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CLINICAL AND PATHOGENETIC FEATURES OF PROLACTIN SECRETION DISORDERS IN REPRODUCTIVE-AGE WOMEN WITH AUTOIMMUNE THYROIDITIS

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ABSTRACT

Autoimmune thyroiditis (AIT) is a prevalent autoimmune thyroid disorder in women of reproductive age, and associated thyroid dysfunction may influence hypothalamic–pituitary regulation of prolactin (PRL). The clinical significance of this relationship remains uncertain in euthyroid and subclinical hypothyroid states, particularly when total circulating PRL is interpreted without assessment of its molecular fractions. This narrative review critically synthesizes evidence concerning thyroid autoimmunity, thyroid functional status, prolactin secretion, macroprolactinemia and reproductive manifestations, drawing on clinical studies, systematic reviews and professional recommendations. The most established mechanism is increased thyrotropin-releasing hormone stimulation of pituitary lactotrophs during primary hypothyroidism. A study published in 2025 reported higher mean PRL concentrations among reproductive-age women with AIT than among controls and in subclinical hypothyroidism compared with euthyroid AIT; however, the observational association does not establish causation. Routine PRL immunoassays may also detect macroprolactin, potentially leading to an overestimation of clinically relevant hyperprolactinemia. When indicated, polyethylene-glycol precipitation and interpretation of post-precipitation PRL against assay-specific reference intervals help distinguish predominant macroprolactinemia from elevated monomeric PRL. An integrated approach incorporating thyroid-stimulating hormone, free thyroxine, thyroid autoantibodies, PRL fractions, clinical symptoms and relevant confounders may improve diagnostic interpretation. Prospective studies using standardized sampling and fraction-specific PRL measurements are needed to establish the frequency and reproductive implications of these abnormalities.

Keywords: autoimmune thyroiditis; Hashimoto thyroiditis; prolactin; hyperprolactinemia; macroprolactin; monomeric prolactin; subclinical hypothyroidism; reproductive health.

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INTRODUCTION

Autoimmune thyroiditis (AIT), most commonly manifested as Hashimoto thyroiditis, is characterized by immune-mediated thyroid injury and the presence of thyroid-directed autoantibodies, particularly antibodies to thyroid peroxidase (TPOAb) and thyroglobulin (TgAb). Its clinical spectrum extends from preserved thyroid function to subclinical and overt hypothyroidism. Among women of reproductive age, AIT is relevant to reproductive endocrinology because thyroid hormones contribute to ovarian physiology, menstrual regulation and fertility-related processes. Nevertheless, associations between thyroid autoimmunity and impaired reproductive outcomes differ across patient groups and study designs, and antibody positivity should not be equated with thyroid hormone deficiency [1–3].

Prolactin (PRL), an anterior pituitary hormone predominantly inhibited by hypothalamic dopamine, represents another component of this endocrine interaction. Thyrotropin-releasing hormone (TRH) can stimulate lactotrophs, and increased TRH drive in primary hypothyroidism offers a physiological explanation for elevated PRL in some patients [4,5]. However, thyroid dysfunction does not invariably produce hyperprolactinemia, and elevated PRL is not specific to AIT. Diagnostic interpretation is further complicated by heterogeneity of circulating PRL: routine assays measure total immunoreactive hormone, which may include macroprolactin with reduced biological activity [6,7]. Against this background, the purpose of the present article is to examine the clinical and pathogenetic relationship between AIT and PRL secretion, synthesize the evidence on reproductive consequences and develop a coherent approach to interpreting thyroid function and prolactin fractions in reproductive-age women.

LITERATURE REVIEW

Research on the relationship between thyroid autoimmunity and reproductive health has developed along two closely connected lines: the biological consequences of altered thyroid hormone availability and the potential reproductive effects of thyroid-directed immune responses. Caturegli and colleagues [2] described the diagnostic distinction between autoimmune thyroid injury and clinically relevant functional impairment, whereas Carafone and colleagues [1] reviewed the complex interactions between autoimmune thyroid disorders and female fertility. More recent publications have addressed ovarian reserve and ovarian hypofunction in autoimmune thyroid disease [3,12], emphasizing that these outcomes cannot be attributed to one hormonal mechanism without accounting for age, ovarian status and concomitant endocrine disorders. Collectively, these studies provide a rationale for assessing thyroid function and reproductive phenotype together, while also demonstrating the limitations of interpreting antibody titres in isolation.

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The endocrine literature establishes that PRL secretion is regulated through dynamic hypothalamic–pituitary mechanisms, with dopaminergic inhibition and TRH-mediated stimulation among the central pathways [4,11]. Professional guidance on hyperprolactinemia and prolactin-secreting pituitary adenomas underscores the importance of considering pregnancy, lactation, medication exposure, renal dysfunction, physiological stress and pituitary disease before attributing an elevated PRL concentration to a single diagnosis [4,5,7,8]. The clinical association between thyroid-stimulating hormone and prolactin has also been explored among women evaluated for infertility, including in a systematic review and meta-analysis [13]. However, evidence obtained in heterogeneous infertility populations does not directly quantify the occurrence of PRL disturbances specifically among women with AIT.

A further strand of research examines the interaction between PRL and immune processes. PRL has recognized immunomodulatory activity, which has prompted hypotheses concerning bidirectional influences between prolactin signaling and autoimmune pathology [9]. Such mechanisms are biologically plausible but remain insufficient to establish that PRL independently initiates or aggravates AIT in an individual patient. Direct clinical data are comparatively scarce: Buldygina and colleagues [10] reported differences in PRL concentrations across thyroid functional categories among reproductive-age women with AIT. Their observations strengthen the clinical relevance of functional stratification while leaving questions of causality, generalizability and potential confounding unresolved.

Laboratory studies and professional position statements highlight a separate methodological limitation: total PRL may be increased because of macroprolactin rather than a clinically significant elevation of the monomeric fraction. Contemporary recommendations support the use of polyethylene-glycol (PEG) precipitation in appropriate circumstances and insist on interpreting residual PRL with assay-specific post-PEG reference intervals [6–8]. Although this approach can reduce misclassification, relatively few studies have assessed prolactin fractions in carefully defined AIT cohorts alongside menstrual, ovulatory and fertility outcomes. The existing literature therefore supports an integrated, fraction-aware diagnostic framework, but not a universal assumption that thyroid autoimmunity directly causes biologically active hyperprolactinemia.

MATERIALS AND METHODS

This study was designed as a narrative clinical literature review and interpretive synthesis rather than a prospective or retrospective patient-based investigation. Relevant publications were identified in PubMed, PubMed Central and journals specializing in endocrinology and reproductive medicine through combinations of the terms ‘autoimmune

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thyroiditis', 'Hashimoto thyroiditis', 'prolactin', 'hyperprolactinemia', 'macroprolactin', 'subclinical hypothyroidism', 'reproductive-age women' and 'female fertility'. Particular emphasis was placed on clinical studies directly examining PRL concentrations in women with AIT, professional recommendations on the diagnosis of hyperprolactinemia and macroprolactinemia, and reviews evaluating thyroid autoimmunity in reproductive medicine. Information was synthesized by thyroid functional category, neuroendocrine mechanism, PRL molecular form, clinical manifestation and diagnostic applicability. Quantitative values are reproduced only where they were reported in the cited study; no patient-level data, new laboratory observations or pooled effect estimates were generated. Because the search was targeted and narrative, no registered systematic review protocol, duplicate independent screening, formal risk-of-bias assessment or meta-analysis was performed. As no human participants were enrolled and no identifiable patient information was processed, ethical approval and individual consent were not applicable to the preparation of this review.

RESULTS

The reviewed evidence indicates that thyroid autoimmunity and thyroid dysfunction should be assessed as related but distinct clinical dimensions. In patients with AIT, TPOAb and TgAb support the autoimmune diagnosis, whereas thyroid-stimulating hormone (TSH) and free thyroxine (FT4) characterize functional status [1,2]. Euthyroid AIT, subclinical hypothyroidism (elevated TSH with FT4 within the reference interval) and overt primary hypothyroidism (elevated TSH with reduced FT4) represent clinically different states and should not be combined when evaluating PRL concentrations. Autoantibody levels do not independently establish the severity of thyroid hormone deficiency, and interpretation of TSH and FT4 remains dependent on the assay's reference intervals and the patient's clinical context.

At the hypothalamic–pituitary level, dopamine provides tonic inhibitory input to lactotrophs through D2 receptors, whereas TRH can stimulate PRL synthesis and release. Reduced thyroid hormone feedback in overt primary hypothyroidism may increase hypothalamic TRH activity, thereby stimulating both thyrotrophs and lactotrophs [4,5,11]. The magnitude of the resulting PRL response is variable, especially in mild or subclinical disease. Sleep, stress, venipuncture-associated distress, exercise, pregnancy, lactation, medication effects and impaired renal clearance may influence PRL independently of thyroid status; consequently, a single elevated result cannot determine its cause [5,8]. In parallel, immunological research suggests potential links between PRL signaling and lymphocyte function, but these observations remain mechanistic hypotheses rather than evidence that PRL causes AIT [9]. Figure 1 summarizes the proposed physiological relationships and the main points at which clinical interpretation may be confounded.

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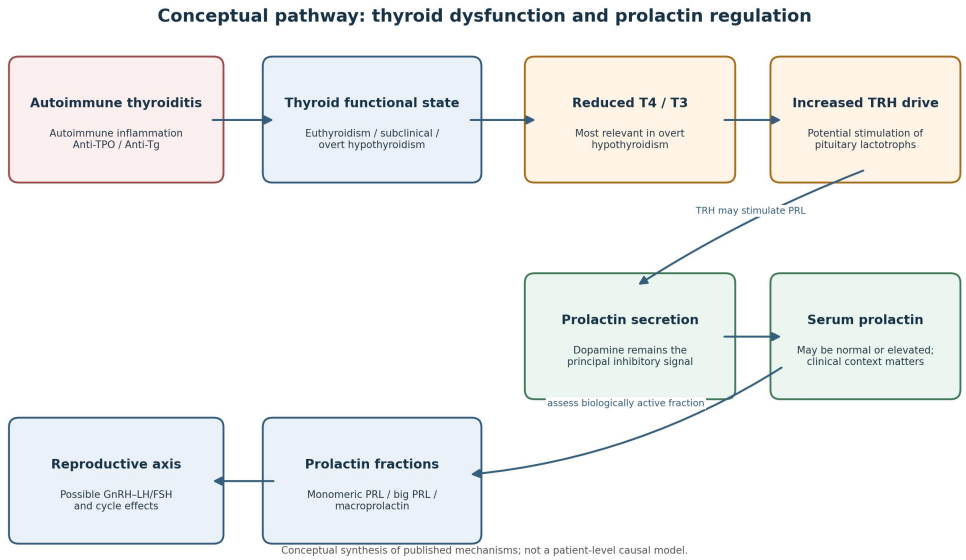


Figure 1. Conceptual pathway linking autoimmune thyroiditis, thyroid functional impairment and prolactin regulation. The scheme illustrates established physiology and a plausible endocrine relationship; it is not a patient-level causal model.

The most directly relevant clinical data were presented by Buldygina and colleagues in 2025. In their study of reproductive-age women, mean PRL was higher in the AIT group than among controls (18.24 ± 1.61 versus 12.24 ± 1.64 ng/mL; $p < 0.05$). Within the AIT cohort, women with subclinical hypothyroidism had higher mean PRL than euthyroid participants (25.45 ± 5.29 versus 16.48 ± 1.46 ng/mL; $p < 0.05$), and PRL showed a weak inverse correlation with FT4 (Spearman $r = -0.27$; $p = 0.043$) [10]. These findings are compatible with a relationship between thyroid functional status and prolactin secretion, but the observational design and modest correlation preclude causal inference. Moreover, the reported group means are not prevalence estimates for all reproductive-age women with AIT; interpretation depends on sample composition, immunoassay characteristics, medication exposure and the assessment of competing causes of PRL elevation. The principal findings are summarized in Table 1.

Table 1. Selected findings reported by Buldygina et al. (2025) [10]. Numerical values originate from the cited study and were not generated for this review.

Parameter	AIT group / subgroup	Reported value	Interpretation
Mean PRL	AIT vs control	18.24 ± 1.61 vs 12.24 ± 1.64 ng/mL; $p < 0.05$	Higher mean PRL in the AIT group in this study.
Mean PRL	Subclinical hypothyroidism + AIT vs euthyroid AIT	25.45 ± 5.29 vs 16.48 ± 1.46 ng/mL; $p < 0.05$	Higher mean PRL in the subclinical hypothyroid subgroup.

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Parameter	AIT group / subgroup	Reported value	Interpretation
PRL–FT4 association	AIT cohort	Spearman r = −0.27; p = 0.043	Weak inverse correlation; not evidence of causality.
Euthyroid AIT	TSH strata around 2.5 mIU/L	No significant PRL difference reported	A higher-normal TSH alone did not identify a significant PRL difference in this study.

Interpretation of circulating PRL also requires recognition of its molecular heterogeneity. Monomeric PRL, with a molecular mass of approximately 23 kDa, constitutes the principal biologically active circulating fraction. Larger molecular forms include 'big' PRL and macroprolactin ('big-big' PRL), the latter frequently consisting of PRL bound to immunoglobulin G. Macroprolactin generally has lower biological availability than monomeric PRL, but both forms may coexist in the same sample [6,7]. As conventional immunoassays differ in their sensitivity to these molecular forms, an isolated elevation in total PRL may overstate the presence of physiologically relevant hyperprolactinemia. Table 2 outlines the main fractions and their interpretive significance.

Table 2. Principal molecular forms of circulating prolactin and their laboratory relevance [6,7]. Molecular-size ranges are approximate.

PRL form	Approximate molecular size	Clinical / laboratory relevance
Monomeric PRL	≈23 kDa	Main biologically active circulating form; post-PEG concentration is clinically relevant.
Big PRL	≈40–60 kDa	Dimeric or intermediate molecular forms; may contribute to total assay result.
Macroprolactin	Usually >150 kDa	Often PRL–IgG complexes; may produce elevated total PRL with limited biological activity.

PEG precipitation is a practical screening procedure for macroprolactin because it removes a substantial proportion of high-molecular-weight PRL complexes, allowing the residual hormone concentration to be measured. PRL recovery is usually expressed as the proportion of appropriately dilution-corrected post-PEG PRL relative to baseline total PRL. According to the 2025 professional position statement, recovery below 40% commonly suggests macroprolactin predominance, while recovery above 60% is more consistent with its absence; intermediate results may require additional investigation [6]. These thresholds must not replace assay-specific post-PEG reference intervals, since low percentage recovery does not guarantee that the remaining biologically active fraction is normal. Macroprolactinemia and monomeric hyperprolactinemia may coexist, and gel-filtration

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chromatography, although less feasible for routine testing, remains an important reference technique for characterization of molecular forms [6,7].

Accordingly, the evaluation of a woman with AIT and suspected PRL disturbance should integrate symptoms, sampling conditions, current medications and plausible alternative explanations for biochemical findings. Modestly elevated or discordant PRL results may warrant repeat measurement under appropriate conditions, with pregnancy, medication effects, thyroid function, renal impairment and possible pituitary pathology considered according to the clinical presentation [5,8]. TSH and FT4 help classify thyroid functional status; TPOAb and, when indicated, TgAb support the autoimmune diagnosis; total PRL and fraction-specific results clarify the endocrine phenotype. Menstrual irregularity, galactorrhea, suspected anovulation and fertility concerns guide the significance of these laboratory findings. The resulting framework is summarized in Table 3 and is intended to support clinical interpretation rather than function as a validated diagnostic score.

Table 3. Literature-informed assessment framework for women with AIT and suspected prolactin disturbance [5–8].

Assessment domain	Suggested evaluation	Purpose / interpretive note
Thyroid function	TSH and FT4	Classify euthyroid, subclinical or overt hypothyroid status.
Autoimmune markers	TPOAb; TgAb when clinically indicated	Support autoimmune thyroiditis diagnosis; antibodies do not substitute for functional tests.
Prolactin	Serum total PRL; repeat if result is modestly elevated or discordant	Use assay-specific reference interval and consider stress / pulsatility.
Prolactin fractions	PEG precipitation; post-PEG PRL and recovery	Assess macroprolactin and residual monomeric PRL.
Confounders	Pregnancy, lactation, medicines, renal and hepatic status, stress	Avoid attributing all PRL elevation to AIT.
Reproductive phenotype	Menstrual history, galactorrhea, ovulatory / fertility history as relevant	Correlate biochemical findings with clinical presentation.

The reproductive implications of these findings depend primarily on sustained biologically active hyperprolactinemia and its cause. Elevated monomeric PRL may suppress hypothalamic gonadotropin-releasing hormone pulsatility and alter gonadotropin secretion, potentially contributing to oligomenorrhea, amenorrhea, anovulation, galactorrhea and impaired fertility [5,8]. Nevertheless, thyroid status, thyroid autoimmunity, age, ovarian reserve and coexisting endocrine disorders can independently

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influence reproductive function [1,3,12]. Consequently, menstrual or fertility problems in women with AIT should not automatically be attributed to PRL, and an elevated total PRL result should not be assumed to reflect a biologically significant excess without appropriate evaluation for macroprolactin. Conversely, a normal PRL result does not exclude reproductive dysfunction associated with thyroid hormone imbalance or another clinical condition.

DISCUSSION

The literature reviewed supports a clinically plausible connection between thyroid dysfunction and prolactin regulation, particularly in overt primary hypothyroidism, where TRH-mediated stimulation of lactotrophs is a well-established physiological mechanism [4,5]. By contrast, the extent to which euthyroid AIT or subclinical hypothyroidism alters PRL secretion remains uncertain. The findings of Buldygina and colleagues [10] provide direct clinical evidence of an association in reproductive-age women and suggest that thyroid functional stratification is important when interpreting PRL. However, observational differences in mean hormone concentrations do not establish that autoimmune activity itself is the causal factor, and the weak inverse correlation with FT4 does not exclude residual confounding or interindividual physiological variability. Studies reporting an association should therefore distinguish autoimmune serological status from the consequences of thyroid hormone insufficiency.

An additional interpretive issue arises from the difference between immunoreactive total PRL and the physiologically relevant monomeric fraction. The inclusion of macroprolactin in an assay result may lead to erroneous classification of hyperprolactinemia, unwarranted pituitary investigations or unnecessary treatment. Recent guidance emphasizes the value of post-PEG measurement, percentage recovery and assay-specific reference limits in appropriate patients [6–8]. This distinction is especially important in research cohorts, because misclassification at baseline could obscure genuine relationships between thyroid status, PRL signaling and reproductive outcomes. The combined assessment of TSH, FT4, thyroid autoantibodies, clinical phenotype and fraction-specific PRL is therefore more informative than reliance on any individual biochemical marker.

Future prospective studies should recruit clearly characterized AIT cohorts, prespecify euthyroid, subclinical and overt hypothyroid categories, and standardize PRL sampling conditions. Pregnancy, lactation, medication use, renal dysfunction, acute stress and suspected pituitary disease should be addressed as exclusion criteria or measured covariates rather than ignored. Laboratory reporting should include total PRL, post-PEG PRL and recovery percentage, with reproductive outcomes assessed using reproducible definitions. The present review is limited by its narrative search strategy, absence of formal

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quality scoring and lack of pooled estimates. Direct studies of PRL molecular fractions specifically within AIT populations remain limited, and the available results cannot be extrapolated to estimate prevalence in Uzbekistan or the Bukhara region. These limitations indicate the need for regional studies capable of distinguishing clinically relevant monomeric hyperprolactinemia from macroprolactinemia across different thyroid functional states.

CONCLUSION

Autoimmune thyroiditis may coexist with altered prolactin secretion, especially when thyroid function is impaired; however, thyroid autoimmunity and hypothyroidism must not be treated as interchangeable explanations for elevated PRL. Increased TRH drive in primary hypothyroidism is an established physiological mechanism, whereas the relationship in euthyroid and subclinical hypothyroid states is less consistent. Clinical evaluation should consider the reproductive phenotype and competing causes of PRL elevation, rather than assuming that total PRL concentration alone reflects biologically active hormone excess. PEG precipitation with appropriate interpretation of post-PEG PRL may help identify macroprolactin predominance and avoid diagnostic misclassification, without overlooking concomitant monomeric hyperprolactinemia. An integrated assessment combining TSH, FT4, thyroid autoantibodies, prolactin fractions and relevant clinical information provides a rational basis for individualized interpretation and future research. Prospective investigations are needed to clarify the frequency and reproductive significance of these endocrine alterations in well-defined populations of women with AIT.

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