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IMPROVING DIAGNOSTIC AND TREATMENT METHODS FOR INFERTILITY IN WOMEN WITH THYROID DISEASES

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ABSTRACT:

Thyroid disorders are one of the major contributors to women's reproductive health issue that affects ovulation, implantation, and even pregnancy. In this article, through extensive literature review we present the latest methods of diagnosing and treating infertility in females suffering from thyroid disorders. Along with discussing modern diagnostic approaches which involve laboratory tests of TSH, free T4, and thyroid antibodies, we also review the various treatment options like the use of levothyroxine and management of autoimmune conditions.

Introduction

Around the world, about 15% of couples have to deal with female infertility, and among the causes, thyroid dysfunction is recognized as a major one. The thyroid gland's hormone production is a vital factor for metabolic balance and developmental processes, and through a "chain" of interactions with the Hypothalamus-Pituitary-Gonadal axis, these hormones directly influence the reproductive system [1]. Thyroid conditions like hypothyroidism, hyperthyroidism, and thyroid autoimmunity can completely or partially block the pathways

of fertility by interfering with the various stages: ovarian maturation, menstrual periodicity, and implantation. It is the fertility but still not the pregnancy that brings the women with such disorders under the radar of medical professionals. Thyroid dysfunction at even subclinical levels or isolated thyroid autoimmunity has started to be seen as a barrier to successful reproduction and, therefore, necessitates evaluation and treatment in women trying to conceive [2]. The rates of thyroid disorders in the female population of childbearing age are reported to be around 2-4% for overt hypothyroidism, up to 15% for subclinical forms, and around 10-20% for the affected women with thyroid autoimmunity [3]. Not only that, the women who go through ART are at a higher risk compared to the general population for both thyroid dysfunction and autoimmunity which indicates a possible two-way relationship between thyroid pathology and reproductive disorders [4]. Yet, the treatment protocols for optimization are still in the process of being standardized [5].

Literature review

The physiological interplay between thyroid activity and female fertility has been widely recognized by researchers around the world. Lainez and Coss's study proved that the lack of thyroid hormones brings about increased prolactin secretion, which in turn inhibits the release of gonadotropin-releasing hormone, and hence the production of follicle-stimulating hormone and luteinizing hormone is reduced, resulting in ovulatory dysfunction [6]. Subclinical hypothyroidism, which is characterized by elevated thyroid-stimulating hormone and normal free thyroxine levels, is becoming a concern in reproductive medicine. The Russian literature has played a major role in revealing the extent to which thyroid disorders affect female fertility. Adamyan and co-workers critically assessed thyroid diseases in women and adolescent girls and stressed the necessity of early diagnosis and therapy to maintain the reproductive potential [7].

Rakhimova and her team presented new ways of diagnosing thyroid diseases by mentioning laboratory and imaging techniques which are now used in clinical practice [8]. Smetnik and Sazonova have studied the impact of thyroid gland pathology on the reproduction of women, thus giving an account of clinical patterns seen in Russian medicine and treatment results after thyroid hormone replacement therapy [9]. The interplay between thyroid autoimmunity and ovarian reserve has been investigated by Morales-Martínez et al., who demonstrated the presence of substantial links between positive thyroid antibodies and reduced levels of anti-Müllerian hormone, which indicates the possibility of the same

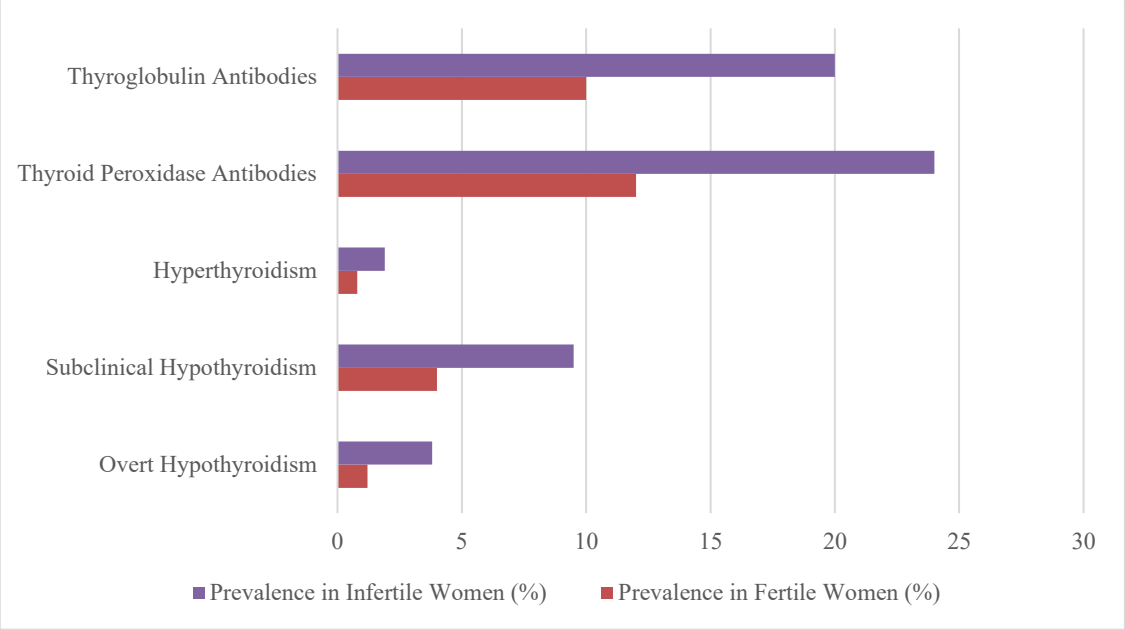
autoimmune mechanisms affecting the functions of both the thyroid and the ovaries [10]. This study lends credence to the theory that thyroid autoimmunity could be one of the markers for the general autoimmune processes that are affecting the reproductive organs.

Research methodology

The topic of this article is infertility treatment and diagnosis of women with thyroid diseases, and it performed a systematic literature review for analyzing the published evidence. The criteria for inclusion were original research articles, systematic reviews, meta-analyses, and clinical guidelines that considered thyroid function evaluation and treatment in infertile women; on the contrary, the criteria for exclusion were restricted to case reports, unsubstantiated opinion pieces, and studies concentrating solely on male infertility or pregnancy management instead of conception. The selected publications were appraised according to methodological quality, clinical practice relevanc, and contribution to the understanding of thyroid-reproductive relationships. Data extraction weighted heavily on the diagnostic methods used, treatment protocols rolled out, outcome measures highlighted, and clinical implications stated. There were specific studies that furnished worthwhile data on the fertility outcome post-thyroid treatment, the prevalence of thyroid dysfunction among infertile population groups, and the comparative effectiveness of different therapeutic means, which drew attention from the research team.

Analysis and results

Current literature analysis has revealed that the relationship between thyroid dysfunction and female infertility is supported by substantial evidence, and the reproductive outcomes are affected in a quantifiable way through various dimensions. Epidemiological studies show that the occurrence of thyroid disorders is significantly higher in women with infertility when compared to women of the same age in the general population, thus indicating the presence of causal relationships rather than just association. The data regarding the prevalence of different thyroid disorders in infertile and fertile women, which has been collected from various global studies, is shown in Picture 1.



Picture 1. Prevalence of Thyroid Disorders in Fertile and Infertile Women

The data displayed throughout the study indicate that there was a significant rise in the thyroid dysfunction prevalence rate in infertile population groups characterized by subclinical diseases being particularly high. The new findings affirmed the suggested routine thyroid screening of women with infertility and mentioned the fact that even minor thyroid disorders could be one of the reasons for the fertility problems. The by 2-3 times or even more increases seen in different thyroid conditions demonstrate their massive clinical relevance and thus, calling for their aggressive diagnosis. Within reproductive endocrinology field diagnostic parameters and the best TSH levels concerning fertility have been extensively studied and argued over. Although normal thyroid-stimulating hormone is usually defined as 0.4-4.5mIU/L based on reference ranges of the general population, the pregnancy and infertility studies recommend that more strict limits should be set for women seeking pregnancy. Table 1 presents the different studies' TSH thresholds and reproductive outcomes ranging from fertility potential to the success rates of assisted reproductive technologies.

Table 1. Thyroid-Stimulating Hormone Levels and Reproductive Outcomes

TSH Range (mIU/L)	Spontaneous Conception Rate (%)	IVF Pregnancy Rate (%)	Early Pregnancy Loss Rate (%)	Clinical Recommendation
<0,4	18,5-22,0	32,0-36,0	22,0-28,0	Evaluate for hyperthyroidism
0,4-2,5	28,0-32,0	42,0-48,0	12,0-15,0	Optimal target range
2,5-4,0	22,0-26,0	35,0-40,0	18,0-23,0	Consider treatment
4,0-10,0	14,0-18,0	24,0-30,0	28,0-35,0	Treatment recommended
>10,0	6,0-10,0	12,0-18,0	42,0-52,0	Treatment essential

The data indicate a major connection between the levels of thyroid-stimulating hormone and the reproductive outcomes, with the best fertility at 0,4 to 2,5 mIU/L thyroid-stimulating hormone. As the levels of thyroid-stimulating hormone rise above 2,5 mIU/L, the rates of conception go down gradually, while the rates of early pregnancy loss show the opposite correlation, increasing significantly as the level of thyroid-stimulating hormone goes up. These results are a strong backing for the current clinical practice of treating subclinical hypothyroidism in women who are trying to get pregnant and keeping thyroid-stimulating hormone levels lower than those that are applied to the general population. The data clearly points to the fact that women with overt hypothyroidism where the level of thyroid-stimulating hormone is over 10,0 mIU/L, suffer a sever reproductive compromise which is manifested by the pregnancy rates that are about 70% lower when compared to euthyroid women. An enormous number of studies have characterized the treatment outcomes after levothyroxine supplementation in hypothyroid infertile women and the majority of them reported a significant improvement in ovulatory function, conception rates, and pregnancy outcomes, respectively. The effectiveness of treatment is variable and is related to the degree of thyroid dysfunction, the existence of thyroid autoimmunity and individual patient factors. Data summarized in Table 2 reflect treatment outcomes across various categories of thyroid dysfunction.

Table 2. Treatment Outcomes in Infertile Women with Thyroid Dysfunction

Patient Category	Pre-Treatment Pregnancy Rate (%)	Post-Treatment Pregnancy Rate (%)	Treatment Duration to Conception (months)	Live Birth Rate (%)
Overt Hypothyroidism	8,0-12,0	32,0-38,0	6,0-12,0	28,0-34,0
Subclinical Hypothyroidism	18,0-24,0	34,0-42,0	4,0-8,0	32,0-38,0
Euthyroid with TPO Antibodies	22,0-28,0	30,0-36,0	3,0-6,0	28,0-34,0
Hyperthyroidism (post-treatment)	12,0-16,0	28,0-34,0	8,0-14,0	24,0-30,0

The data on treatment outcomes have shown that there was a considerable increase in the rate of pregnancies after the adoption of proper thyroid hormone replacement or antithyroid treatment. The most noteworthy increase was in the case of women with overt hypothyroidism. About 3 to 4 times larger pregnancy rates are seen in these patients with levothyroxine supplementation, but the conception is usually six to twelve months of treatment to reach the optimal thyroid hormone levels and restore the function of the reproductive system. The treatment of women with subclinical hypothyroidism is also very helpful, and their pregnancy rates are increasing from about 20% to 38%, which is a huge clinical benefit. The treatment of euthyroid women with positive thyroid peroxidase antibodies has been showing not so impressive results, indicating that thyroid autoimmunity's impact on reproduction may be via mechanisms other than just thyroid hormones deficiency. There is still the current evidence that supports the use of levothyroxine in antibody-positive euthyroid women receiving assisted reproductive technologies, although the benefits for spontaneous conception remain rather vague. The time to get pregnant after starting the treatment varies a lot, with most pregnancies happening within three to twelve months depending on the initial dysfunction severity and other factors of the individual patient such as age, ovarian reserve, and the presence of additional fertility factors.

The diagnostic approaches were analyzed and it was found that a thorough thyroid check up should include the measurement of thyroid-stimulating hormone, free thyroxine, and antithyroid antibodies in the first infertility evaluation with ultrasound imaging being done only for patients with antibody positivity or visible thyroid abnormalities. Isolated thyroid autoimmunity or central hypothyroidism might be missed by measuring thyroid-stimulating hormone only, while the comprehensive assessment uncovers about 15-25% more women with thyroid diseases that are either clinically relevant for treatment or monitoring. One of the major implications of subclinical hypothyroidism in fertility has been supported by studies which showed that this condition does not only compromise gold fertility but does also benefit from treatment. Even if the controversy on the general population's thyroid-stimulating hormone limit of 2.5 mIU/L rages on, current evidence still stands firm in advocating treatment for subclinical hypothyroidism in women trying to conceive with thyroid-stimulating hormone greater than 2.5 mIU/L. The lower target is the result of infertility specialists' requirements for the turning of every possible factor to their advantage and the big ground of evidence backing up the improvement of outcomes with treatment. In general, dosing of Levothyroxine for fertility enhancement starts at 25-50 micrograms per day for mild subclinical hypothyroidism and at 50-100 micrograms per day when the increase is more significant, with further adjustments depending on the results of thyroid-stimulating hormone checked every four to six weeks until the target levels are reached.

Conclusion

Based on the thorough review of existing literature, it is concluded that thyroid dysfunction is one of the major and modifiable factors for female infertility which can be corrected by using the evidence-based diagnostic and treatment approaches. Thyroid abnormalities are noted in women with infertility two to three times more than in normal women and roughly 15-30% of women undergoing fertility treatment are affected by thyroid disorders when the subclinical conditions and thyroid autoimmunity are considered. Thyroid hormones as well as reproductive system are interlinked through various ways like direct impact on ovarian, oocyte quality and endometrium as well as indirectly through gonadotropin modulation and metabolism. Clinically, overt or subclinical hypothyroidism is the main cause of infertility by anovulation, defective luteal phase and poor implantation while autoimmune thyroiditis is responsible for reproductive failure in even euthyroid women by inflammatory and ovarian failure mechanisms. Diagnostic routes for infertility should include routine thyroid screening tests such as thyroid-stimulating hormone, free

thyroxine, and antithyroid antibodies as the main components of evaluation rather than secondary tests which are done only after excluding other causes. Evidence implicates strict thyroid-stimulating hormone benchmarks for women who seek to conceive and the best fertility is noticed when the titers are from 0.4 to 2.5 mIU/L which is lower than the general population reference range going up to 4.5mIU/L. Treatment with levothyroxine effectively restores reproductive function in hypothyroid women, with pregnancy rates improving three-to-four-fold following appropriate supplementation. Subclinical hypothyroidism treatment provides clinically meaningful benefits, supporting recommendations for intervention when thyroid-stimulating hormone exceeds 2,5 mIU/L in fertility contexts.

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