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Thyroid Hormone Dysregulation and Ovulatory Pathogenesis in Women: A Systematic Review and Meta-Analysis of Endocrine and Reproductive Biomarkers

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ABSTRACT

Background: Thyroid hormones play a major role in the maintenance of the hypothalamic-pituitary-ovarian axis and any form of imbalance may significantly impact on reproductive physiology. This meta-analysis and systematic review study aims at establishing the linkage between thyroid dysfunction and ovulatory disturbances in relation to its implication on reproductive health and infertility treatment. **Methods**: The study followed PRISMA guidelines and articles published till 2024 were retrieved from PubMed, Scopus, Web of Science, and the Cochrane Library. Studies that examined the association between thyroid malfunctioning and ovulatory/menstrual abnormalities were included. Studies lacking quantitative data for thyroid or ovulatory disorders were excluded. Risk of bias was measured using Newcastle-Ottawa Scale, and the quality of evidence was determined through GRADE assessment. Meta-analysis was performed using MetaAnalysisOnline tool. **Results**: The findings indicated a positive correlation between thyroid dysfunction and ovulatory defects (pooled risk ratio 3.20, 95% CI: 2.00–5.13, $p < 0.0001$). The heterogeneity was moderate ($I^2 = 74.9\%$, $p < 0.0001$) and sensitivity analysis supported the accuracy of the study results. **Conclusion**: Subclinical hypothyroidism was the most commonly implicated condition, especially in women with Polycystic Ovary Syndrome (PCOS), reduced ovarian reserve and unexplained infertility. Additional longitudinal studies with standardized assessment protocols of hormones are needed to resolve the causality and to develop optimal patient-specific treatment strategies.

Keywords: Polycystic Ovary Syndrome, Thyroid Hormones, Thyrotropin, Triiodothyronine, Thyroxine, Ovulation Disorders, Infertility, Meta-Analysis

Introduction

Thyroid hormones are becoming more and more important in reproductive medicine as regulators in the hypothalamic-pituitary-ovarian (HPO) axis and ovulatory function [1]. These hormones – triiodothyronine (T3), thyroxine (T4) and thyroid stimulating hormone (TSH) – act in a multi-level manner on reproductive tissues influencing the development of ovarian follicles, luteal phase integrity and gonadotropic secretion [2]. Thyroid hormones regulate reproductive homeostasis through hormonal feedback precision and cellular responsiveness. Subclinical impairments in their function may interfere with ovulation and menstrual regularity, causing infertility or other gynecological disorders [3].

Research shows that both hypothyroidism and hyperthyroidism can disrupt the fine hormonal balance needed for ovulation hence influencing fertility potential [4]. The altered thyroid profiles have been demonstrated to impact the dynamics of reproductive hormones and receptivity of endometrium [5,6].

Various clinical and observational studies have tried to draw the exact correlation between thyroid dysfunction and ovulatory disorders, but the results have been inconclusive because of heterogeneous study population, hormone threshold definition, and diagnostic algorithm [7,8]. A unified approach to the explain the role of thyroid hormones in disturbing the ovulatory patterns is urgently needed [9].

The purpose of this study is to perform a systematic review and meta-analysis in order to examine the association between thyroid hormone dysfunction (subclinical and clinical) and the risk of ovulatory disorders in women of reproductive age, and to synthesize quantitative evidence to justify the clinical relevance of thyroid profiling in the evaluations of fertility.

Methodology

This review examined the relationship between thyroid hormone dysfunction and ovulatory disorders by following PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure methodological rigour and transparency [10].

Inclusion and Exclusion Criteria

The eligible criteria for studies to be included was human female participants of reproductive age, quantitative data for their thyroid hormone levels, reported association between thyroid dysfunction and clinically defined ovulatory disorders. The studies excluded were animal or in vitro studies, articles without ovulatory/thyroid outcome data, and reviews, commentaries, case reports, or conference abstracts.

Data Sources

A thorough search was made in the large electronic databases (PubMed, Scopus, Web of Science, and the Cochrane Library) to retrieve the articles published from January 2013 to August 2024. Studied that were published in English only were considered.

Search Strings Used

The search strategy applied a combination of MeSH terms and free-text keywords, such as: “Thyroid Hormones” OR “Hypothyroidism” AND “Ovulation Disorders” OR “Anovulation” OR “Infertility” OR “Menstrual Irregularity”. For search refinement, Boolean operators were used, and individual filters specific to the databases were used to improve the precision of search.

Study Selection

Study selection included identification by database search, title and abstract screening, and full-text eligibility assessment. All records were evaluated by two independent reviewers at every phase. Disagreements were resolved in a consensus-based discussion by a third senior reviewer.

Data Extraction

A standard data extraction table was created to document key variables from included studies such as study design, population demographics, thyroid dysfunction type, confounders and outcome measured.

Primary Outcome

How the thyroid hormone dysfunction (hypothyroidism and subclinical hypothyroidism) is related to ovulatory disorders in women in terms of the probability to develop reproductive abnormalities with anovulation, oligomenorrhea, disrupted menstrual cycles, and disrupted reproductive biomarkers (e.g., anti-Mullerian hormone, AMH).

Quality Assessment

Quality evaluation of included studies was analyzed using Newcastle-Ottawa Scale (NOS) and ROBINS-I tool were used was used for non-interventional studies [11,12]. The GRADE framework was applied to establish the overall certainty of the evidence in different outcomes [13].

Statistical Analysis

Statistical synthesis was performed using MetaAnalysisOnline, using the random-effects model to describe between-study variability [14]. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were computed to determine the strength of association between thyroid dysfunction and ovulatory disorders. Heterogeneity was measured in the form of I^2 statistic and sensitivity analysis was performed using leave-one-out method, to evaluate the significance of each included study.

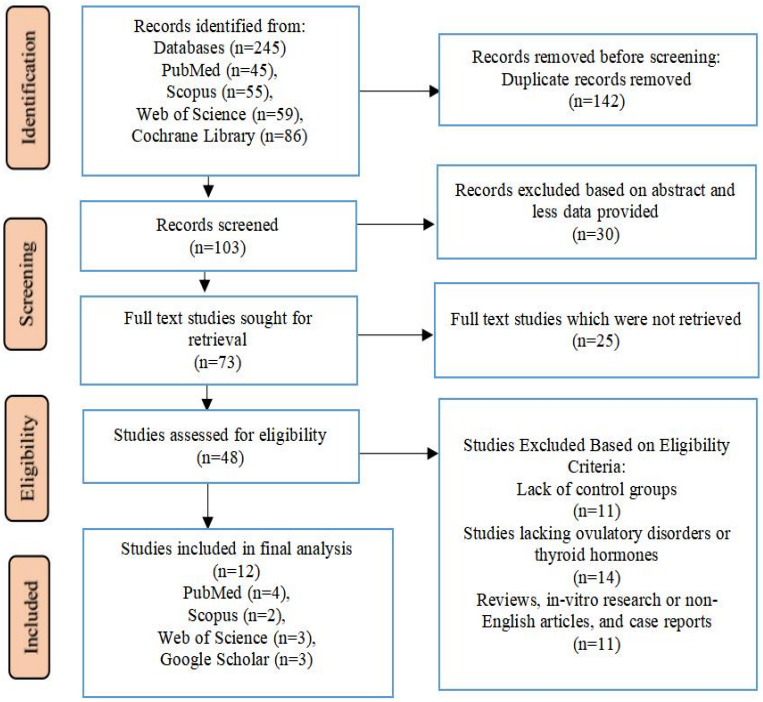

Figure 1: PRISMA Workflow Diagram for Study Selection

Results

A total of 245 studies were retrieved after database search. After deduplication and abstract screening, 172 studies were removed. Further 25 studies we excluded screened on the basis of full-text availability. Among the 48 screened studies 25 were excluded because the studies lack control groups or information regarding ovulatory disorders or thyroid hormone was not provided. Studies (11) based on in vitro research, reviews, and case reports were also excluded. The remaining 12 studies were included in this study. The PRISMA workflow diagram for study selection is shown in Figure 1.

A total of 12 studies were analyzed to study the schematic role of thyroid hormone dysfunctions in ovulatory disorders in context of reproductive medicine. Different study design (i.e., cross-sectional, case-control and interventional designs) and sample sizes ranging from focused clinical groups to large epidemiological cohorts were used to establish the quantitative synthesis. Table 1 summarizes a comparative overview of included research whereby thyroid imbalances affect major reproductive parameters and lead to the pathogenesis of ovulatory dysfunction within the context of reproductive medicine.

Table 1: Characteristics and Key Findings of Individual Studies

Study (Author, Year)	Study Design	Sample Size	Thyroid Dysfunction Type	Primary Outcome	Study Confounders
Al-Azzawi et al. 2015 [15]	Case-control	150	Subclinical and clinical thyroid dysfunction (hypothyroidism)	Serum AMH concentration differences between infertile and fertile women	BMI, Age, LH, FSH, T3, T4, TSH, TG
Nasir et al. 2016 [16]	Cross-sectional	168	Hyperthyroidism (18.45%), Hypothyroidism (1.78%)	Menstrual irregularities across thyroid status	Type of infertility, menstrual history, age, BMI, or reproductive hormone profiles.
Moustafa et al. 2019 [17]	Hospital-based case-control	70	Primarily subclinical hypothyroidism (via elevated TSH)	Differences in TSH, LH, FSH, and BMI between PCOS and controls	Age, BMI, reproductive hormone levels (LH, FSH), Small control group
Khatiwada et al. 2016 [18]	Retrospective cross-sectional study	233	Subclinical hypothyroidism (14.2%), subclinical hyperthyroidism (6.9%), overt hyperthyroidism (3%), overt hypothyroidism (1.7%)	Thyroid dysfunction among women with irregular cycles, amenorrhea, or menorrhagia	Age, menstrual disorder type
Ajmani et al. 2015 [19]	Cross-sectional case-control	100	Subclinical hypothyroidism (20%), overt hypothyroidism (14%), overt hyperthyroidism (8%), subclinical hyperthyroidism (2%)	Prevalence of thyroid dysfunction and anti-TPO positivity in menstrual disorder vs control group	Age, parity, socioeconomic status, anti-TPO antibody, endometrial findings
Saran et al. 2016 [20]	Prospective interventional cohort	98	Untreated primary hypothyroidism	Change in reproductive hormone levels before and after achieving euthyroidism	Internal control (pre/post in same patients), healthy comparison group
Himabindu et al. 2024 [21]	Cross-sectional observational study	120	Subclinical hypothyroidism (25%), clinical hypothyroidism (15%)	Association of TSH, FT4, FT3, and TPOAb with menstrual patterns	Menstrual disorder type, age, TPOAb status
Morgante et al. 2013 [22]	Prospective observational cohort	306	Subclinical hypothyroidism (elevated TSH, normal FT4)	TSH changes after 6 months of insulin sensitizer treatment in IR-PCOS patients	PCOS phenotype (obese vs lean), insulin resistance, hyperandrogenism, BMI
Zhang et al. 2021 [23]	Retrospective observational cohort study	4126	Subclinical hypothyroidism (TSH elevation, normal FT4)	Association of TSH, FT3, FT4 with age and blood sampling time in infertile women	Age, sampling time, hormonal profile (TSH, FT3, FT4)

Kabodmehri et al. 2021 [24]	Prospective cross-sectional study	314	Mild TSH elevation (not necessarily overt/subclinical hypothyroidism)	Relationship between serum TSH and diminished ovarian reserve (AMH < 1.1 ng/mL)	Age ≥35 subgroup, BMI, FSH, E2, FT4 considered; AMH stratification used
Khatun et al. 2024 [25]	Cross-sectional observational study	166	Hypothyroidism (10.8%), subclinical hypothyroidism (3.6%), hyperthyroidism (2.4%)	Prevalence of thyroid dysfunction and association with menstrual disorder types	Menstrual pattern (e.g., menorrhagia, oligomenorrhea, amenorrhea), age
Kadhim et al. 2024 [26]	Pre-experimental study	80	Subclinical hypothyroidism, euthyroid	Correlation between hypothyroidism and serum AMH levels	Age (<30 years), thyroid function status
Abbreviations: *AMH, anti-Müllerian hormone. BMI, Body-mass index. LH, Luteinizing hormone. TSH, Thyroid stimulating hormone. FSH, Follicular stimulating hormone. T3, triiodothyronine. T4, Thyroxine. TG, Thyroglobulin. PCOS, Polycystic Ovary Syndrome. TPO, Thyroid peroxidase. Ab, antibody. IR, Insulin resistant. E2, Estradiol. FT4, Free thyroxine.*					

The results showed a positive relationship between thyroid dysfunctions, notably, hypothyroidism and subclinical hypothyroidism and a few ovulatory abnormalities (anovulation, oligomenorrhea, menstrual disturbances). These instabilities had direct effect on the fertility and treatment planning. Various studies had reported altered levels of reproductive biomarkers (anti-Mullerian hormone, AMH) in women with thyroid disorder which indicated that thyroid hormone can interfere with the reproductive reserve and development of the ovary. Taken together, the findings identified the significance of including the endocrine screening in the regiments of reproductive medicine in women with ovulatory dysfunction. The included observational studies showed high predominance of low to moderate risk when assessing thyroid-ovulatory relationships using Newcastle-Ottowa scale (Table 2).

Table 2: Risk of Bias Assessment of Observational Studies using Newcastle-Ottawa Scale

Study (Author, Year)	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total Score (max 9)
Al-Azzawi et al. (2015) [15]	★★★☆	★★	★★☆	7
Nasir et al. (2016) [16]	★★☆☆	★☆	★★☆	5
Moustafa et al. (2019) [17]	★★★☆	★★	★★☆	7
Khatiwada et al. (2016) [18]	★★★★	★★	★★★	9
Ajmani et al. (2015) [19]	★★★☆	★★	★★☆	7
Himabindu et al. (2024) [21]	★★☆☆	★☆	★★☆	5
Morgante et al. (2013) [22]	★★★★	★★	★★★	9
Zhang et al. (2021) [23]	★★★★	★★	★★★	9
Kabodmehri et al. (2021) [24]	★★★☆	★★	★★☆	7
Khatun et al. (2024) [25]	★★☆☆	★☆	★☆☆	4
Kadhim et al. (2024) [26]	★★☆☆	★★	★★☆	6
Total Score (max 9): Higher scores suggest a lower risk of bias and greater methodological rigor. 7–9 stars: Low risk of bias, 4–6: Moderate risk of bias, <4: High risk of bias				

The non-randomized intervention study had moderate risk because it lacks randomization (Table 3).

Table 3: Risk of Bias Assessment of Non-Randomized Interventions using ROBINS-I Tool

Study	Confounding	Selection	Intervention	Missing Data	Outcome Measurement	Reporting	Overall Risk
Saran et al. (2016) [20]	Moderate	Low	Low	Low	Low	Low	Moderate

The included 12 studies were subjected to statistical analysis using MetaAnalysisOnline tool. Based on a random-effects model, pooled analysis showed a statistically significant overall odds ratio of 3.20 (95% CI: 2.00–5.13; $p < 0.0001$), whereby women with thyroid dysfunction are three times more likely to have ovulatory or reproductive abnormalities than euthyroid women. The prediction interval was between 0.68 and 15.12 indicating variation in the true effect among various clinical and demographic populations (Figure 2).

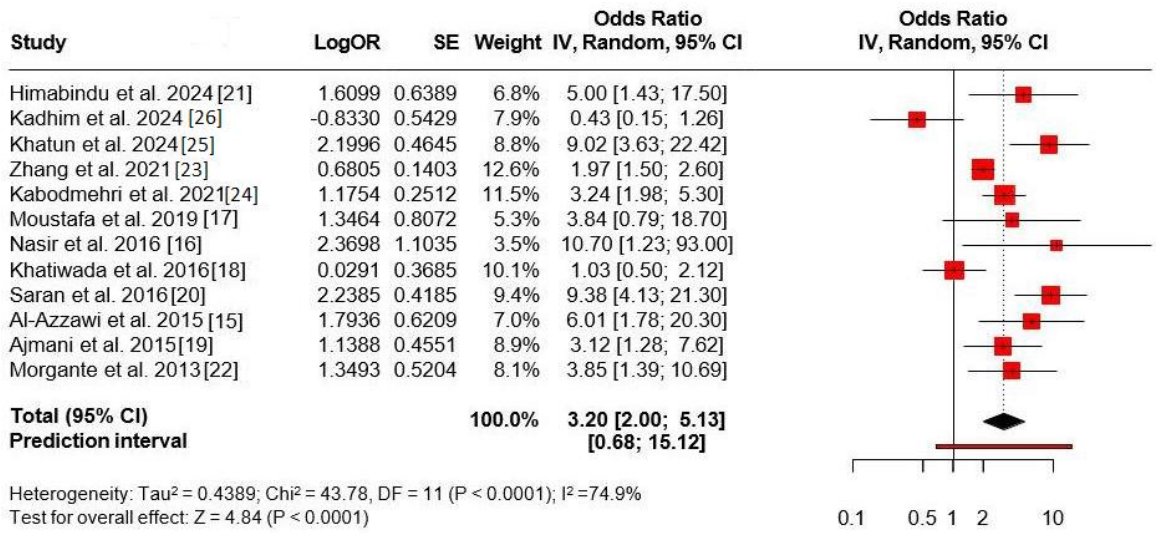

Figure 2: Forest Plot Depicting Association between Thyroid Dysfunction and Ovulatory/Reproductive Abnormalities

Significant heterogeneity was observed among the included studies ($I^2 = 74.9\%$, $p < 0.0001$), which might be due to differences in design of the studies, types of thyroid dysfunction investigated (subclinical vs. overt hypothyroidism), measured reproductive outcomes (e.g. AMH levels, menstrual irregularities, PCOS profiles), and population characteristics (age, BMI, and hormonal profiles). Despite the study heterogeneity, the direction of association was consistent to a negative effect of thyroid dysfunction on reproductive health, especially with regard to ovulatory disorders. The sensitivity analysis verified the robustness of the pooled estimates, since no single study substantially affected the overall association. GRADE framework was used to assess the certainty of evidence associating thyroid hormone dysfunction to ovulatory disorders and related reproductive outcome.

Discussion

Thyroid hormones are critical regulators of female reproductive physiology and are especially relevant to maintaining the integrity of the HPO axis [27]. This review combines the existing data on association between thyroid dysfunction (both overt and subclinical, hypothyroidism and hyperthyroidism) and ovulatory disturbances, providing an overview of how endocrine disturbances can manifest as irregularities of the menses and reduced fertility [28,29]. In different populations and study designs, results showed that abnormal thyroid function is linked to disturbed ovulatory cycles, supporting the hypothesis that thyroid hormones are essential regulators of ovarian function [30].

The association between increased TSH and decreased AMH levels in multiple studies implies that dysfunction of the thyroid may be associated with decreased ovarian reserve [31]. This link may help explain why hypothyroid women have a greater incidence of menstrual abnormality and infertility [32,33]. In addition, the effect of thyroid autoimmunity, specifically anti-thyroid peroxidase (anti-TPO) antibodies, was apparent in different populations including euthyroid individuals [34,35]. These results indicated that the immunologic component of thyroid dysfunction should not be neglected when assessing reproductive health, particularly when dealing with patients whose ovulatory disorders cannot be explained [36,37]. Although some degree of heterogeneity exists regarding the study design, populations and confounding factors, the overall trend of evidence points to the need for routine thyroid function screening for women with ovulatory dysfunction or infertility [38,39]. Early detection of subclinical hypothyroidism or mild hormonal oscillation in clinical assessments may be a chance to intervene therapeutically, perhaps reversing ovulatory cycles and enhancing fertility results. This combination of endocrinological examination and reproductive medicine improves the prospects of individualized patient care [40].

This study has several limitations. Most of the included studies were observational in nature, which limits the ability to make causal inferences. Inconsistencies of diagnostic criteria for thyroid dysfunction, the diversity of assay sensitivity and the small sample size of some studies may create bias and decrease generalizability. In addition, not all studies had accounted for important reproductive confounders. One of the weaknesses of review process includes the possibility of selection bias caused by differences between the study designs, and lack of adjustment for potential confounders across the included studies. Further research is required using standardized hormone concentration thresholds, longitudinal research techniques, and larger and more heterogeneous cohorts to enhance current understanding of the causal mechanisms, and to enhance diagnostic and treatment interventions in the discipline of reproductive endocrinology.

Conclusion

This review gathered up the current evidence of association between thyroid dysfunction, in particular, hypothyroidism, and ovulatory and menstrual dysfunctions, and illustrated the point of critical overlap between endocrine health and reproductive medicine. The results supplemented a hormone-focused approach to treat female infertility. Future studies need more standardized methodologies and longitudinal patterns to determine causality, as well as to guide clinical interventions in a more specific way.

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Conflict of Interest

None

Authors' Contribution

NA and ZT has participated in conception and design of study, collection and assembly of data and statistical analysis. MT participated in collection and assembly of data, analysis and interpretation of the data. MT, FA, MA, and KU have approved the study and are guarantor of the article. FA and EEK participated in drafting of the article and performed statistical analysis. MA and KU have participated in critical revision of the article for important intellectual content. MA and KU performed statistical analysis.

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