Thyroid and Infertility

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Introduction

Infertility is defined as the failure to achieve a clinical pregnancy after at least 12 months of regular unprotected sexual intercourse [1]. Infertility which can be either attributed to male factor, female factor, or both, while in some cases the cause is not detected (idiopathic infertility), represents an ongoing challenge globally [2].

Thyroxine is essential in early pregnancy and crucial for fetal brain development and growth and thyroid dysfunction and/or autoimmunity are quite common in women of reproductive age, as reported in previous chapters. Apart from that, it is now well reported that the hypothalamus-pituitary-thyroid axis interacts with the hypothalamus-pituitary-gonads axis in various levels and ways. Recent evidence suggests that on top of these interactions, a local action of thyroid hormones in reproductive tissues is highly probable. Thyroid hormone and TSH receptors (TRs and TSHRs respectively) have been detected in the granulosa cells, the follicular fluid, and the endometrium; and deiodinases 2 and 3 have been detected in the ovaries [3]. Interestingly TRs that are located in the endometrium seem to cross talk with the estrogen receptors (ERs) and are expressed differently during the different phases of menstrual cycle [4]. According to experimental data, TRα1 and TRβ1are expressed in mid-luteal phase. An increase has been reported during secretory phase, followed by a decrease [4]. This is clinically interested as it has been suggested that TR and TSHR expression is related to human endometrium receptivity [5].

TR and TSHR are also found in granulosa and ovarian stromal cells [6]. TR α1 and TR β1 are found in the epithelium, but the receptors are differently distributed in the oocytes and granulosa cells at the different developmental stages of the follicle. The presence of the thyroid and TSH receptors in the reproductive tissues

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implies a local action of thyroid hormone and TSH, respectively. It is already known that T_3 inhibits aromatase activity in granulosa cells and that, together with FSH, enhances granulosa cells proliferation and inhibits granulosa cells apoptosis by the PI3K/Akt pathway [7].

Hypothyroidism and Infertility

Hypothyroidism, including subclinical hypothyroidism, is a common disease in women of reproductive age. Subclinical hypothyroidism is defined as an elevated serum TSH with a normal serum free thyroxine concentrations. Both overt and subclinical hypothyroidism have been linked to infertility, higher miscarriage rate, lower live birth rate, preterm deliveries, and low birthweight for gestational age (Fig. 1). Hypothyroidism per se can cause ovulatory disorders that in turn can comprise a challenge to fertility.

According to an observational cohort study involving women desiring pregnancy with history of miscarriage or subfertility from 49 hospitals across the UK [8], overt hypothyroidism, defined as having a TSH > 4.50 mIU/L and fT4 < 10 pmol/L, was diagnosed in 0.2% of women (95% CI, 0.1–0.3) and overt hyperthyroidism, defined as having a TSH < 0.44 mIU/L and fT4 > 21 pmol/L, in 0.3% (95% CI, 0.2–0.3) of the women. Interestingly, only 2.4% (95% CI, 2.1–2.6) of the women were diagnosed with subclinical hypothyroidism, defined as having a TSH > 4.50 mIU/L. Of course, if the cutoff for TSH is lowered to 2.50 mIU/L, then subclinical hypothyroidism would have been diagnosed in 19.9% (95% CI, 19.3–20.5) of the women. TPOAb were detected in 9.5% of the women. A retrospective study that involved 2279 women with normal thyroid function and 289 with subclinical hypothyroidism has shown that subclinical hypothyroidism is linked to lower AMH concentrations (median: 2.05 vs. 2.51 ng/mL, $p = 0.015$) and lower antral follicle counts (median: 10.0 vs. 11.0, $p = 0.013$) in comparison to euthyroidism [9]. A Cochrane meta-analysis with the aim to evaluate levothyroxine replacement in subfertile women with either subclinical hypothyroidism or euthyroidism with thyroid autoimmunity

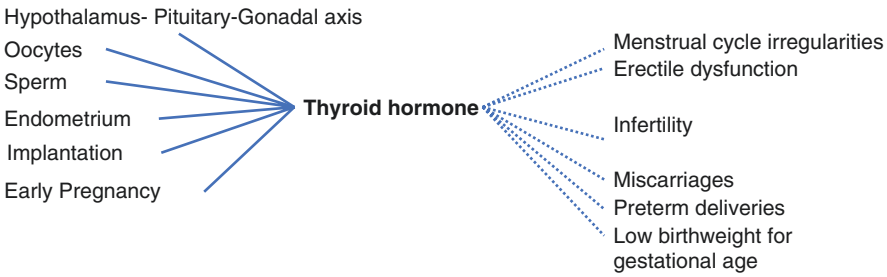

Fig. 1 Targets of thyroid hormone actions and reproduction-related symptoms of thyroid dysfunction

undergoing assisted reproduction was unable to draw strong conclusions mainly because of the low quality of the available evidence [10]. Another meta-analysis on the same topic though had suggested that LT_4 supplementation may be recommended for women with subclinical hypothyroidism or euthyroidism with thyroid autoimmunity undergoing IVF/ICSI, mainly as a protection from miscarriages [11].

According to the 2021 European Thyroid Association (ETA) guidelines [12] all women planning assisted reproduction should be screened for TSH and TPOAb/and TPOAb concentrations. Treatment with LT4 should be discussed in infertile women with TAI and serum TSH >2.5 mIU/L. In fact, as infertility per se is a risk factor of thyroid dysfunction, all women with infertility should be screened for thyroid dysfunction and autoimmunity.

Among infertile men subclinical hypothyroidism may affect up to 7.4%. It has been suggested that in men with hypothyroidism the increased oxidative stress in the testis may be the main trigger for sperm abnormalities reported in these men [13]. Though the effects of overt hypothyroidism in the male reproductive system have been thoroughly described (abnormal sperm parameters including morphology and motility) less is known about subclinical hypothyroidism. In specific, hypothyroidism seems to decrease both the activity of glutathione reductase and catalase transcript expression and activity [14]. This is believed to cause a reduction in sperm mitochondrial activity and acrosome integrity [15]. Regarding the erectile function, there is evidence to support that this is strongly affected by thyroid hormone concentrations. It has been reported that untreated hypothyroidism may lead to delayed ejaculation [16].

It has been suggested that men with subclinical hypothyroidism may have deteriorated reproductive outcomes after assisted reproduction technology (ART) in comparison to euthyroid men [17]. However, it seems that this is the case for men older than 35 years [17]. In any case, according to the 2021 ETA guidelines all men with impaired sperm parameters should be screened for thyroid disease [12].

To sum up, all infertile women as well as infertile men with impaired sperm parameters should be screened for thyroid dysfunction. Thyroid supplementation, if necessary. Should start at the earliest convenience, as thyroid function is crucial for the normal development of the pregnancy.

Hyperthyroidism and Infertility

Hyperthyroidism both men and women has been linked to compromised reproductive outcomes. Hyperthyroidism is defined as an excess of thyroid hormone production and is commonly symptomatic. Similar to hypothyroidism, hyperthyroidism can be either overt or subclinical (TSH below the reference range, T3 and fT4 within the normal range). Thyrotoxicosis is another entity, defined as an excess of thyroid hormone concentration (and not necessarily production). Graves' disease is the leading cause of hyperthyroidism in both men and women. Other causes of hyperthyroidism and/or thyrotoxicosis include toxic multinodular goiter, thyroid toxic

adenoma, iodine-induced hyperthyroidism (Jod-Basedow phenomenon), de Quervain, postpartum, and factitious thyroiditis. Main symptoms include fatigue, excessive sweating and tremor, palpitations, anxiety, heat intolerance, and diarrhea. Menstrual irregularities in women are not uncommon, and sometimes they comprise the main presenting symptom. It has been suggested that 5.8% of hyperthyroid women may be infertile [18].

Men with hyperthyroidism may experience symptoms related to decreased libido, gynecomastia, and/or premature ejaculation. Their sperm parameters may be strongly affected (sperm motility and morphology) [3]. As such infertility can be caused by hyperthyroidism either due to decreased libido, erectile dysfunction, or impaired spermatogenesis.

Hyperthyroid women commonly present with symptoms related to menstrual irregularities, including amenorrhea, oligomenorrhea, and hypomenorrhea [3]. It has been reported that in women with hyperthyroidism testosterone, Δ4-androstenedione but also estradiol and sex hormone binding globulin (SHBG) are all increased. Luteinizing hormone (LH) response to gonadotropin-releasing hormone (GnRH) is also higher in women with hyperthyroidism than those in euthyroid state. In any case, the effects of hyperthyroidism in fertility potential seem to be magnified when thyroid autoimmunity is also present, the latter being a common clinical scenario. Indeed, the presence of anti-TSH antibodies have specifically been associated with infertility (both primary and secondary).

According to a multi-center observational cohort study from 49 centers in the UK, overt hyperthyroidism (TSH < 0.44 mIU/L, fT4 > 21 pmol/L) was present in 0.3% (95% CI 0.2–0.3) of the 19,213 infertile women studied [8]. However, the rates of thyroid dysfunction may be underestimated in this study due to its study design. Older studies have calculated the prevalence of clinical and subclinical hyperthyroidism to be 2.1% in infertile women [18]. Vice versa, it has been suggested that infertility is present in 5.8% of women with hyperthyroidism [19].

In conclusion, both men and women with infertility and hyperthyroidism (subclinical and clinical) may present with symptoms and signs that will lead to the hyperthyroidism diagnosis. When treated hyperthyroidism, in both men and women, reproductive plans should be discussed as they may affect the hyperthyroidism treatment options.

Thyroid Autoimmunity and Infertility

Thyroid autoimmunity (TAI) is defined as the presence of Anti-TPO and/or anti-Tg antibodies and comprises the most common endocrine disease in women of reproductive age, with a prevalence between 5 and 20% [20]. It is now evident that when TAI is present, the relative risk for female infertility increases. On top of that, women with recurrent miscarriages have a higher incidence of Tg- and/or TPO-abs, amounting as high as 25% [20].

According to a meta-analysis involving nine studies and a total of 4396 women, live birth rate (LBR) of women with TAI is lower in comparison to that of those without TAI [odds ratio (OR): 0.73, 95% CI: 0.54–0.99, $p = 0.04$; I^2: 41%)] [21].

Various theories have been put forward to explain how TAI may influence female fertility: According to the first theory, it is not TAI per se, but the abnormal autoimmune background that results in the negative impact on fertility. A recent registry-based retrospective study from Taiwan demonstrated that women with Hashimoto thyroiditis had a 2.40-fold higher risk of premature ovarian failure than those without Hashimoto thyroiditis with a hazard ratio (HR) of 2.40 (95% confidence interval (CI) = 1.02–5.68) [22]. According to another theory on the same direction, TAI is not a cause, just a confounding factor, with age being the main cause that results in detrimental effects on female fertility [3]. The presence of TAI does increase with age anyway. Another theory however suggests that TAI results in a relative deficiency in thyroid hormone. Thus, women with TAI have a diminished "reservoir" of thyroid hormone. Lastly it has been suggested that TAI may have a cytotoxic reaction in the follicle fluid damaging the oocyte and, thus, can lead to poorer oocyte quality and decreased developmental potential [3]. Thyroid antibodies have been indeed detected in the follicular fluid and recent evidence demonstrates decreased T cell cytotoxicity in women with repeated implantation failure and TAI in comparison to those without TAI [23]. Anyway, TAI has been directly linked with other causes of infertility, such as endometriosis, ovarian failure, and polycystic ovarian syndrome [3].

According to the guidelines of ETA all women with infertility should be screened for thyroid function and presence of thyroid autoimmunity (anti-TPO and/or antiTG) [12]. In these guidelines, the presence of thyroid autoimmunity has a significant impact on the decision of providing thyroid hormone supplementation as this is suggested for women with TSH levels >2.5 mIU/L and thyroid autoimmunity, whereas this is not the case for those with same TSH values without thyroid autoimmunity [12].

Summary

Thyroid dysfunction and/or autoimmunity are quite common in women of reproductive age and thyroxine is essential in early pregnancy and crucial for fetal brain development and growth. Thyroid disease in women (including hypothyroidism and hyperthyroidism (both subclinical and overt) and/or thyroid autoimmunity have been linked to adverse reproductive outcomes. Similarly thyroid dysfunction in men is associated with erectile dysfunction and disturbances is sperm parameters. Early detection of thyroid disorders and thyroid hormone supplementation, when needed, is crucial for the improvement of fertility potential of both men and women.

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