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Review

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Thyroid disorders; an insidious cause leading to female infertility

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Abstract

The review aims to describe the effect of thyroid diseases on fertility. There are many causes of infertility in couples and thyroid dysfunction is a critical cause. Thyroid hormones and the hypothalamic-pituitary-ovarian axis interact in several ways and thyroid hormones may modulate ovarian functions. Hypothyroidism causes ovulatory dysfunction and luteal hypoplasia due to decreased progesterone production. Levothyroxine supplementation restores the ovulatory function and ultimately resolves the fertility issues. Regarding the elevated concentrations of antithyroid antibodies in infertile women, high concentrations are associated with a three- to four-fold increased risk of recurrent miscarriages. Moreover, women with positive antithyroid antibodies tend to develop thyroiditis postpartum. In assisted reproduction cycles the presence of antithyroid antibodies is correlated with poorer embryo quality, lower fertilization rates and increased risk of spontaneous abortion. Lastly, hyperthyroid women, especially with thyrotoxicosis, have menstrual disorders such as oligomenorrhea and polymenorrhea. In hyperthyroid women the incidence of infertility is higher.

Key words: Infertility, assisted reproduction techniques, thyroid hormones, hypothyroidism, hyperthyroidism, thyroid antibodies

Introduction & Background

Infertility is the inability to conceive and to become pregnant following twelve months of sexual relations without preventive or contraceptive mea-

sures[1]. Thyroid hormones and the hypothalamic-pituitary-ovarian axis interact in multiple ways. The interdependent relationship between FSH and T3 can directly influence granulosa cell function, the development of LH/hCG receptor and prevention of apoptosis[2]. Thyroid hormones alter the way the ovary functions to a certain degree, by influencing nitric oxide synthase, decreasing aromatase activity of granulosa cells and inhibiting the development of precursor follicles[3]. Thyroid receptors exist in developing and mature oocytes, while T3, T4 and thyroid antibodies are present in the follicular fluid[2].

There are many causes of infertility in couples. Among this multitude of factors that can adversely affect conception and ultimately the pregnancy is thyroid dysfunction. The loss of follicles during a woman's reproductive years is intimately tied to ovarian aging. When ovarian reserve is compromised by illness or injury including thyroid abnormalities, it cannot be replaced, increasing her risk of infertility. Additionally, thyroid dysfunction is linked to implantation abnormalities and can lead to many clinical abortions in pregnancy[4,5].

The investigation of the causal role of thyroid dysfunction in reproductive disorders has been studied before in several research articles, with a particular emphasis on endocrine disturbances during pregnancy. In the present review, we aim to present the most important articles in the literature related to thyroid dysfunction, infertility and pregnancy outcomes.

Review

Infertility in Women with Hypothyroidism

Hypothyroidism, especially in acute cases, causes ovulatory dysfunction and luteal hypoplasia, resulting in decreased progesterone production[6]. Menstrual disorders in the form of oligo- or hypermenorrhea have been estimated at 25-60% of cases, in comparison to 10% of hypothyroid women[7]. Levothyroxine treatment is helpful in treating infertility by addressing hormonal changes and normalizing the menstrual cycle. Levothyroxine therapy is helpful in treating infertility because it addresses hormonal changes and leads to normalization of the menstrual cycle. However, it is believed that LT4 therapy leads to spontaneous pregnancy in hypothyroid women only in cases of ovarian dysfunction, but not in cases where male infertility, endometriosis, or ovarian obstruction is present. Currently, when abnormal thyroid function is evident and TSH levels are above 4.0 mIU/L, early initiation of LT4 therapy is indicated according to guidelines[3-5]. It's important to take notice of how thyroid hormones affect follicular fluid, how thyroid hormone receptors operate, and how TSH affects reproductive organs.

There is no sufficient evidence in the current literature to support the influence of overt hypothyroidism on female infertility. In a retrospective study, Lincoln et al. evaluated the prevalence of hypothyroidism in a cohort of 704 infertile women with no indication of hypothyroidism, of whom 16, or 2.3%, had elevated TSH levels. Of these women, 68% of participants experienced ovulation disorders and 64% achieved pregnancy at the start of LT4 treatment[8]. A retrospective study in Finland of 335 infertile females screened for hypothyroidism. 12 women, 4%, were in the range of 5.7-32 mIU/L. Oligomenorrhea or amenorrhea existed in 67% of hypothyroid women ($p < 0.05$)[9]. Unplanned pregnancy in women with apparent hypothyroidism is associated with increased risk of miscarriage[10]. A research of 150 pregnancies in 114 hypothyroid women found that in the overt hypothyroidism group the miscarriage rate was 60%[9].

In recent years the effects of mild thyroid dysfunction on infertility has been studied extensively. Most of these studies report a hypothyroidism rate of 2.3 to 4% among 28 to 35-year-old infertile women. Hence the incidence of hypothyroidism

in this infertile group did not differ from the age-matched controls[11,12]. On the other hand, there are retrospective studies that report a three- to four-fold increase in incidence rates of hypothyroidism[7]. Poppe et al. showed that the correlation between subclinical hypothyroidism and certain causes of infertility was evident only in women with increased concentrations of antithyroid peroxidase antibodies. They also found the mean TSH concentration in the infertility group being statistically significantly higher than in the control group (1.3 mIU/L vs. 1.1 mIU/L; p = 0.006), particularly in females with ovulatory disorders (1.5 mIU/L vs. 1.1 mIU/L; p <0.05)[6]. Similarly, a study by Orouji Jokar et al. in hypothyroid women with idiopathic infertility, showed that TSH levels were increased in comparison with the control group[11]. Two studies on female infertility have evaluated the association between the presence of mild thyroid failure and low ovulation rate, primarily in Turner syndrome[13]. The second study showed interconnection between low free triiodothyronine levels and low antral follicle counts[14]. Yoshioka et al. treated 69 infertile women with mild hypothyroidism and TSH levels higher than 3.0 mIU/L with levothyroxine for an average of 3.3 years (0.6 to 6 years). Of the 69 women treated, 58 became pregnant, 84% (21 spontaneous pregnancies and 37 assisted reproduction pregnancies). Of the women who became pregnant, 17 (29%) miscarried. Antithyroid peroxidase antibodies or antithyroglobulin antibodies were detected in 42% of those tested, and the detection rate was the same in both groups[10]. In the study by Verma et al. Levothyroxine was administered to 94 infertile women with hypothyroidism. 59 women were diagnosed with mild thyroid dysfunction (TSH 4-6 mIU/L) and 35 with acute overt hypothyroidism (TSH >6.0 mIU/L). 76.6% of the treated patients had a successful pregnancy between six weeks and one year after initiation of treatment[15].

Infertility in women with Antithyroid Antibodies

The high levels of antithyroid peroxidase antibodies or antithyroglobulin antibodies in the serum of women with infertility has been an area of research interest. The relationship between anti-thyroid antibodies and the hypothalamus-pituitary-ovarian axis was verified in a study of seventeen infertile women. In this group these antibodies were detected in the follicular fluid and their concentration was positively associated with the corresponding serum concentration of these antibodies[16]. Other factors that may adversely affect fertility in women with autoimmune thyroid disease include advanced age, higher thyrotropin levels in comparison to healthy women, and the coexistence of other autoantibodies, such as antibodies to ovarian antigens, as in the case of autoimmune multiple cystic fibrosis[17]. The presence of antithyroid antibodies in women with infertility can be up to 18%, higher than the approximately 10% of women of reproductive age. In fact, 19% of women with normal thyrotropin levels and positive antithyroid antibodies at conception begin to have mild thyroid failure during pregnancy. The presence of thyroid-antibodies is associated with a three- to four-fold increased risk of spontaneous abortion Postpartum thyroiditis affects over 50% of pregnant women who test positive for antithyroid antibodies[18].

Recent studies have shown a possible association between high levels of antithyroid peroxidase antibodies and low ovarian reserve (LOvR) as assessed by the presence of antimullerian hormone and the number of antral follicles[19]. In a recent review study, antithyroid peroxidase antibodies were positive in 28.6% of women with low ovarian reserve, compared to 15.7% with normal and 9.5% with normal ovarian reserve (p = 0.020). Korevaar et al. showed that higher concetrations of antithyroid peroxidase antibodies in the low ovarian reserve group with

unexplained infertility (p < 0. 01), but no correlation was confirmed regarding antithyroglobulin antibodies[14]. The only prospective randomized study to date conducted in anti-TPO positive hypothyroid females, known as TABLET (Thyroid Antibodies and Levothyroxine Trial), proved that treatment with levothyroxine did not affect pregnancy rates.

There are several studies in the literature examining the association of autoimmune thyroid disorders on the likelihood of becoming pregnant with assisted reproduction techniques[20-23]. These studies are mainly retrospective and are distinguished by their heterogeneity, considering the various initial causes of infertility, the diversity of thyroid dysfunction (hypothyroidism, clinical hypothyroidism) and the different IVF methods (IVF, ICSI, IUI). It was previously mentioned that the presence of antithyroid antibodies is associated with poorer embryo quality, lower fertility rates and increased risk of spontaneous abortion[24-26]. Busnelli et al. reviewed the outcomes of twelve studies (six prospective and six retrospective) on the effect of antithyroid peroxidase and antithyroglobulin antibodies on the result of IVF/ICSI. Fertilization rates, pregnancy rates and clinical pregnancy rates did not differ significantly[27]. However, higher spontaneous abortion rates (OR 1. 44, 95% CI: 1. 06-1. 95 p = 0. 02) and lower live-birth rates (OR 0. 75, 95% CI: 0. 54-0. 99; p = 0. 04) were found. Poppe et al. compared 290 women with autoimmune thyroid disease with 1565 women without autoimmune thyroid disease in a ICSI cycle. The authors showed better pregnancy rates and lower incidence of miscarriage and suggested that ICSI, could be helpful for women with autoimmune thyroid disease, The European Thyroid Association, recommends ICSI as the most effective ART technique in infertile women with autoimmune thyroid disease[28]. On a recent systematic review on the impact of thyroid autoantibodies on clinical IVF outcomes, the authors concluded that most studies did not show an adverse effect of the positivity of these antibodies on IVF outcomes. However, they highlighted a tendency toward higher spontaneous abortion rates in women with antithyroid peroxidase and antithyroglobulin antibody positivity and IVF outcomes[29].

The influence of levothyroxine treatment on fertility rate, spontaneous abortion rate, and natality rate in infertile females with autoimmune thyroid disease undergoing IVF procedures was assessed in two prospective randomized clinical studies. Negro et al. presented the outcome of a research in which 72 infertile women that had antithyroid peroxidase antibodies were randomized to be given placebo or levothyroxine. The control group included 412 women who were infertile and were negative for antithyroid peroxidase antibodies. IVF results showed no difference in fertility rates among the three groups: 56% in the levothyroxine group, 49% in the placebo group, and 55% in the reference group. Women with positive antithyroid peroxidase antibodies had a higher risk of spontaneous abortion compared to controls (RR 2.01, 95% CI: 1.13-3.56, p = 0.028). Therefore, the authors suggest that levothyroxine treatment in women with positive antithyroid peroxidase antibodies did not improve the pregnancy rate in IVF cycles[30]. In another study on this topic, Wang et al. assessed the effects of levothyroxine treatment in infertile women with positive antithyroid peroxidase antibodies undergoing in IVF/ICSI. In this research, 600 infertile women were randomly assigned to a placebo group (n=300) or levothyroxine treatment group (n=300), and levothyroxine was administered at an initial dose of 25-50 μg/day 2-4 weeks before ovarian stimulation. The authors observed no statistically significant differences between the treatment and control groups in fertility rates (35.7% vs. 37.7%, p = 0.61), spontaneous abortion rates (10.3% vs. 10.6%, p = 0.94) and live birth rates (31.7% vs. 32.3%, p = 0.86)[31].

Infertility in Women with Hyperthyroidism

Increased SHBG, total estradiol, testosterone, and androstenedione concentrations are noticed in hyperthyroidism. This is due to the higher conversion rate of hormones from testosterone to estradiol and androstenedione to estrone. LH concentrations are increased but, in the majority of hyperthyroid women ovulation is maintained[32,33]. The most observed menstrual changes are oligomenorrhea and polymenorrhea (22% vs. 8%) comparing to normothyroid women. The prevalence of hyperthyroidism in infertile women is 2.1%, while the prevalence of infertility is 5.8-50% in women with hyperthyroidism[34]. Zähringer et al. studied the variation of FSH and LH levels in women with Graves' Disease. Study results showed an increase in LH secretion but there were no significant differences on pulse characteristics during LH and FSH secretion in comparison with healthy controls. The mechanism supporting elevated serum LH and FSH in women with hyperthyroidism is not yet clear. However, it has been supported that hyperthyroxinemia increases the gonadotropin response to GnRH[33].

The recurrence of menstrual irregularities differs in newer studies compared to older ones. Recent data suggest that menstrual abnormalities were found in 21.5% of women with hyperthyroidism. Kakuno et al. studied 586 reproductive age women with Graves' disease. The authors found that 18.3% of the sample had menstrual disorders. Furthermore, the presence of dysmenorrhea in patients with thyrotoxicosis (3.7%) was notably higher than in the healthy control group (0%)[32]. Quinto-Moro et al. investigated infertility in a study of 193 women with Graves' disease aged 18-50 years. The results showed that the incidence of infertility in Graves' disease was 52.3%. The mean age at diagnosis was 36.5 years. The average number of pregnancies was lower among women under 35 years of age at diagnosis and was always lower after diagnosis, regardless of age[35].

Regarding the pathophysiological mechanisms linking hyperthyroidism and female infertility, an increase in serum SHBG is considered an important and essential factor, resulting in an increase in androgens, their conversion rate, and estradiol. The second mechanism that can cause infertility in women with Graves' disease is through thyroid autoimmunity, where autoimmune processes cause infertility and miscarriage[36]. Thyroid antibodies are an indication of various levels of autoimmunity, suggesting that other autoimmune processes are responsible for infertility and miscarriage[37].

Conclusion

The present review aimed to investigate the impact of thyroid disorders on female fertility in association with infertility and early pregnancy issues such as miscarriages. Thyroid hormones and the hypothalamic-pituitary-ovarian axis interact in several ways and thyroid hormones may modulate ovarian functions. Hypothyroidism, especially in acute cases, causes ovulatory dysfunction and luteal hypoplasia as a result of decreased progesterone production. Levothyroxine supplementation restores the ovulatory function and ultimately resolves issues of infertility. There is insufficient evidence regarding the impact of overt hypothyroidism on female infertility.

Elevated serum concentrations of antithyroid peroxidase and antithyroglobulin antibodies in infertile women has been studied extensively. The recurrence of anti-thyroid antibodies in infertile women is high and is associated with a three- to four-fold increased risk of recurrent miscarriage. In addition, women with positive antithyroid antibodies tend to develop thyroiditis postpartum. The presence of anti-thyroid antibodies is associated with poorer embryo quality, lower fertilization rates and increased risk of spontaneous abortion. However, pregnancy rates and clinical pregnancy rates did not differ signifi-

cantly in most studies. Interestingly, recent studies have shown a possible association between high levels of antithyroid peroxidase antibodies and low ovarian reserve.

Regarding hyperthyroidism, increased levels of SHBG, total estradiol, testosterone, and androstenedione are noticed. Nonetheless, most hyperthyroid females maintain ovulatoty function. Disruptions in the menstrual cycle occur in women with thyrotoxicosis and the most frequently observed menstrual changes are oligomenorrhea and polymenorrhea. In hyperthyroid women the incidence of infertility is higher. The relationship between both hypothyroidism and hyperthyroidism and female infertility is a topic requiring further studies.

Author Contributions

Conceptualization, E.D. (Ekaterini Domali) and S.S.; methodology, A.P. and N.M.; validation, D.M. and R.V.; writing—original draft preparation, A.P. and I.C.; writing—review and editing, T.K. and E.D. (Eirini Drakaki); visualization, A.P. and P.P.; supervision, P.D. and E.D. (Ekaterini Domali); project administration, S.S. All authors have read and agreed to the published version of the manuscript.

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