in HT in the absence of GD. Some children develop hypothyroidism gradually over months or years, and some adolescent patients achieve spontaneous remission [92].

Genetic susceptibility is present in HT. Associations have been observed between HT and HLA-DR3, DR4, or DR5. Familial clusters of HT are common, the incidence in siblings or parents of affected children possibly being as high as 25%. AntiTPO antibodies are demonstrable in the sera of 90% of children with HT. TSH receptor-blocking antibodies are frequently present, especially in hypothyroid HT patients, and are believed to be the cause of hypothyroidism [92].

The aim of treatment of hypothyroidism in the pediatric population is to achieve normal growth and neurological and pubertal development. The drug of choice is Na LT4.

Hypothyroidism in males

Hormonal changes

Hypothyroidism is associated with a variety of endocrine disorders and hormonal changes, depending on the patient's age and severity of the disease [92, 93].

Hypothyroidism is less common in men than in women and has a less clear-cut effect on reproductive function [50, 77, 94–98]. TH physiology is presented in Fig. 2. Primary hypothyroidism results in a decrease in SHBG and total T concentrations, while free T concentrations are reduced in approximately 60% of males with hypothyroidism (Table 2). In a prospective study of ten men with primary hypothyroidism, plasma free T levels were low and increased after starting LT_4 therapy [99]. It has been reported that TH administration to hypothyroid men induces a rise in both SHBG and total serum T [100].

Although PRL elevation is the common link between primary hypothyroidism and gonadal dysfunction in females, males with primary hypothyroidism seldom exhibit elevated serum PRL concentrations, excepting those with long-standing and severe hypothyroidism. Severe primary hypothyroidism may result in pituitary hyperplasia in men with hyperprolactinemia and hypogonadotropic hypogonadism [101]. Replacement therapy with TH reverses these abnormalities [35, 101, 102]. The mechanism underlying hypogonadism associated with primary hypothyroidism without PRL elevation has been sought. Most studies indicate that hypothyroid men with concomitant hypogonadism have normal LH and FSH levels, suggesting that the primary defect is not in the Leydig cells, but, instead, presumably results from a defect at the hypothalamic and/or pituitary level. Blunted gonadotropin responses to GnRH support the notion that primary hypothyroidism impairs the ability of the pituitary gland to respond to GnRH [17]. Another finding that supports the above notion is that hCG produces an exaggerated response of serum T in these patients, which is in contrast to what would be expected if the primary defect was in Leydig cells. The latter may also be explained in part by the impaired clearance of the above hormones and drugs with which hypothyroidism is associated [103, 104]. The net consequence of an impaired HPG axis is that free T levels may be subnormal in men with primary hypothyroidism. Dehydroepiandrosterone (DHEA), DHEA-sulfate (DHEA-S), estrogenic metabolites of DHEA (androstenediol and its sulfate), and pregnenolone sulfate are decreased in the serum of men with hypothyroidism, compared to normal controls [105].

Sexual dysfunction, spermatogenesis, and fertility

Hypothyroidism is associated with decreased libido or impotence [106, 107]. In the studies by Carani et al. [36] and Krassas et al. [37], sexual behavior was investigated in males with hypothyroidism, both before and after thyroid hormone treatment. In the first study [36], 14 adult hypothyroid males showed an overall 64% prevalence of HSD, DE, and ED, and 7% for PE. After euthyroidism was restored, half of the patients with DE had no complaints, ED almost disappeared, and patients with HSD had significant improvement in symptoms

while on therapy. In the second study [37], 44 hypothyroid patients and 71 controls were investigated using the SHIM questionnaire. A global score between 25 and 22 was considered normal, between 21 and 11 it was indicative of mild to moderately severe ED, and 10 or less was diagnostic of severe ED. Thirty-seven of 44 hypothyroid patients (84%) had a SHIM score of 21 or less, compared with only 24 of 71 controls (33.8%; $p < 0.0001$). Thirteen patients (35.1%) with ED had a SHIM score of 10 or less, indicative of severe ED, compared with only 6 controls (25%) ($p < 0.01$). Negative correlations were found between the SHIM scores and serum TSH levels ($p < 0.001$). After treatment of hypothyroidism, a significant increase in SHIM scores was noted. The conclusion of this study was that ED was common in hypothyroid males, and that treatment restored normal erectile function, indicating that screening for thyroid dysfunction is recommended in all men presenting with ED.

Nikoobakht et al. [108] investigated 24 patients with hypothyroidism and 66 normal individuals. Serum levels of TSH, T_4, FSH, LH, PRL, and T were measured and semen analysis was conducted in all participants. Erectile function was evaluated using the International Index of Erectile Function (IIEF-5) questionnaire. They concluded that hypothyroidism adversely affected erectile function and sperm parameters, including sperm count, morphology, and motility. The authors suggested that assessment of thyroid status is recommended in patients with sperm abnormalities and/or erectile dysfunction.

Little is known about the effects of hypothyroidism on human spermatogenesis and fertility. Older studies with small numbers of patients proposed that hypothyroidism may have an effect on sperm motility, seminal volume, and sperm count [109–113]. It appears that short-term post-pubertal

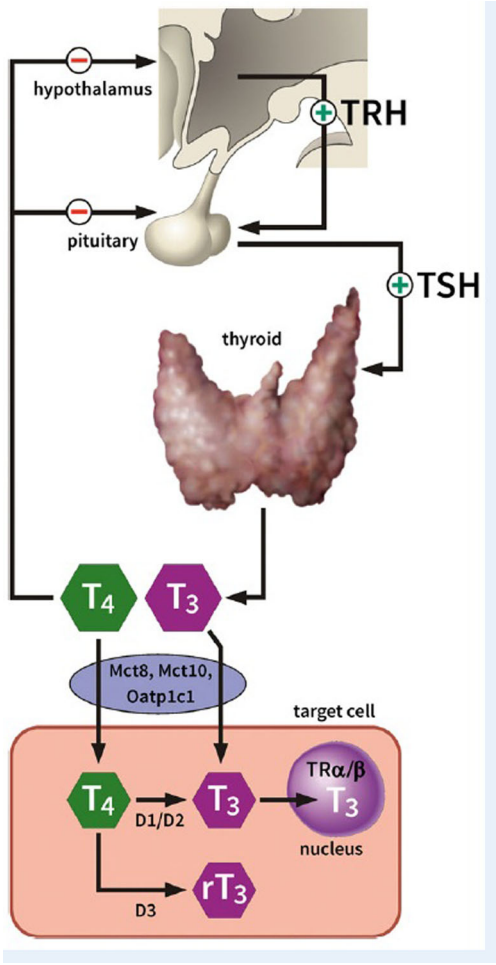

Fig. 2 Thyroid hormone physiology. Circulating thyroid hormone concentrations are regulated via a negative feedback system at the level of the hypothalamus and the pituitary. The production of thyroid hormone by the thyroid is regulated by thyroid-stimulating hormone (TSH) produced by the anterior pituitary, which itself is regulated by thyrotropin-releasing hormone (TRH) produced by the hypothalamus. Thyroid hormone circulates as the inactive prohormone thyroxine (T4) and as the active hormone triiodothyronine (T3). Thyroid hormone can enter target cells only by virtue of specific transporters (MCT8, MCT10, and OatpI cl). In target cells, thyroid hormone can be activated (T4 to T3) or inactivated (T4 to rT3 or T3 to T2), depending on the local activity of specific deiodinases (D1, D2, and D3). Subsequently, active T3 can bind to the nuclear thyroid hormone receptors (TR-alpha and TR-beta) and induce transcription. Reproduced from Vissenberg R et al. [79], with permission

Table 2 Hormonal changes in male and female patients with hypothyroidism

	Hypothyroidism	
	Males	Females
SHBG	↓ or N	↓
E_2	N	↓
Estrone	-	↓
Production rate of estrogens	-	→ or ↓
Metabolic clearance rate of estrogens or androgens	↓	↓
Free E_2	-	N
Testosterone	↓	↓
Δ4-androstendione	↓	↓
DHEA	↓	-
Free testosterone	↓	N
Bioavailable testosterone	-	-
Conversion of testosterone to Δ4-androstendione	↓	↑
Androgen conversion to estrone	-	-
Progesterone	-	↓ or →
LH	N	N
FSH	N	N
After GnRH	↓	↓
LH	↓	↓
FSH		

SHBG sex hormone-binding globulin, ↓ decrease, *N* normal, *E_2* estradiol, - not available, → no change, *DHEA* dehydroepiandrosterone, ↑ increase, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *GnRH* gonadotropin-releasing hormone

Reproduced from Krassas GE & Pontikides N[107]

hypothyroidism does not cause seminal alterations of sufficient intensity to impair male fertility.

The effects of hypothyroidism on male spermatogenesis were investigated in a more recent prospective, controlled study [114]. A total of 25 hypothyroid men and 15 normal individuals were investigated, with semen analysis, fructose and acid phosphatase measurements, teratozoospermia index (TZI), and the acridine orange test determined both before and 6 to 9 months after treatment with LT_4 [114]. The conclusion was that hypothyroidism had an adverse effect on human spermatogenesis, with sperm morphology the only parameter that was significantly affected.

Finally, an important question is whether male patients with infertility have hypothyroidism more often than euthyroid men. Two studies utilizing patients from infertility clinics have examined this question. Lotti et al. [32] investigated a cohort of 163 men free of genetic abnormalities seeking medical care at an andrology clinic for couple infertility. All subjects underwent a complete andrological and physical examination, biochemical and hormonal assessment, scrotal and transrectal CDUS, and semen analysis including sIL-8 levels. Among the patients studied, 145 (88.9%) were euthyroid, six (3.7%) had subclinical hyperthyroidism, and 12 (7.4%) had subclinical hypothyroidism. No patient had overt hyper- or hypothyroidism. In univariate analysis, no associations between TSH or TH levels and sperm parameters were observed. On the other hand, positive associations among FT_3 and FT_4 levels, ejaculate volume, and seminal fructose levels were noted. In a multivariate model, after adjusting for confounders such as age, BMI, smoking habits, sexual abstinence, and calculated FT_4, PRL, and sIL-8 levels, only the associations found for FT_3 levels were confirmed. When CDUS features were investigated, using the same multivariate model, they found positive associations between FT_3 levels and SV volume, both before and after ejaculation. In addition, after adjusting for confounders, negative associations between FT_4 levels and epididymal body and tail diameters were detected. No significant associations between TSH or TH levels and CDUS features of other organs of the male genital tract, including the testes and prostate, were found. Finally and most importantly, when the features of subjects with euthyroidism and subclinical hypo- and hyperthyroidism were compared, no significant differences in seminal or hormonal parameters were observed. Conversely, evaluating CDUS parameters, subjects with subclinical hyperthyroidism showed a greater difference between SV longitudinal diameters measured before and after ejaculation when compared with subclinical hypothyroid men, even after adjusting for confounders. All other male genital tract CDUS characteristics did not differ among groups [32]. These data support a positive effect of THs on SV size and a permissive role on SV volume before and after ejaculation likely through an action on SV and epididymal contractility. However, this study has a number of drawbacks. First, the number of patients with subclinical diseases is small. Second, it concerns only patients from a region of Italy, and third, it is a cross-sectional analysis. Thus, the above results do not support a systematic evaluation of thyroid function in males of infertile couples.

Vaghela et al. [33] investigated whether there was any impact of hyper- and hypothyroidism on human semen quality and reproductive levels. A total of 351 subjects attending a fertility clinic were recruited. Thyroid hormone levels, reproductive hormone levels, and semen quality were measured. The subjects were grouped on the basis of TH profile as hyper-, hypo-, and normal thyroid function with respect to semen quality and reproductive hormone levels. Of the total, 45 subjects (12.82%) were hypothyroid, 39 (11.11%) were hyperthyroid, and the remaining 267 (76.05%) had normal thyroid function. Mean sperm count was lower in hyper- and hypothyroid subjects compared to controls. Fast and total progressive motility was significantly decreased and non-motile sperms were significantly higher in the hyper- and hypothyroid groups. Sperm morphology did not differ between the groups, although the normal percentage was slightly higher in the euthyroid group. They concluded that THs have some role to play in male reproduction.

However, it is of note that in the study by Lotti et al. [32], patients with thyroid dysfunction had mild disease, all being subclinical, while in the study of Vaghela et al. [33], the patients had overt disease, which might explain the difference between the results of the two studies.

Trummer et al. [34] investigated 305 men with idiopathic infertility. Measuring TSH, FT_4, FT_3, antiTPO, antiTG antibodies, and TRAK, they reported a prevalence of thyroid disease in this group as well as a correlation with gonadal hormones and the results of semen analyses. Subclinical thyroid dysfunction (abnormal basal TSH, FT_4, or FT_3) was diagnosed in 11.5%, while ten patients (3.3%) had pathologic TSH (nine had elevated TSH and one decreased TSH). No correlation between thyroid dysfunction and semen parameters was detected. TSH correlated significantly with PRL. Antithyroid antibodies were elevated in 7.5%. Elevated antiTPO antibodies were weakly correlated with pathozoospermia and asthenozoospermia. They concluded that subclinical thyroid dysfunction had no impact on semen parameters, but that underlying autoimmunity might play a role. In patients with elevated antiTPO antibodies, sperm abnormalities should be considered. Antisperm antibodies were not measured in this study [34].

In summary, the data suggest that short-term hypothyroidism in adults has minimal effects on male reproductive function. Severe prolonged hypothyroidism, particularly when the onset occurs in childhood, may impair reproductive function. However, more studies are needed with larger numbers of patients to determine the effects of hypothyroidism on male reproductive function.

Pathophysiological mechanisms

Three major mechanisms are implicated in defective spermatogenesis. The first is a hormonal mechanism involving low levels of biologically active thyroid hormones, the second is Sertoli cell deficiency, and, finally, there is a third proposed mechanism which concerns T_3 levels. The latter are involved in the production of connexin 43, a constituent protein of gap junction [115]. Low levels of T_3 leading to connexin 43 alteration are believed to have an impact on spermatogenesis [116] through intracellular junctions, which play an instrumental role by allowing Sertoli cells to communicate with germ cells.

Hypothyroidism in females

Effects of hypothyroidism in early life

Given that the reproductive tract apparently develops normally in cretins, hypothyroidism during fetal life does not appear to interfere with the normal development of the reproductive tract. Hypothyroidism in prepubertal years generally leads to short stature and may result in a delay in sexual maturation [49]. An interesting syndrome, described by Kendle [46] and Van Wyk and Grumbach [117], may occasionally be seen, which is characterized by precocious menstruation, galactorrhea, and sellar enlargement in girls with juvenile hypothyroidism. This is probably due to a "spillover" effect, because TSH, PRL, FSH, and LH are all glycoproteins and may have overlapping actions at the receptor level. However, axillary and public hair is usually not affected because there is no pubertal increase in adrenal androgen production [49]. Therapy with LT_4 doses results in prompt alleviation of the symptoms.

Hormonal changes

Figure 3 presents the mechanism of action of thyroid hormone on the reproductive system. Hypothyroid women have decreased rates of the metabolic clearance of androstenedione and estrone and exhibit an increase in peripheral aromatization [118, 119]. The 5α/β ratio of androgen metabolites is also decreased in hypothyroid women, and there is an increase in excretion of 2-oxygenated estrogens [120]. Levels of SHBG are decreased, which results in decreased plasma concentrations of both total T and E_2, but their unbound fractions are increased. Alterations in steroid metabolism disappear when a euthyroid state is restored [121]. Gonadotropin levels are usually normal [122]. However, blunted or delayed LH responses to GnRH have been reported in some hypothyroid women [123, 124] (Table 2). When there is delayed LH response, serum PRL concentrations may be increased, this possibly being due to hypothalamic TRH increasing both TSH and PRL secretion. Galactorrhea may also occur, but these disturbances disappear after LT_4 administration [125, 126].

Menstrual disturbances

In women of reproductive age, hypothyroidism results in changes in cycle length and amount of bleeding, i.e., oligomenorrhea and amenorrhea, polymenorrhea, and menorrhagia. The latter is probably due to estrogen breakthrough bleeding secondary to anovulation [127]. Defects in hemostasis factors (such as decreased levels of factors VII, VIII, IX, and XI, and altered platelet function) that occur in hypothyroidism may also contribute to polymenorrhea and menorrhagia [128].

Menstrual disturbances in hypothyroidism have been reported since the second half of the previous century. Amenorrhea, metropathia hemorrhagica, menorrhagia, polymenorrhea, and oligomenorrhea are the main symptoms mentioned [64–66, 129]. Taken together, the findings of the above studies indicate that approximately 55–65% of female patients have menstrual disturbances. However, in a prospective, controlled study [127], only 23% of patients had irregular cycles (compared to only 8% in controls). Only five patients had amenorrhea [127]. Moreover, in another controlled study [68], it was found that patients with severe hypothyroidism had a higher prevalence (34.8%) of menstrual disturbances than mild-to-moderate cases (10.2%). Secondary amenorrhea, oligomenorrhea, and polymenorrhea were the main menstrual abnormalities [68].

In sum, these findings indicate that the frequency of menstrual disturbances in hypothyroidism is approximately three times greater than in the normal population.

Fertility in subclinical hypothyroidism

Both hypo- and hyperthyroidism have been associated with altered ovarian function, menstrual irregularities, subfertility, and higher miscarriage rates [130, 131], suggesting that thyroid hormone affects female reproductive function. The prevalence of antiTPO antibodies is 8–14% in women of reproductive age [130]. The presence of antiTPO antibodies is associated, even with normal thyroid function, with subfertility, recurrent embryo implantation failure, early pregnancy loss, and adverse pregnancy outcomes [131, 132]. For women with positive antiTPO antibodies, no effective treatment is available at present. Selenium (Se) administration may be of benefit, especially in Se-deficient areas [67].

One potential pathophysiological mechanism for this association may be inadequate adaptation of the thyroid to the increased demand for thyroid hormones during pregnancy due to underlying chronic lymphocytic thyroiditis.

The association between subclinical hypothyroidism and infertility has been evaluated in a number of studies, although most of these were retrospective and uncontrolled.

Grassi et al. [133] investigated 129 women of infertile couples with ovulatory dysfunction (OD): six women (4.6%) had serum TSH levels above 4.5 mIU/L and five of these had AITD. The mean duration of infertility was significantly longer in patients with thyroid abnormalities than in controls (3.8 vs. 2.6 years; $p = 0.005$). In this study, women with tubal or pelvic factors, including endometriosis (13.4% of the original cohort), were excluded, this possibly explaining the higher prevalence of subclinical hypothyroidism compared to other studies. Another uncontrolled retrospective study [134] revealed elevated serum TSH concentration in 12 of 299 women (4%) with infertility. In three of the 12 cases, hypothyroidism had been diagnosed previously, but the women had been treated with an inadequate dose of LT_4. The prevalence of increased serum TSH values was higher in the group with OD and lower in the group with tubal damage (6.3 vs. 2.6%; difference not statistically significant) [134].

A controlled prospective study was carried out in 438 women with various causes of infertility with the aim of assessing the prevalence of AITD and undisclosed alterations of thyroid function [76]. Overall, median TSH was significantly higher in patients with female infertility compared to controls. Elevated serum TSH values were not more prevalent in infertile women than in controls. Only one patient in the OD group and one in the idiopathic infertility group had subclinical hypothyroidism, yielding an overall prevalence of 0.5%. Both patients had positive thyroid antibodies. There were also two patients with overt hypothyroidism (OH) and positive antiTPO antibodies. The impact of subclinical hypothyroidism treatment has been evaluated in only one prospective study in women with infertility. A group of 283 women referred for infertility were studied prospectively [135]. All patients had a TRH test, and subclinical hypothyroidism was defined as a serum TSH response above 15 mU/L. Women with a diagnosis of subclinical hypothyroidism were treated with LT_4 and followed over a 5-year period. Thirty-four percent had subclinical hypothyroidism, an unusually high prevalence, reflecting a bias due to the specific referral pattern. Among the women who became pregnant during the follow-up period, over 25% still had subclinical hypothyroidism at conception. Furthermore, these women, who never had a basal serum TSH level less than 2.5 mIU/L or a TRH-stimulated

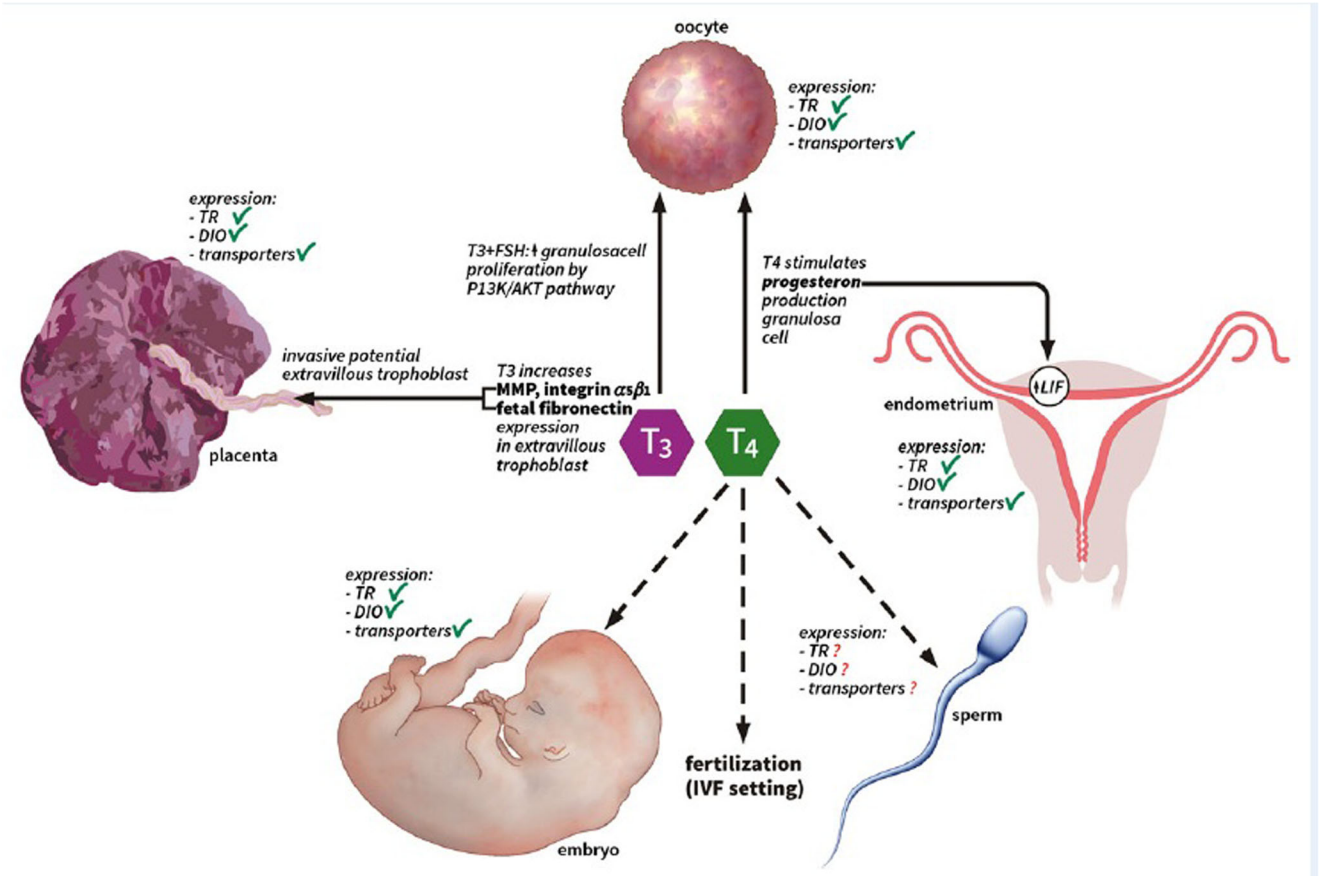

Fig. 3 Mechanisms of action of thyroid hormones on the reproductive system. Schematic summary of known thyroid hormone effects and/or associations with the reproductive system. Solid lines indicate an effect of T4 administration. Dotted lines indicate associations without evidence of causality. For each tissue/cell-type expression of TR, deiodinases (DIOs), and thyroid hormone transporters is indicated. Thyroid peroxidase autoantibody (TPO-Ab) is not shown because a lack of evidence of a causal relationship between TPO-Ab and function of the reproductive system. MMP, metalloproteinases. Reproduced from Vissenberg R. [79] with permission

TSH level less than 20 mIU/L, became pregnant less frequently than those who did. Finally, more frequent miscarriages were observed in those women with a higher basal serum TSH level, irrespective of the presence of autoimmune thyroid diseases [135].

Abalovich et al. [136] retrospectively evaluated 244 women during infertility consultation and 155 healthy women with confirmed fertility. TSH and antiTPO antibodies were measured in all patients, and a TRH test was performed in 71 patients to check for subclinical hypothyroidism. The latter was diagnosed in 14% of infertile women and in 4% of controls. Patients with precocious ovarian failure, tubal disturbances, and OD had significantly higher subclinical hypothyroidism rates than controls (40%, 18%, and 15%, respectively). There was no significant difference in prevalence of AITD between infertile women and controls. When treated with LT_4, women with subclinical hypothyroidism achieved a pregnancy success rate of 44%.

Yoshioka et al. [137] investigated 69 infertile female patients with subclinical hypothyroidism and the effect of LT_4 treatment on pregnancy rates and pregnancy outcomes. They found that 58 patients (84.1%) successfully conceived during the T_4 treatment period, although 17 patients (29.3%) had miscarriage afterward. The remaining 11 patients continued to be infertile. They concluded that T_4 enhanced fertility in infertile patients with subclinical hypothyroidism. This notion is further supported by a recent study [138] which investigated the potential role for thyroid function or autoimmunity in female infertility when the cause of the latter remains unknown, such as in women with diminished ovarian reserve (DOR) or unexplained infertility. Markers such as day 3 FSH and antral follicle count (AFC) were used. A total of 436 women and 530 AFC measurements were investigated in this study. There was no association of thyroid function of antiTPO antibodies positivity with AFC. However, antiTG antibody positivity was associated with a higher AFC. In women with DOR or unexplained infertility, lower FT_3 and antiTPO antibody positivity were associated with lower AFC, while antiTG antibody positivity was not associated with AFC. Neither thyroid function nor thyroid antibody positivity was associated with the day 3 FSH concentration. They concluded that lower FT_3 and antiTPO antibody positivity are associated with lower AFC in women with DOR or unexplained infertility [138].

The design of the studies, as well as definitions used for subclinical hypothyroidism, differed and therefore direct comparison among the different studies is difficult [68].

Finally, an important question is if thyroid dysfunction has an effect on libido and sex drive among these patients. In a recent investigation [39], two separate patient samples with benign thyroid diseases were investigated, one across-sectional sample consisting of 754 women and 118 men, and the other a longitudinal sample consisting of 358 women and 74 men. The ThyPRO, a thyroid-specific questionnaire, was used to measure patient-evaluated thyroid-related sex life impairment. In the cross-sectional sample, 36% of women and 31% of men reported what they perceived to be thyroid-attributable impaired sex life. Women with autoimmune thyroid diseases reported more impairment than those with non-autoimmune thyroid diseases. In patients with GD, lower levels of educational attainment, and in patients with toxic nodular goiter, comorbidities were associated with impaired sex life. Overall, quality of life was lower in patients with thyroid-related sex life impairment. In the longitudinal sample, 42% of women and 33% of men had impaired sex life at baseline, which improved at 6-month follow-up only in women; moreover, on analysis of individual diagnoses separately, a statistically significant correlation was found among those with autoimmune hypothyroidism. Sexual impairment was associated with low education in patients with toxic nodular goiter and with high plasma T_3 concentrations in patients with GD. In autoimmune hypothyroidism, a younger age was associated with sex life impairment. The researchers concluded that patients with benign thyroid diseases, especially young women with autoimmune thyroid diseases, have a high frequency of self-reported, thyroid-related sex life impairment [39]. The latter persisted in women treated for GD, suggesting that normalization of thyroid function is not sufficient to restore sexual function.

However, this study has limitations. First is the lack of control group, second the small number of male patients, and finally, that only Danish patients are included, this meaning that it concerns only a single ethnic group. Furthermore, no pathophysiological mechanism is provided to explain why, for example, women with positive thyroid antibodies have high prevalence of impaired sex life.

Fertility in overt hypothyroidism

Studies that examined the incidence of infertility in hypothyroid patients are scarce. Ideally, this question should be evaluated prospectively by determining the incidence of infertility in hypothyroid patients compared with a matched control group. However, such data are as yet not available, most studies dealing with the prevalence of infertility in a cross-sectional design with hypothyroid patients, or the evaluation of the prevalence of hypothyroidism in selected (and therefore biased) populations presenting at specialized infertility clinics [107, 139].

Serum TSH levels were measured in 704 infertile women without previous thyroid disorders [140]. Among these, 2.3% had increased serum TSH (with both overt and subclinical hypothyroidism). The frequency was comparable to that found in the general female population of reproductive age, although no control population was included in the study. The authors concluded that women with OD should be screened for hypothyroidism. In 2000, Arojoki et al. [134]

retrospectively determined the prevalence of hypothyroidism in 299 women with different causes of infertility. Overall, 4% had increased serum TSH and 3.3% had OH. The highest percentage with increased TSH was found in the group with OD (6.3%), compared to 4.8% in the idiopathic group, 2.6% in the tubal infertility group, and none in the endometriosis group. No statistical differences were observed when comparing the frequency of hypothyroidism between the different groups of women with infertility [134]. Patients with overt thyroid failure are probably detected before referral to infertility clinics, thereby introducing a bias in the estimated prevalence of infertility disorders. Given the possibility of hypothyroidism as a cause of OD, screening is certainly justified in the presence of OD [69, 139].

Altered peripheral estrogen metabolism, hyperprolactinemia, defects in hemostasis, and disturbances in GnRH secretion that result in an abnormal pulsatile release of LH are some of the main causes of the high frequency of infertility in hypothyroid women [141]. Moreover, both gonadotropins and T_4 appear necessary to achieve maximum fertilization rates and blastocyst development.

Conclusions

Hyperthyroidism occurs much less commonly in children than hypothyroidism, with GD being the most common cause. Current treatment options include ATD, surgery, and RAI. Sexual behavior and semen quality may be affected in thyrotoxic men, although many of these patients may have normal androgen levels. Meanwhile, menstrual irregularities and reduced fertility are the most common reproduction-related symptoms in thyrotoxic women. Though hypothyroidism in males is associated with decreased libido or impotence, little is at present known about the effects of hypothyroidism on spermatogenesis and fertility. Nonetheless, it has been suggested that in hypothyroid men, sperm morphology and motility are mainly affected, while changes in cycle length and amount of bleeding are common in hypothyroid women, who also suffer from reduced fertility and higher miscarriage rates.

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