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Role of Sex Bias in Hypothyroidism

Does Sex Bias Play a Role for Dissatisfied Hypothyroid Patients?Elizabeth A. McAninch, M.D.,¹ Jennifer S. Glueck, M.D.,¹ and Antonio C. Bianco, M.D.²¹*Division of Endocrinology and Metabolism, Rush University Medical Center, Chicago, IL, USA;*²*Section of Endocrinology, Diabetes and Metabolism, University of Chicago, Chicago, IL, USA*

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The current state of the diagnosis and management of thyroid disease cannot be separated from the larger context of women's health due to (i) the disproportionate incidence and prevalence of functional and structural thyroid diseases among women versus men, (ii) the role of thyroid health on fertility, pregnancy and postpartum, and (iii) the challenge posed in managing the nonspecific symptoms of functional thyroid disease in the context of menopause. Here we explore the hypothesis that sex bias has played a role in the management of thyroid diseases historically, and has extended into the modern medical era. Once knowledge gaps that may have resulted from sex bias are recognized, we can strive to overcome this bias, and develop better treatments to improve patient outcomes universally.

Sex bias played a role in the history of thyroid disease. We hypothesize that sex bias may persist today and contribute to patient dissatisfaction in hypothyroidism.

Background

Ms. A.D., a previously healthy, 38-year-old G1P1 woman, presented to her obstetrician at 4 months postpartum with new complaints of tremor, palpitations, heat intolerance, menstrual irregularities, and anxiety. Duloxetine was initiated for postpartum mood disorder. After two months, her symptoms intensified, prompting referral to psychiatry. The patient felt dismissed and alienated by this recommendation, and was overwhelmed with caring for her newborn in the context of these symptoms. An internet search led her to conclude that she could have a thyroid abnormality, prompting her to present to endocrinology. At our initial encounter, six months postpartum, labs included serum TSH 0.01 uIU/mL, free T4 1.2 ng/dL, and total T3 104 ng/dL.

Our interest in women's health and thyroid disease was ignited while studying the historical foundation underlying the dissatisfaction that at least 15% of hypothyroid patients experience on levothyroxine monotherapy (1). Given that thyroid disorders are more common in women (2) and the distinction between psychiatric and thyroid disorders has not always been straightforward (3-5), these two factors combined could have led to sex bias historically, as was commonplace in many medical disciplines, that persisted into the modern era. Indeed, patient dissatisfaction and the feeling of being dismissed, particularly in hypothyroidism, remains common (6), making management of hypothyroidism a controversy in modern medicine (1). Anecdotal observations in our own thyroid practices are that dissatisfied hypothyroid women do feel dismissed and seek a physician that believes them. Here we explore the role of sex in the context of thyroid disease; we propose studies that can illuminate these problems to empower female patients where they once felt dismissed.

Epidemiology and Difficult Diagnosis Set the Stage for Sex Disparity

Thyroid disorders can be considered generally in three categories: (i) functional diseases, the clinical syndromes resulting from excess or inadequate supply and/or action of thyroid hormone (i.e. hyper- and hypothyroidism respectively), (ii) structural diseases, such as thyroid nodules and cancer, and (iii) the functional and structural thyroid diseases resulting from iodine deficiency. Yet the epidemiology is consistent across this broad spectrum of pathologies: thyroid diseases afflict far more women than men. Hypothyroidism and hyperthyroidism are about 10 times more common in women than men (2); thyroid nodules and thyroid cancer are about 3 times more common in women than men (2). This epidemiologic discrepancy has been recognized for over a century (3,4). In addition, during pregnancy and postpartum women are uniquely susceptible to certain thyroid conditions such as postpartum thyroiditis, thyroid disease can have a role in female fertility and, in perimenopause, nonspecific symptoms of thyroid disease are notoriously difficult to diagnose and manage. Recognition of the epidemiologic sex discrepancy in thyroid disease has driven much investigation, leading to growth in our understanding of underlying disease mechanisms.

The difficulty in the differential diagnosis between thyroid diseases and primary psychiatric disorders stems from the fact that overt hypo- and hyperthyroidism can present with dramatic, secondary behavioral symptoms. In ancient times extending into the 19th century, women were thought to be uniquely subject to the psychiatric condition hysteria (now termed conversion disorder), from the Greek word for uterus (4). The treatment of hysteria could include vaginal douching and asylum committal (4). But by the mid-19th century, some hypothesized that an underlying thyroid pathology could be contributing to these women's mental state (3). Dr. Robert Graves proposed that women suffering from hysteria had an underlying thyroid condition in his seminal description of what would later be known as Graves' disease (3). And by the early 20th century other clinicians also directly implicated the thyroid as a cause of hysteria (4,5), noting skepticism about the theory that implicated the uterus as being the organ from which the psychological symptoms arose: "hysteria has never yet been definitely defined. There has never been a lesion found; the condition has never been explained. What better etiology do we require to explain the manifold manifestations of hysteria than in disturbance of this emotional [thyroid] gland?" (5).

Some physicians began to acknowledge that not only were supposed cases of hysteria actually secondary manifestations of functional thyroid disorders, but they were able to tease out differences in the clinical presentations between hyper- and hypothyroidism in noting the particular features exhibited, "the crying, the laughing, the flushing, the sweating, the rapid heart, the pains without reason, and even the hysterical fever can all be accounted for by reference to the thyroid. The opposite hysterical indifference, apathy, slow heart, hysterical moroseness, and even hysteroepilepsy, may be accounted for by subsecretion, or hyposecretion, of the thyroid" (5).

We feel that the case of Ms. A.D. illustrates the present day problem: despite it being well-established that thyroid disorders are epidemiologically female predominant (2) and can present with secondary psychiatric symptoms, some clinicians lack adequate awareness and can miss early opportunities to appropriately screen, diagnose, and treat women with thyroid disease.

Dismissal Then and Now

Because of the difficulty distinguishing between thyroid and primary psychiatric diseases (3-5), and the observation that children with cretinoid features often had mothers with goiter (4), physicians concluded that women with Graves' disease (5) and thyroid disease in general,

“should not marry”. Thus, through the early 20th century women with thyroid diseases were being dismissed in the absence of adequate diagnostic and therapeutic tools.

A recent, large survey demonstrated that in 10664 female and 502 male respondents, women were more likely to be dissatisfied with their hypothyroid treatments than men (OR=1.68; $p<0.001$) (6). The dissatisfaction that some hypothyroid patients harbor for their physicians is high (6); thus, it is conceivable that some dismissal of patients with thyroid disease persists to this day. It is becoming more accepted that many hypothyroid patients express dissatisfaction with their treatment plans due to concerns including weight management, fatigue, mood and memory problems (1,6). It is not clear whether dissatisfied patients experience (i) both hypothyroidism and primary mood disorder, in which case consultation with a psychiatric expert would be appropriate, or (ii) residual secondary mood symptoms due to their primary thyroid disease. While true that mood disorders are also very prevalent, and women have a 2-3 fold increased risk of depression versus men, the overlap with hypothyroidism has not been clarified.

Sex bias has been shown to impact a broad spectrum of diseases (7). Thus the evidence that women are more dissatisfied with their hypothyroid treatments than men (6) supports the logical hypothesis that sex bias plays a role in hypothyroidism. Studies to specifically investigate the impact of potential bias against women with hypothyroidism are justified; pursuit of such research would be in accordance with recent recommendations from the American College of Physicians (7). Clinical investigators should report sex-specific data (e.g. subgroup analyses for treatment satisfaction), address sex-specific differences in disease treatments, and include women participants of diverse races or ethnicities (7). Only when we clearly define the problem can we develop and apply solutions.

While true that endocrinology is increasingly female provider predominant (8), this might not be enough to reduce sex bias for patients with hypothyroidism. Positive developments include increased interest by professional societies in founding women’s groups within the field. Fifteen years ago the American Thyroid Association (ATA) started a Women in Thyroidology group with the mission to recruit more women and better address women’s thyroid health topics at meetings; the ATA also supports research grants focusing on projects involving thyroid in pregnancy and fetal development. Similarly, the Endocrine Society has a women’s group, Women in Endocrinology. In our opinion, more effort could be targeted to this important issue, starting with research to pinpoint the extent of any potential sex bias in thyroid disease, and hypothyroidism specifically.

Conclusions

The extent and direct impact that sex bias has had in the development of our contemporary standards of care in hypothyroidism remains undefined. Only through recognition of potential knowledge gaps that may have resulted from sex bias, can we perform research to clarify any potential bias and develop strategies to improve patient outcomes universally. It is important to acknowledge the potential impact of bias for the quality of life of all patients with thyroid disease. Hopefully patients that were once dismissed, like Ms. A.D., will become a fleeting memory in thyroid history.

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EAM: formulated hypotheses, performed literature search, drafted manuscript, edited manuscript; JSG: prepared clinical vignette, edited manuscript; ACB: discussed hypotheses and edited manuscript

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