

# Thyroid dysfunction and subfertility

Moon Kyoung Cho

Department of Obstetrics and Gynecology, Chonnam National University Medical School, Gwangju, Korea

The thyroid hormones act on nearly every cell in the body. Moreover, the thyroid gland continuously interacts with the ovaries, and the thyroid hormones are involved in almost all phases of reproduction. Thyroid dysfunctions are relatively common among women of reproductive age, and can affect fertility in various ways, resulting in anovulatory cycles, high prolactin levels, and sex hormone imbalances. Undiagnosed and untreated thyroid disease can be a cause of subfertility. Subclinical hypothyroidism (SCH), also known as mild thyroid failure, is diagnosed when peripheral thyroid hormone levels are within the normal reference laboratory range, but serum thyroid-stimulating hormone levels are mildly elevated. Thyroid autoimmunity (TAI) is characterized by the presence of anti-thyroid antibodies, which include anti-thyroperoxidase and anti-thyroglobulin antibodies. SCH and TAI may remain latent, asymptomatic, or even undiagnosed for an extended period. It has also been demonstrated that controlled ovarian hyperstimulation has a significant impact on thyroid function, particularly in women with TAI. In the current review, we describe the interactions between thyroid dysfunctions and subfertility, as well as the proper work-up and management of thyroid dysfunctions in subfertile women.

**Keywords:** Hypothyroidism; Infertility; Autoimmunity; Thyroid hormones

## Introduction

The thyroid hormones act on nearly every cell in the body. They act to increase the basal metabolic rate, affect protein synthesis and regulate long bone growth and neural maturation. The thyroid hormones are essential for the proper development and differentiation of all cells of the human body. The thyroid hormones also affect the female reproductive organs. In combination with follicle-stimulating hormone, triiodothyronine (T3) enhances granulosa cell proliferation and inhibits granulosa cell apoptosis by the phosphatidylinositol 3-kinase/Akt (also known as protein kinase B) pathway [1]. Leukemia inhibitory factor (LIF) is involved in the embryo implantation process and expressed in the mid-secretory endometrium [2]. Thyroid-stimulating hormone (TSH) significantly upregulates LIF expression in en-

dometrial cell cultures, suggesting a potential role of TSH in the implantation process [3]. Moreover, T3 increases the expression of matrix metalloproteinases (MMP), MMP-2, MMP-3, fetal fibronectin, and integrin  $\alpha 5 \beta 1$  T3 in cultured early placental extravillous trophoblasts, suggesting that it plays a vital role in regulating the invasive potential of extravillous trophoblasts [4]. The thyroid hormones are involved in almost all phases of reproduction, from folliculogenesis to placentation. This review focuses on the interactions between thyroid dysfunctions and subfertility, as well as the proper work-up and management of thyroid dysfunctions in subfertile women.

## Thyroid hormone disorders and subfertility

Overt hyperthyroidism results in the alteration of estradiol metabolism and the augmentation of gonadotropin in response to gonadotropin-releasing hormone. Baseline gonadotropin concentrations are also frequently elevated. The current prevalence of irregular cycles is 21.5%, which is a dramatic decrease from the previously reported figure of 65%, due to the earlier detection and treatment of hyperthyroidism [5]. These features become normalized after the administration of antithyroid drugs. Studies on the prevalence of subfertility

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Corresponding author: **Moon Kyoung Cho**

Department of Obstetrics and Gynecology, Chonnam National University Medical School, 160 Baekseo-ro, Dong-gu, Gwangju 61469, Korea  
Tel: +82-62-220-6376 Fax: +82-62-227-1637 E-mail: chomk@chonnam.ac.kr

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in women with hyperthyroidism are limited. Moreover, most such studies are uncontrolled, retrospective, and small in size. The prevalence of primary or secondary infertility associated with hyperthyroidism has been described to be 0.9% to 5.8% [6,7]. Nonetheless, the exact impact of hyperthyroidism on fertility remains ill-defined.

Hypothyroidism has been associated with altered ovulatory function, menstrual irregularities, subfertility, and higher (recurrent) miscarriage rates. Usually, treatment corrects these problems. More recent studies have reported a lower frequency of menstrual abnormalities [8].

Subclinical hypothyroidism (SCH) is defined by an increase in serum TSH concentrations with normal free thyroxine (FT4) levels. The prevalence of SCH in subfertile women has been reported to vary from 0.7% to 43% [9]. The wide range of prevalence is due to the differences in sensitivity of serum TSH measurement. The revised clinical practice guidelines of the Endocrine Society recommend the measurement of serum TSH in order to screen for thyroid dysfunction in women over the age of 30 years with infertility or a prior history of miscarriage [10]. The data are insufficient to conclude that SCH is clearly associated with subfertility. However, some investigators have suggested that SCH may be associated with subfertility. In one study of 509 subfertile women planning an *in vitro* fertilization cycle, TSH levels were significantly higher among women who produced oocytes that failed to be fertilized (mean, 5.1  $\mu$ U/mL) [11]. In clinical practice guidelines for hypothyroidism in adults, the American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA) have recommended that treatment with L-thyroxine should be considered in women of childbearing age with SCH when they are planning a pregnancy [12]. Two small randomized trials have evaluated whether the administration of L-thyroxine for SCH improved pregnancy outcomes in *in vitro* fertilization cycles. These studies found that the miscarriage rate was significantly lower in the L-thyroxine group than in the placebo group, while the clinical pregnancy rate and delivery rate were both significantly higher [13,14].

## Thyroid autoimmunity and subfertility

Autoimmune disease is a cause of infertility. Thyroid autoimmunity (TAI) is the most prevalent autoimmune condition (5%–20%) in women of fertile age. TAI is characterized by the presence of anti-thyroid antibodies, which include anti-thyroperoxidase and anti-thyroglobulin antibodies [9]. It may remain latent, asymptomatic, or even undiagnosed for an extended period [15]. Numerous studies have investigated the prevalence of TAI in women with subfertility. Pooling the results of these studies suggests that TAI is significantly more prevalent in women with subfertility than in controls, with an overall estimated relative risk of 2.1 ( $p < 0.0001$ ) [9]. In a recently published

meta-analysis, the presence of anti-thyroid antibodies was associated with an increased risk of unexplained subfertility (odds ratio [OR], 1.5; 95% confidence interval [CI], 1.1–2.0), miscarriage (OR, 3.73; 95% CI, 1.8–7.6) and recurrent miscarriage (OR, 2.3; 95% CI, 1.5–3.5) [16]. Therefore, the AACE recommends that anti-thyroid antibodies should be measured in women with subfertility or a history of miscarriage as well as SCH [12]. The pathogenesis of subfertility and increased pregnancy loss in women with TAI remains to be not fully elucidated. One hypothesis is that despite the presence of overall euthyroidism, TAI could be associated with a subtle deficiency in thyroid hormones, which are involved in fetal development and placental physiology. Serum TSH levels in antibody-positive but euthyroid women are higher than in antibody-negative women, with a difference of  $0.81 \pm 0.58$  mU/L ( $p = 0.005$ ) [17]. Proposed thyroid-independent mechanisms involve abnormal innate and humoral immunity, vitamin D deficiency, and cross-reactivity of thyroid antibodies with extrathyroid sites. (1) The presence of anti-thyroid antibodies in ovarian follicles may play a critical role in female subfertility. In one study, anti-thyroid antibodies were measured in all samples of follicular fluid drawn from women with TAI ( $n = 14$ ) on the day of oocyte retrieval, whereas they were absent in women without TAI ( $n = 17$ ). The follicular fluid concentrations of anti-thyroid antibodies were approximately half of those found in the serum on the day of oocyte retrieval. A strongly positive correlation was found between follicular fluid and serum levels of anti-thyroglobulin antibodies ( $r = 0.95$ ,  $p < 0.05$ ) and anti-thyroperoxidase antibodies ( $r = 0.99$ ,  $p < 0.05$ ). Oocyte fertilization and grade A embryos were less common and the pregnancy rates were lower in women with TAI than in controls, whereas the early miscarriage rate was higher [18]. Moreover, changes have been observed in endometrial T cells, polyclonal B cell, and cytotoxic natural killer cells in women with TAI. (2) Vitamin D deficiency ( $< 10$  ng/mL) has been suggested to be a predisposing factor to autoimmune diseases. Vitamin D has also shown to be reduced in patients with TAI. In turn, vitamin D deficiency is also linked to subfertility and pregnancy loss, suggesting a potential interplay with TAI in the context of subfertility [19]. (3) Anti-thyroid antibodies have also been suggested to alter fertility by targeting zona pellucida antigens [20].

Treatment strategies have reflected the proposed pathophysiological mechanisms underlying subfertility and pregnancy loss in patients with TAI. Modulation of the immune system in patients with TAI has been reported with the use of intravenous immunoglobulins [21–23]. Intracytoplasmic sperm injection, which requires no interaction between the sperm cell and the zona pellucida, may be used as the insemination technique in subfertile women with TAI to avoid the failure of assisted reproduction techniques (ART) [18]. If the presence of TAI is associated with a subtle deficiency in thyroid hormones, these patients require treatment with L-thyroxine. Two stud-

ies have been reported to date. In a study performed by Negro et al. [24], women with TAI were randomly assigned to two different groups (one receiving L-thyroxine and the other one without treatment), and women without TAI served as controls. In the no-treatment group, serum TSH levels increased progressively during gestation. The controls and women in the treated group maintained normal serum FT4 levels, while FT4 levels decreased by 30% in the no-treatment group during gestation. Supplementation with L-thyroxine in women with TAI reduced the risk of miscarriage compared to the controls. Women with TAI who underwent no treatment had a four-fold increased risk of miscarriage. The only intervention study with L-thyroxine treatment in women with TAI who became pregnant through ART was published by Negro et al. [25]. In that study, the miscarriage rate was reduced to 33% in the treated group, compared to 52% in untreated controls ( $p=0.034$ ). The studies by Negro et al. should be confirmed by a double-blinded placebo-controlled trial with an appropriate number of patients.

## Work-up and management of thyroid dysfunction in subfertile women

When evaluating women with recurrent miscarriage or subfertility, TSH and anti-thyroid antibodies should be measured. Women with overt hyperthyroidism or hypothyroidism should be treated. Additionally, treatment with L-thyroxine should be considered in women of childbearing age with SCH when they are planning a pregnancy (TSH  $\geq 10$  mIU/L, 1.6  $\mu\text{g}/\text{kg}/\text{day}$ ; TSH  $< 10$  mIU/L, 25–75  $\mu\text{g}/\text{day}$ ). The management of subfertile women with normal TSH levels is described in the clinical practice guidelines for hypothyroidism in adults by published by the AACE and ATA [12].

The normal reference range for a third generation TSH assay in non-pregnant women is 0.4 to 4.12 mIU/L [12]. However, during pregnancy, several changes occur with respect to thyroid function. Hyperestrogenism during pregnancy is accompanied by an increase in serum thyroxine-binding globulin. Furthermore, during pregnancy, iodine clearance increases, the peripheral metabolism of thyroid hormones is modified, and thyroid hormone requirements are increased. In the case of impaired thyroid function, the increased thyroid hormone requirements cannot be met, and these conditions result, in turn, in reduced T4 concentrations and a compensatory increase in serum TSH levels. Therefore, in pregnant women, the reserve of thyroid gland should be sufficient, meaning that the upper limits of the normal TSH reference range should be lowered. The AACE and ATA recommend that the upper limits of the normal range of TSH levels be as follows [26]: first trimester, 2.5 mIU/L; second trimester, 3.0 mIU/L; third trimester, 3.5 mIU/L.

It has also been demonstrated that controlled ovarian hyperstimu-

lation (COH) involves a rapid increase in plasma estradiol concentrations, thereby inducing an additional strain on the thyroid gland, similar to pregnancy, particularly in women with TAI. When measuring TSH and FT4 before COH and subsequently every 20 days after COH during the first trimester of pregnancy, serum TSH levels among TAI-positive women were significantly higher than in TAI-negative women ( $p=0.010$ ). The opposite was observed for the FT4 curve ( $p=0.020$ ) [27]. Alexander et al. [28] clearly identified the need to increase rapidly the dosage of L-thyroxine in pregnant women treated for primary hypothyroidism. In the same study, the authors also pointed out the necessity of increasing the dose of L-thyroxine earlier and to a greater extent in subjects who underwent COH than in natural pregnancies. Serum estradiol concentrations at 7 weeks of gestation were significantly higher in women who had become pregnant by COH ( $1,506 \pm 460$  pg/mL) than in women who became pregnant spontaneously ( $484 \pm 265$  pg/mL) ( $p < 0.01$ ) [28]. It is more important to have a sufficient reserve of thyroid hormone in cases of COH than in natural pregnancies. It is therefore advisable to measure thyroid function and detect TAI in subfertile women before COH. Moreover, if subfertile women with TAI plan to undergo COH, the upper limit of the normal reference range of TSH should be 2.5 mIU/L, as in the first trimester [12].

Women of childbearing age who are plan to undergo COH in the immediate future, should be treated with L-thyroxine if they have positive levels of serum anti-thyroid antibodies and their TSH level is over 2.5 mIU/L. Women with positive levels of serum anti-thyroid antibodies or with a TSH level higher than 2.5 mIU/L who are not treated with L-thyroxine should be monitored every 4 weeks in the first 20 weeks of pregnancy for the development of hypothyroidism [12].

## Conclusion

The thyroid hormones are involved in almost all phases of reproduction. Altered thyroid hormone levels are associated with disturbed folliculogenesis, a lower fertilization rate, and lower embryo quality. Therefore, screening for thyroid function and autoimmunity should be performed as part of the work-up of women with subfertility or miscarriage. L-thyroxine should be administered when SCH is present in women of childbearing age if they plan a pregnancy, in order to improve the likelihood of successful pregnancy outcomes. Moreover, women of childbearing age who plan to undergo COH in the immediate future, should be treated with L-thyroxine if they have positive results for serum anti-thyroid antibodies and TSH levels higher than 2.5 mIU/L, because COH places an additional strain on the thyroid gland.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

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