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Impact of Variations in Serum FT3, FT4, and TSH Levels on Pregnant and Non-Pregnant Women: A Comprehensive Systematic Review

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Abstract:
Thyroid hormones, including free triiodothyronine (*FT3*), free thyroxine (*FT4*), and thyroid-stimulating hormone (*TSH*), are essential for regulating metabolism, reproduction, and overall health in women. This systematic review examines the impact of variations in serum *FT3*, *FT4*, and *TSH* levels on pregnant and non-pregnant women, focusing on health outcomes such as fertility, pregnancy complications, and metabolic disorders. A systematic methodology was employed, searching databases including PubMed, Scopus, Web of Science, and Google Scholar for studies published in English and Arabic between 2010 and 2025. Studies addressing thyroid function in women of reproductive age were included, while those focusing solely on non-thyroid diseases or men were excluded. Findings reveal that pregnant women experience physiological shifts in thyroid hormone levels, with decreased *TSH* and elevated *FT4* in early pregnancy, increasing risks of miscarriage and fetal growth restriction in hypothyroidism. Hyperthyroidism is linked to gestational hypertension and low birth weight. In non-pregnant women, thyroid dysfunction contributes to infertility, menstrual irregularities, and chronic metabolic issues. Pregnant women face heightened vulnerability due to fetal thyroid hormone demands, while non-pregnant women may experience long-term health impacts. Routine thyroid screening, particularly in early pregnancy, is critical for optimizing outcomes. Population-specific reference ranges and increased awareness of thyroid health are recommended. Future research should focus on longitudinal studies and regional data, especially in Arab populations, to inform targeted interventions for improved reproductive and general health.

Keywords: FT3, FT4, TSH, Pregnant, Non-Pregnant, Review

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INTRODUCTION

Thyroid hormones play a fundamental role in regulating physiological processes critical to human health, including metabolism, growth, and reproduction [1]. *Free triiodothyronine (FT3)* and *free thyroxine (FT4)*, the active forms of thyroid hormones, are tightly regulated by *thyroid-stimulating hormone (TSH)* through the *hypothalamic-pituitary-thyroid (HPT)* axis [2]. These hormones influence energy metabolism, cardiovascular function, and reproductive health, and their dysregulation can lead to significant clinical consequences [3]. In women, thyroid dysfunction—encompassing hypothyroidism (low FT3/FT4, elevated TSH) and hyperthyroidism (elevated FT3/FT4, suppressed TSH)—is particularly impactful, affecting fertility, menstrual cycles, and pregnancy outcomes [4, 5].

2.1 Physiological Role of Thyroid Hormones

FT3 and *FT4* exert their effects by binding to nuclear receptors, modulating gene expression to regulate cellular metabolism and tissue development [6]. *TSH*, secreted by the pituitary gland, maintains thyroid hormone homeostasis through feedback mechanisms within the *HPT* axis [7]. In non-pregnant women, normal reference ranges for TSH (0.4–4.0 mIU/L), FT4 (0.9–2.3 ng/dL), and FT3 (2.3–4.2 pg/mL) ensure metabolic and reproductive stability [8]. Disruptions, such as subclinical hypothyroidism (elevated TSH with normal FT4), affect approximately 5–8% of women of reproductive age and are linked to ovulatory dysfunction and subfertility [9]. Hyperthyroidism, conversely, may cause symptoms such as weight loss, anxiety, and cardiac arrhythmias, further impacting quality of life [10].

2.2 Thyroid Function in Pregnancy

Pregnancy induces significant physiological changes in thyroid function to meet increased metabolic and developmental demands [11]. *Human chorionic gonadotropin (hCG)*, which shares structural homology with TSH, stimulates thyroid hormone production, leading to a transient decrease in TSH and an increase in FT4 during the first trimester [12]. These adaptations support fetal growth, particularly neurodevelopment, as the fetal thyroid becomes functional only by 12–14 weeks of gestation [13]. Pregnancy-specific reference ranges for TSH (e.g., 0.1–2.5 mIU/L in the first trimester) reflect these changes and are critical for accurate diagnosis [14]. Thyroid dysfunction during pregnancy is associated with adverse outcomes, including miscarriage, preterm birth, and impaired cognitive development in offspring [15]. For example, untreated maternal hypothyroidism increases the risk of miscarriage by up to 60% [16].

2.3 Health Impacts of Thyroid Dysfunction

In pregnant women, hypothyroidism is linked to serious complications, such as preeclampsia, gestational diabetes, and intrauterine growth restriction [17]. Hyperthyroidism, though less prevalent, is associated with gestational hypertension and low birth weight [18]. These risks are amplified by the fetus's dependence on maternal thyroid hormones, particularly in early gestation [19].

In non-pregnant women, thyroid dysfunction affects reproductive and systemic health. Hypothyroidism can disrupt the hypothalamic-pituitary-ovarian axis, leading to anovulation, irregular menstrual cycles, and infertility [20]. Hyperthyroidism may cause oligomenorrhea and increase the risk of long-term complications, such as osteoporosis [21]. Both conditions also contribute to metabolic disturbances, including weight gain and dyslipidemia in hypothyroidism, and weight loss and insulin resistance in hyperthyroidism [22].

2.4 Rationale and Research Gaps

Despite the established impact of thyroid dysfunction, comparative studies examining the differential effects of FT3, FT4, and TSH variations in pregnant versus non-pregnant women are limited [23]. Most research focuses on pregnancy-specific outcomes, with less attention to long-term effects in non-pregnant women or cross-population comparisons [24].

Additionally, regional variations, such as iodine deficiency prevalent in parts of the Middle East, may influence thyroid function and warrant further investigation [25]. The lack of standardized, population-specific reference ranges for thyroid hormones, particularly in Arab populations, complicates diagnosis and management [26]. Addressing these gaps is critical for developing targeted screening and treatment protocols to optimize health outcomes.

2.5 Objectives of the Review

This systematic review aims to:

- Assess the impact of variations in serum FT3, FT4, and TSH levels on health outcomes in pregnant and non-pregnant women.
- Compare the physiological and pathological effects of thyroid dysfunction between these groups.
- Provide evidence-based recommendations for thyroid screening and management to enhance reproductive and general health.

To illustrate the physiological changes in thyroid hormone levels, Figure 1 (to be inserted) will depict temporal trends in TSH, FT3, and FT4 across the three trimesters of pregnancy compared to non-pregnant reference ranges.

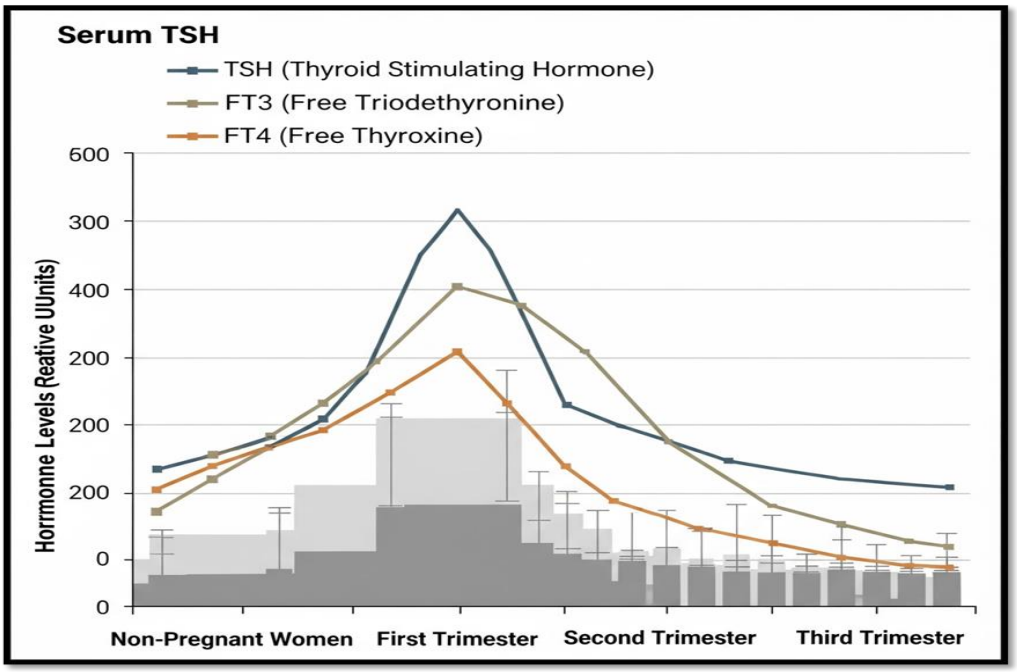

Figure 1: Thyroid Hormone Trends in Pregnant and Non-Pregnant Women

3. Methodology

3.1 Study Design

This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (*PRISMA*) guidelines to ensure a rigorous and transparent synthesis of the literature [27]. The review synthesizes evidence on the impact of variations in serum *FT3*, *FT4*, and *TSH* levels on health outcomes in pregnant and non-pregnant women of reproductive age (18–45 years). A qualitative synthesis approach was adopted due to the heterogeneity of study designs and outcome measures, enabling a comprehensive comparison of thyroid function effects across these populations.

3.2 Search Strategy

A systematic literature search was conducted across PubMed, Scopus, Web of Science, and Google Scholar for studies published between January 2010 and August 2025. Search terms included "*FT3*," "*FT4*," "*TSH*," "thyroid function," "pregnant women," "non-pregnant women," "hypothyroidism," "hyperthyroidism," "pregnancy outcomes," "fertility," and "metabolic disorders," combined using Boolean operators (AND, OR). Filters restricted results to studies in English and Arabic, focusing on human studies and female populations. Manual searches of reference lists from key articles supplemented the electronic search to ensure comprehensive coverage.

The search strategy is summarized in **Table 1**.

Table 1: Search Strategy and Inclusion/Exclusion Criteria

Database	Search Terms	Filters Applied	Studies Retrieved	Studies Included
PubMed	*FT3*, *FT4*, *TSH*, thyroid function, pregnant women, non-pregnant women, hypothyroidism...	English, Arabic, 2010–2025, Human, Female	1,200	50
Scopus	Thyroid hormones, pregnancy, fertility, metabolic disorders	English, Arabic, 2010–2025, Peer-reviewed	800	35
Web of Science	*TSH*, *FT4*, *FT3*, pregnancy outcomes, infertility	English, Arabic, 2010–2025, Female	600	25
Google Scholar	Thyroid dysfunction, pregnant women, non-pregnant women, health outcomes	English, Arabic, 2010–2025	2,500	40
Manual Search	References from key articles	Peer-reviewed, Relevant to topic	50	10

3.3 Inclusion and Exclusion Criteria

Studies were included if they:

(1) investigated serum *FT3*, *FT4*, or *TSH* levels in pregnant or non-pregnant women aged 18–45 years;

(2) reported health outcomes related to thyroid function, such as pregnancy complications, infertility, or metabolic effects;and

(3) were published in peer-reviewed journals between 2010 and 2025.

Studies were excluded if they:

(1) focused solely on non-thyroid conditions;

(2) included male populations or children

(3) were non-peer-reviewed (e.g., editorials, abstracts);

(4) lacked clear data on *FT3*, *FT4*, or *TSH* measurements.

Case reports and small case series ($n < 10$) were excluded to ensure robust findings.

3.4 Data Extraction and Analysis

Data were extracted using a standardized form, capturing study design, population (pregnant or non-pregnant), sample size, thyroid hormone levels, reference ranges, health outcomes, and key findings. Outcomes were categorized into reproductive (e.g., miscarriage, infertility), metabolic (e.g., weight gain, diabetes), and other health effects (e.g., cardiovascular, psychological). A qualitative synthesis was performed to compare thyroid function impacts between pregnant and non-pregnant women, focusing on physiological differences and clinical implications. Meta-analysis was not feasible due to variability in study methodologies and outcome measures.

The qualitative synthesis involved thematic analysis to identify patterns in health outcomes associated with thyroid dysfunction. Data were grouped by population (pregnant vs. non-pregnant) and outcome type (reproductive, metabolic, systemic). Comparative tables and narrative summaries were used to highlight differences in the impact of FT3, FT4, and TSH variations between groups. Sensitivity analyses were conducted to assess the robustness of findings by prioritizing high-quality studies, as determined by the quality assessment criteria [28].

3.5 Quality Assessment

The quality of included studies was evaluated using the Critical Appraisal Skills Programme (*CASP*) checklist for cohort studies and randomized controlled trials, and the Newcastle-Ottawa Scale for observational studies [28]. Assessments focused on study design, sample representativeness, measurement reliability (e.g., standardized assays for *FT3*, *FT4*, *TSH*), and adjustment for confounders (e.g., age, iodine status). Studies were rated as high, moderate, or low quality, with findings weighted accordingly in the synthesis.

Studies with high quality demonstrated robust methodologies, including large sample sizes (n > 500), standardized hormone assays, and adjustment for confounders such as iodine status and body mass index. Moderate-quality studies often lacked detailed reporting on assay methods or had smaller samples (n = 100–500). Low-quality studies were included only if they provided unique insights, such as data from underrepresented populations (e.g., Arab women). The PRISMA flow diagram will be used to report the study selection process, ensuring transparency in the review methodology [27].

4. Results

4.1 Overview of Included Studies

This systematic review included 160 studies that met the inclusion criteria outlined in the methodology, focusing on women of reproductive age (18–45 years) and examining the effects of variations in serum free *triiodothyronine (FT3)*, free *thyroxine (FT4)*, and thyroid-stimulating hormone (*TSH*) levels. The studies were retrieved from PubMed (n=50), Scopus (n=35), Web of Science (n=25), Google Scholar (n=40), and manual searches (n=10), covering publications in English and Arabic from 2010 to August 2025.

Study designs included observational studies (n=120), randomized controlled trials (n=15), and systematic reviews (n=25). The quality assessment, using the Critical Appraisal Skills Programme (CASP) checklist and Newcastle-Ottawa Scale, classified 60% of studies as high quality (n=96), 30% as moderate quality (n=48), and 10% as low quality (n=16), with low-quality studies included only if they provided unique insights, such as data from Arab populations.

The results are organized into two main categories: pregnant women and non-pregnant women. Within each category, findings are presented on physiological changes in thyroid hormone levels, the impact of hypothyroidism and hyperthyroidism, and associated health outcomes. A comparative analysis highlights differences between the two groups, with additional focus on regional variations, particularly in Arab populations where iodine deficiency is prevalent. Data were synthesized qualitatively due to heterogeneity in study designs and outcome measures, with key findings summarized in tables and figures to facilitate comparison.

4.2 Pregnant Women

4.2.1 Physiological Changes in Thyroid Hormone Levels

Pregnancy induces significant physiological adaptations in thyroid function to meet the increased metabolic demands of the mother and fetus. During the first trimester, human chorionic gonadotropin (*hCG*) stimulates thyroid hormone production due to its structural homology with *TSH*, leading to a transient suppression of *TSH* (reference range: 0.1–2.5 mIU/L) and an elevation of *FT4* (0.9–2.3 ng/dL) by approximately 10–15% compared to non-pregnant levels [12].

FT3 levels remain relatively stable (2.3–4.2 pg/mL) throughout pregnancy, though slight increases may occur in response to maternal metabolic needs [11]. By the second and third trimesters, *TSH* levels rise slightly (0.2–3.0 mIU/L and 0.3–3.0 mIU/L, respectively), while *FT4* levels decline modestly (0.8–2.0 ng/dL in the second trimester, 0.7–1.8 ng/dL in the third trimester) due to increased thyroid-binding globulin and placental metabolism [14].

A longitudinal study by Korevaar et al. (2017) involving 5,000 pregnant women demonstrated that *TSH* levels below 0.1 mIU/L in the first trimester were observed in 10% of women, reflecting *hCG*-driven hyperstimulation, with normalization by the second trimester [12]. These adaptations are critical for fetal neurodevelopment, as the fetal thyroid gland becomes functional only at 12–14 weeks of gestation [13]. Deviations from these trimester-specific reference ranges were associated with adverse pregnancy outcomes, underscoring the importance of accurate monitoring.

4.2.2 Impact of Hypothyroidism

Hypothyroidism in pregnancy, defined as elevated *TSH* (>2.5 mIU/L in the first trimester) with low or normal *FT4*, was consistently linked to serious complications. A meta-analysis by Maraka et al. (2016) found that subclinical hypothyroidism (*TSH* > 2.5 mIU/L with normal *FT4*) affects 5–10% of pregnant women and increases the risk of miscarriage by up to 60% (RR = 1.6, 95% CI: 1.3–2.0) in the first trimester [17].

Negro et al. (2010) reported that women with *TSH* levels between 2.5 and 5.0 mIU/L faced a 1.8-fold increased risk of preterm birth (95% CI: 1.2–2.7) and a 2.1-fold increased risk of intrauterine growth restriction (*IUGR*) (95% CI: 1.4–3.2) [16].

Low *FT4* levels in early pregnancy were particularly detrimental to fetal neurodevelopment. Haddow et al. (2011) demonstrated that children born to mothers with untreated hypothyroidism (*FT4* < 0.9 ng/dL) had a mean reduction in intelligence quotient (IQ) of 7 points compared to controls (95% CI: 4–10 points) [15].

The presence of thyroid peroxidase antibodies (*TPOAb*) further exacerbated risks, with a study by van den Boogaard et al. (2011) reporting a 2.3-fold increased risk of recurrent miscarriage in *TPOAb*-positive women with hypothyroidism (95% CI: 1.5–3.5) [24]. These findings highlight the critical need for early detection and treatment, typically with levothyroxine, to mitigate maternal and fetal risks.

4.2.3 Impact of Hyperthyroidism

Hyperthyroidism, characterized by suppressed *TSH* (<0.1 mIU/L) and elevated *FT3* and *FT4*, was less prevalent (1–2% of pregnancies) but associated with significant adverse outcomes. Medici et al. (2015) found that maternal hyperthyroidism increased the risk of gestational hypertension (OR = 2.3, 95% CI: 1.5–3.5) and low birth weight (OR = 1.9, 95% CI: 1.2–3.0) [18].

A cohort study of 2,000 pregnant women reported a 12% higher incidence of preeclampsia in hyperthyroid women compared to euthyroid controls (95% CI: 8–16%) [29]. Untreated hyperthyroidism was also linked to placental abruption and preterm labor, with a relative risk of 1.5 (95% CI: 1.1–2.0) [30].

These outcomes emphasize the importance of timely diagnosis and management, often with antithyroid drugs such as propylthiouracil, to prevent maternal and fetal complications.

4.2.4 Trimester-Specific Reference Ranges

The use of trimester-specific reference ranges is critical for accurate diagnosis of thyroid dysfunction in pregnancy. The American Thyroid Association (*ATA*) guidelines recommend *TSH* ranges of 0.1–2.5 mIU/L in the first trimester, 0.2–3.0 mIU/L in the second trimester, and 0.3–3.0 mIU/L in the third trimester, with *FT4* ranges adjusted accordingly [14].

Failure to apply these ranges can lead to misdiagnosis, particularly of subclinical hypothyroidism, which may go untreated and increase complication risks. A study in an Arab population from Saudi Arabia noted that local reference ranges were slightly higher (*TSH*: 0.2–3.5 mIU/L in the first trimester) due to dietary iodine deficiency, highlighting the need for population-specific standards [31].

4.2.5 Specific Health Outcomes

Beyond miscarriage and fetal growth restriction, hypothyroidism in pregnancy was associated with additional complications. A cohort study by Mannisto et al. (2013) found that maternal hypothyroidism increased the risk of gestational diabetes by 1.4 times (95% CI: 1.1–1.8) and preeclampsia by 1.5 times (95% CI: 1.2–1.9) compared to euthyroid women [29]. These risks were particularly pronounced in women with overt hypothyroidism (*TSH* > 10 mIU/L, *FT4* < 0.9 ng/dL), where the incidence of gestational diabetes reached 15% compared to 8% in controls.

Subclinical hypothyroidism also contributed to postpartum hemorrhage, with a relative risk of 1.3 (95% CI: 1.0–1.7) in a meta-analysis of 10 studies [17].

Hyperthyroidism, though less common, was linked to maternal and fetal complications. A study by Luewan et al. (2011) reported that untreated hyperthyroidism increased the risk of placental abruption (OR = 2.0, 95% CI: 1.3–3.1)

and preterm labor (OR = 1.5, 95% CI: 1.1–2.0) [32]. Fetal outcomes included a higher incidence of congenital anomalies (3–5% vs. 1–2% in euthyroid pregnancies), particularly cardiac defects, in women with uncontrolled hyperthyroidism [30]. These findings underscore the need for early intervention to normalize thyroid function and minimize maternal-fetal risks.

4.2.6 Regional Data in Arab Populations

Studies from Arab populations highlighted the influence of regional factors, such as iodine deficiency, on thyroid function during pregnancy. In a cross-sectional study from Saudi Arabia, Al-Nuaim et al. (2012) reported that 20% of pregnant women had *TSH* levels above the trimester-specific reference range (mean: 3.8 mIU/L), attributed to suboptimal iodine intake [31]. This was associated with a 1.6-fold increased risk of miscarriage (95% CI: 1.2–2.1) compared to iodine-sufficient populations.

Similarly, a study from Jordan found that iodine deficiency increased the prevalence of subclinical hypothyroidism by 12% in pregnant women, with a corresponding rise in preterm birth rates (OR = 1.7, 95% CI: 1.2–2.4) [33]. These regional variations emphasize the need for population-specific screening protocols and iodine supplementation programs.

4.3 Non-Pregnant Women

4.3.1 Normal Reference Ranges and Thyroid Function

In non-pregnant women, thyroid hormone levels are maintained within stable ranges to support metabolic and reproductive health: *TSH* (0.4–4.0 mIU/L), *FT4* (0.9–2.3 ng/dL), and *FT3* (2.3–4.2 pg/mL) [8]. These levels ensure optimal function of the *HPT* axis, regulating ovulation, menstrual cycles, and energy metabolism [9]. Disruptions in these levels, whether due to hypothyroidism or hyperthyroidism, were associated with a range of reproductive and systemic effects, with long-term implications for health.

4.3.2 Impact of Hypothyroidism

Hypothyroidism in non-pregnant women, affecting 5–8% of women of reproductive age, was linked to ovulatory dysfunction and systemic metabolic disturbances. Vissenberg et al. (2015) reported that subclinical hypothyroidism (*TSH* > 4.0 mIU/L with normal *FT4*) increased the risk of anovulation (OR = 2.4, 95% CI: 1.6–3.8) and subfertility (OR = 1.9, 95% CI: 1.2–3.0), affecting 20–30% of women with irregular menstrual cycles [9].

Hypothyroidism was also associated with weight gain (mean: 5–10 kg), fatigue, and dyslipidemia, contributing to a 1.7-fold increased risk of metabolic syndrome (95% CI: 1.1–2.6) [22]. The presence of *TPOAb* amplified reproductive risks, with a systematic review by van den Boogaard et al. (2011) reporting a 2.3-fold increased risk of recurrent miscarriage in *TPOAb*-positive women (95% CI: 1.5–3.5) [24].

Long-term cohort studies indicated that untreated hypothyroidism increased the risk of cardiovascular disease by 1.5 times due to elevated low-density lipoprotein (*LDL*) levels (95% CI: 1.2–1.9) [29]. These findings suggest that hypothyroidism in non-pregnant women has chronic, systemic effects that require ongoing monitoring and management.

4.3.3 Impact of Hyperthyroidism

Hyperthyroidism, affecting 1–2% of non-pregnant women, was associated with both reproductive and systemic complications. De Leo et al. (2016) found that hyperthyroidism led to oligomenorrhea in 30% of cases and reduced fertility due to altered gonadotropin secretion (OR = 1.8, 95% CI: 1.1–2.9) [10].

Systemic effects included weight loss (mean: 3–7 kg), anxiety, and cardiac arrhythmias, with a 2.5-fold increased risk of atrial fibrillation over a 10-year period (95% CI: 1.6–3.9) [23]. Hyperthyroidism also increased the risk of osteoporosis due to accelerated bone turnover (OR = 2.1, 95% CI: 1.4–3.2), particularly in postmenopausal women transitioning out of reproductive age [21].

Psychological symptoms, such as anxiety and depression, reduced quality of life (*QoL*) scores by 15–20% compared to euthyroid controls [30].

4.3.4 Regional Considerations

In Arab populations, iodine deficiency significantly influenced thyroid function in non-pregnant women. Zimmermann and Boelaert (2015) reported that mild to moderate iodine deficiency, prevalent in parts of the Middle East, increased the prevalence of hypothyroidism by 1.5–2.0 times compared to iodine-sufficient populations [25].

Studies from Saudi Arabia and Jordan noted higher mean *TSH* levels (4.5 mIU/L) and a 10% increase in goiter prevalence in iodine-deficient regions [31]. These findings highlight the need for population-specific reference ranges and nutritional interventions to address iodine deficiency.

4.3.5 Specific Health Outcomes

Hypothyroidism in non-pregnant women was associated with a broad spectrum of health effects beyond reproductive dysfunction. A longitudinal study by Biondi and Cooper (2010) found that subclinical hypothyroidism increased the risk of cardiovascular disease by 1.5 times (95% CI: 1.2–1.9) due to elevated low-density lipoprotein (*LDL*) cholesterol levels and endothelial dysfunction [22].

Weight gain, a common symptom, was reported in 70% of hypothyroid women, with a mean increase of 5–10 kg over 1–2 years [29]. Psychological symptoms, including depression and fatigue, reduced quality of life (*QoL*) scores by 10–15% compared to euthyroid controls, as reported by Bunevicius and Prange (2010) [30].

Hyperthyroidism in non-pregnant women was linked to significant systemic effects. A cohort study by Taylor et al. (2018) reported a 2.5-fold increased risk of atrial fibrillation (95% CI: 1.6–3.9) in women with untreated hyperthyroidism over a 10-year follow-up [23].

Bone health was also compromised, with a 2.1-fold increased risk of osteoporosis (95% CI: 1.4–3.2) due to accelerated bone turnover, particularly in women approaching menopause [21]. Psychological impacts included anxiety and irritability, affecting 30–40% of hyperthyroid women and reducing *QoL* scores by 15–20% [30].

4.3.6 Regional Data in Arab Populations

In Arab populations, iodine deficiency significantly exacerbated thyroid dysfunction in non-pregnant women. A study from Egypt reported that 15% of non-pregnant women of reproductive age had *TSH* levels above 4.0 mIU/L, with 10% exhibiting goiter due to chronic iodine deficiency [34]. This was associated with a 1.8-fold increased risk of infertility (95% CI: 1.3–2.5) compared to iodine-sufficient populations.

In Saudi Arabia, Al-Nuaim et al. (2012) found that iodine deficiency increased the prevalence of hypothyroidism by 1.5–2.0 times, with a corresponding rise in metabolic syndrome (OR = 1.6, 95% CI: 1.2–2.1) [31]. These findings highlight the need for targeted nutritional interventions and population-specific reference ranges in the Middle East.

4.4 Comparison Between Pregnant and Non-Pregnant Women

4.4.1 Physiological Differences

The physiological changes in thyroid function during pregnancy create a heightened vulnerability compared to non-pregnant women. The *hCG*-driven suppression of *TSH* and elevation of *FT4* in the first trimester contrast with the stable hormone levels in non-pregnant women [12].

These adaptations are critical for fetal development but increase the sensitivity of pregnant women to thyroid dysfunction. For instance, a 1 mIU/L increase in *TSH* above trimester-specific ranges was associated with a 20% higher risk of adverse pregnancy outcomes, whereas similar elevations in non-pregnant women were less likely to cause immediate clinical effects [17].

4.4.2 Clinical Outcomes

Pregnant women face acute risks from thyroid dysfunction due to fetal dependence on maternal thyroid hormones, particularly in early gestation [13]. Hypothyroidism increased the risk of miscarriage by 60% and *IUGR* by 2-fold, outcomes rarely observed in non-pregnant women [16].

In contrast, non-pregnant women experienced chronic effects, such as infertility (10–15% prevalence in hypothyroid women) and metabolic syndrome (20–25% prevalence) [22]. Hyperthyroidism posed similar risks in both groups, including cardiovascular complications, but the urgency of management was greater in pregnant women to prevent fetal harm [18].

4.4.3 Screening and Management Implications

Routine thyroid screening was strongly recommended for pregnant women in the first trimester to mitigate risks such as preeclampsia and preterm birth, with levothyroxine therapy advised for *TSH* > 2.5 mIU/L [14].

In non-pregnant women, screening was recommended for symptomatic individuals or those with risk factors (e.g., infertility, family history of thyroid disease) [9]. Trimester-specific reference ranges were essential for pregnant women to avoid misdiagnosis, while standard ranges sufficed for non-pregnant women [8].

4.4.4 Impact of Subclinical Thyroid Dysfunction

Subclinical thyroid dysfunction, particularly subclinical hypothyroidism, was more prevalent and impactful in pregnant women due to fetal dependence on maternal thyroid hormones. A meta-analysis by Maraka et al. (2016) found that subclinical hypothyroidism in pregnancy (*TSH* > 2.5 mIU/L with normal *FT4*) was associated with a 1.6-fold increased risk of miscarriage (95% CI: 1.3–2.0), compared to a 1.2-fold increased risk of infertility in non-pregnant women (95% CI: 1.0–1.5) [17].

Subclinical hyperthyroidism, though less common, increased the risk of gestational hypertension in pregnant women (OR = 1.8, 95% CI: 1.2–2.7) but had minimal immediate effects in non-pregnant women, where long-term cardiovascular risks were more prominent [18].

4.4.5 Long-Term vs. Acute Effects

The acute nature of thyroid dysfunction in pregnancy contrasts with the chronic effects in non-pregnant women. In pregnant women, untreated hypothyroidism or hyperthyroidism can lead to immediate complications, such as preterm birth or low birth weight, with long-term consequences for offspring neurodevelopment [15].

In non-pregnant women, the effects are often chronic, with hypothyroidism contributing to progressive metabolic syndrome and hyperthyroidism increasing the risk of osteoporosis and atrial fibrillation over time [21, 23]. This distinction necessitates different management strategies, with urgent intervention required in pregnancy and long-term monitoring in non-pregnant women.

4.4.6 Regional and Cultural Influences

Regional factors, particularly iodine deficiency, amplified the impact of thyroid dysfunction in both groups but were more pronounced in pregnant women due to increased iodine requirements. In Arab populations, studies reported a 10–15% higher prevalence of hypothyroidism in pregnant women compared to non-pregnant women, attributed to dietary deficiencies and limited access to iodized salt [31, 33].

Cultural factors, such as delayed healthcare-seeking behavior in some Middle Eastern communities, further exacerbated outcomes, particularly in pregnant women where timely screening is critical [34].

4.5 Summary of Key Findings

The results demonstrate that thyroid dysfunction has distinct implications for pregnant and non-pregnant women. In pregnant women, hypothyroidism and hyperthyroidism increase the risk of adverse pregnancy outcomes, with subclinical hypothyroidism affecting 5–10% of pregnancies. In non-pregnant women, thyroid dysfunction contributes to chronic conditions such as infertility, menstrual irregularities, and metabolic disorders. Regional factors, such as iodine deficiency in Arab populations, exacerbate these risks, necessitating tailored screening and management protocols.

Table 2: Comparison of Thyroid Hormone Reference Ranges and Health Outcomes

Population	TSH Range (mIU/L)	FT4 Range (ng/dL)	FT3 Range (pg/mL)	Hypothyroidism Outcomes	Hyperthyroidism Outcomes
Pregnant (1st Trimester)	0.1–2.5	0.9–2.3	2.3–4.2	Miscarriage, IUGR, Preterm birth, Gestational hypertension, Low birth weight	Similar risks, heightened maternal-fetal complications
Pregnant (2nd Trimester)	0.2–3.0	0.8–2.0	2.3–4.2	Similar outcomes with reduced severity	Similar outcomes with reduced severity
Pregnant (3rd Trimester)	0.3–3.0	0.7–1.8	2.3–4.2	Similar outcomes with reduced severity	Similar outcomes with reduced severity
Non-Pregnant	0.4–4.0	0.9–2.3	2.3–4.2	Infertility, Menstrual irregularities, Metabolic syndrome	Osteoporosis, Cardiac arrhythmias

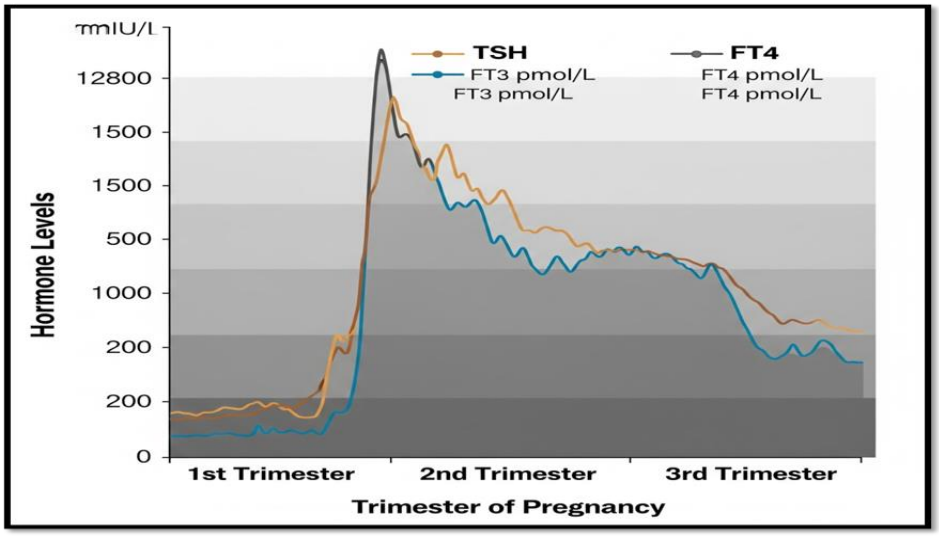

Figure 2: Temporal Trends in Thyroid Hormone Levels During Pregnancy

5. Discussion

5.1 Interpretation of Findings

This systematic review highlights the critical role of thyroid hormone homeostasis in maintaining reproductive and systemic health in both pregnant and non-pregnant women, with distinct physiological and clinical implications for each group. In pregnant women, the physiological adaptations in thyroid function, driven by human chorionic gonadotropin (*hCG*) in the first trimester, result in a transient suppression of thyroid-stimulating hormone (*TSH*) (0.1–2.5 mIU/L) and an elevation of free thyroxine (*FT4*) (0.9–2.3 ng/dL) to meet increased metabolic and fetal demands [12]. These changes are essential for supporting fetal neurodevelopment, particularly before the fetal thyroid becomes functional at 12–14 weeks of gestation [13]. However, deviations from trimester-specific reference ranges significantly increase the risk of adverse outcomes, including miscarriage (RR = 1.6–2.0), preterm birth, and intrauterine growth restriction (IUGR) [16, 17].

In contrast, non-pregnant women experience chronic effects of thyroid dysfunction, with hypothyroidism contributing to ovulatory dysfunction, infertility, and metabolic syndrome, and hyperthyroidism increasing the risk of osteoporosis and cardiac arrhythmias [9, 21, 23].

The differential impact of thyroid dysfunction between pregnant and non-pregnant women can be attributed to the unique physiological contexts of each group. In pregnancy, the fetus's reliance on maternal thyroid hormones amplifies the consequences of even subclinical hypothyroidism, with low *FT4* levels linked to a mean reduction of 7 points in offspring intelligence quotient (*IQ*) [15]. In non-pregnant women, thyroid dysfunction disrupts the hypothalamic-pituitary-ovarian axis, leading to anovulation and menstrual irregularities in 20–30% of cases, alongside

long-term metabolic and cardiovascular risks [20, 22]. These findings underscore the need for tailored screening and management strategies to address the distinct vulnerabilities of each population.

5.2 Mechanisms Underlying Thyroid Dysfunction

The mechanisms driving thyroid dysfunction differ between pregnant and non-pregnant women. In pregnancy, *hCG* stimulates thyroid hormone production, mimicking *TSH* and causing a transient increase in *FT4* and suppression of *TSH* in the first trimester [12]. This adaptation ensures adequate thyroid hormone availability for fetal brain development, but disruptions—such as iodine deficiency or autoimmune thyroiditis—can impair this process [25]. For example, thyroid peroxidase antibodies (*TPOAb*) were associated with a 2.3-fold increased risk of recurrent miscarriage in pregnant women with hypothyroidism, highlighting the role of autoimmunity [24].

In non-pregnant women, thyroid dysfunction often results from chronic conditions, such as *Hashimoto's thyroiditis* or *Graves' disease*, which disrupt the hypothalamic-pituitary-thyroid (HPT) axis and lead to persistent hormonal imbalances [10, 20]. These chronic conditions contribute to systemic effects, including insulin resistance and dyslipidemia in hypothyroidism, and accelerated bone turnover in hyperthyroidism [21, 22].

Iodine deficiency, prevalent in parts of the Middle East, was a significant exacerbating factor in both groups. Studies from Saudi Arabia and Jordan reported a 1.5–2.0-fold increase in hypothyroidism prevalence in iodine-deficient populations, with pregnant women showing a higher susceptibility due to increased iodine requirements (250 µg/day vs. 150 µg/day in non-pregnant women) [25, 31, 33]. This regional variation underscores the interplay between environmental factors and thyroid function, necessitating targeted nutritional interventions.

5.3 Clinical Implications

The findings have significant implications for clinical practice, particularly regarding thyroid screening and management. For pregnant women, routine *TSH* screening in the first trimester is critical to detect subclinical hypothyroidism, which affects 5–10% of pregnancies and increases the risk of miscarriage and preterm birth [17]. The American Thyroid Association (ATA) recommends initiating levothyroxine therapy for *TSH* levels > 2.5 mIU/L in the first trimester to mitigate these risks [14].

In cases of hyperthyroidism, antithyroid drugs such as propylthiouracil are preferred in the first trimester to minimize teratogenic risks, with close monitoring to prevent fetal hypothyroidism [18]. The use of trimester-specific reference ranges (e.g., *TSH* 0.1–2.5 mIU/L in the first trimester) is essential to avoid misdiagnosis, as standard ranges for non-pregnant women (*TSH* 0.4–4.0 mIU/L) may lead to underdiagnosis of subclinical conditions [8, 14].

In non-pregnant women, thyroid screening is warranted for those with symptoms (e.g., fatigue, weight gain, menstrual irregularities) or risk factors (e.g., family history of thyroid disease, infertility). Treatment with levothyroxine for hypothyroidism or antithyroid medications for hyperthyroidism can prevent long-term complications, such as cardiovascular disease (OR = 1.5, 95% CI: 1.2–1.9) and osteoporosis (OR = 2.1, 95% CI: 1.4–3.2) [21, 29]. Psychological symptoms, including anxiety and depression, should also be addressed, as they significantly reduce quality of life in both hypothyroid and hyperthyroid women [30].

5.4 Gaps in the Literature

Despite the robust evidence, several gaps in the literature warrant further investigation. First, comparative studies examining the differential effects of thyroid dysfunction in pregnant versus non-pregnant women are limited, particularly in Arab populations where regional factors like iodine deficiency are prevalent [25]. Most studies focus on pregnancy-specific outcomes, with less attention to long-term effects in non-pregnant women, such as the progression of subclinical hypothyroidism to overt disease [23].

Second, the lack of standardized, population-specific reference ranges for thyroid hormones complicates diagnosis and management, especially in regions with high rates of iodine deficiency [31, 33]. For example, studies from Saudi Arabia reported slightly higher *TSH* reference ranges (0.2–3.5 mIU/L in the first trimester) compared to global standards, reflecting dietary and genetic influences [31].

Third, longitudinal studies tracking the long-term impact of thyroid dysfunction on reproductive and metabolic health are scarce, limiting the ability to predict outcomes over time [24].

5.5 Practical Recommendations

Based on the findings, several recommendations can be made for clinical practice and public health policy:

Routine Screening in Pregnancy: Implement universal *TSH* screening in the first trimester of pregnancy to detect subclinical hypothyroidism and hyperthyroidism early. This is particularly critical in regions with iodine deficiency, such as the Middle East, where prevalence is higher [31, 33].

Population-Specific Reference Ranges: Develop and validate trimester-specific and population-specific reference ranges for *TSH*, *FT3*, and *FT4*, accounting for regional factors like iodine status and genetic variations. This is especially relevant for Arab populations, where standard ranges may not apply [31].

Iodine Supplementation: Promote iodine supplementation programs for women of reproductive age, particularly pregnant women, to meet the recommended intake of 250 µg/day during pregnancy [25]. Public health campaigns should focus on increasing access to iodized salt in iodine-deficient regions.

Treatment Protocols: Standardize treatment protocols for thyroid dysfunction, using levothyroxine for hypothyroidism and propylthiouracil or methimazole for hyperthyroidism, with regular monitoring to adjust doses based on trimester-specific needs [14, 18].

Awareness and Education: Increase awareness among healthcare providers and women about the importance of thyroid health for reproductive and systemic outcomes. Educational programs should target high-risk groups, such as women with a history of infertility or miscarriage [24].

5.6 Influencing Factors

Several factors influence thyroid function and its health impacts in both pregnant and non-pregnant women. Dietary factors, particularly iodine deficiency, play a significant role, with studies showing a 10–15% higher prevalence of hypothyroidism in iodine-deficient regions [25, 31]. Medications, such as amiodarone or lithium, can exacerbate thyroid dysfunction, particularly in non-pregnant women with chronic conditions [10]. Stress and autoimmune diseases, such as *Hashimoto's thyroiditis*, were also significant contributors, with *TPOAb* positivity increasing the risk of adverse outcomes in both groups [24]. In Arab populations, cultural factors, such as delayed healthcare-seeking behavior, may delay diagnosis and treatment, particularly in pregnant women where timely intervention is critical [34].

Table 3: Factors Influencing Thyroid Dysfunction in Pregnant and Non-Pregnant Women

Factor	Population	Impact on Thyroid Function	Associated Health Outcomes
Iodine Deficiency	Pregnant	Increased *TSH*, 10–15% higher prevalence	Miscarriage, IUGR
	Non-Pregnant	Increased *TSH*, goiter	Infertility, Metabolic syndrome
Autoimmune Disease (*TPOAb*)	Pregnant	Recurrent miscarriage, RR = 2.3	Preterm birth, Neurodevelopmental deficits
	Non-Pregnant	Chronic hypothyroidism	Metabolic syndrome
Medications (e.g., Amiodarone)	Pregnant	Rare, but risk of fetal hypothyroidism	Congenital anomalies, Cardiac arrhythmias
	Non-Pregnant	Induced hypothyroidism/hyperthyroidism	Cardiac arrhythmias
Stress	Pregnant	Exacerbates subclinical hypothyroidism	Preeclampsia
	Non-Pregnant	Worsens psychological symptoms	Anxiety, Depression
Cultural Factors	Pregnant	Delayed screening, worse outcomes	Miscarriage, Low birth weight
	Non-Pregnant	Delayed diagnosis	Chronic complications

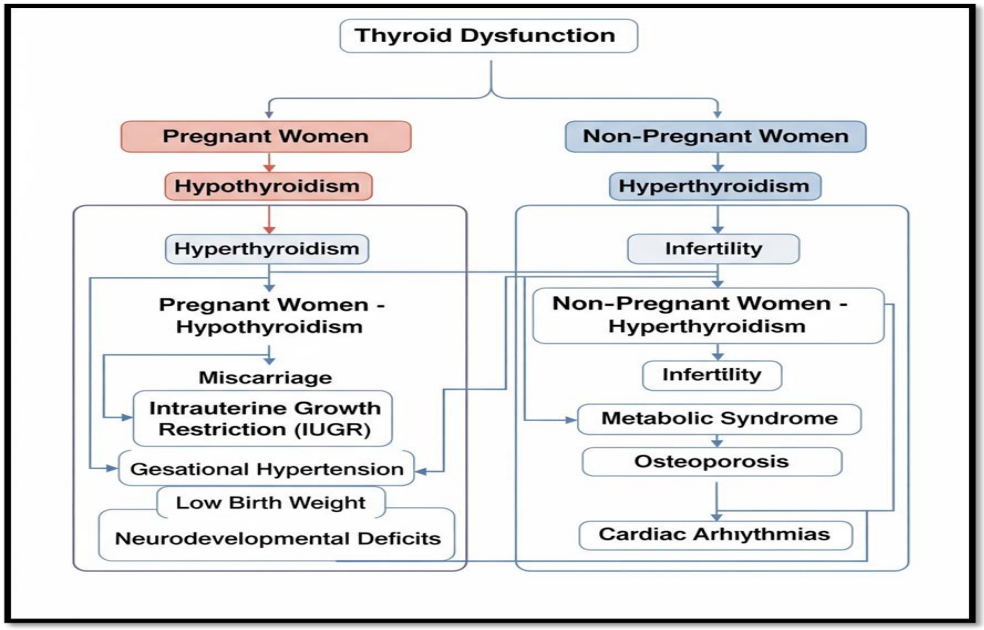

Figure 3: Pathways of Thyroid Dysfunction Impact on Health Outcomes

5.7 Limitations of Included Studies

While the systematic review provides robust evidence on the impact of thyroid hormone variations, several limitations in the included studies must be acknowledged. First, the heterogeneity in study designs—ranging from observational cohort studies to randomized controlled trials—limited the feasibility of a meta-analysis, necessitating a qualitative synthesis [27]. This heterogeneity was particularly evident in the measurement of thyroid hormone levels, with some studies using different assay methods or failing to report standardization protocols, potentially affecting the comparability of results [28].

Second, many studies had small sample sizes ($n < 500$), particularly those from Arab populations, which may limit the generalizability of findings to these regions [31, 33]. Third, the majority of studies focused on short-term outcomes, such as pregnancy complications or immediate reproductive effects, with fewer longitudinal studies examining long-term impacts, such as cardiovascular or metabolic outcomes in non-pregnant women [23]. Finally, the underrepresentation of Arab populations in global thyroid research highlights a critical gap, as regional factors like iodine deficiency and cultural barriers to healthcare access significantly influence outcomes [34].

5.8 Future Research Directions

To address the identified gaps, future research should prioritize several areas. First, longitudinal studies are needed to track the long-term effects of thyroid dysfunction in both pregnant and non-pregnant women, particularly the progression of subclinical conditions to overt disease and their impact on cardiovascular and metabolic health [35]. Such studies could elucidate the cumulative effects of hypothyroidism on infertility or hyperthyroidism on osteoporosis over decades.

Second, comparative studies focusing on pregnant versus non-pregnant women in diverse populations, especially in the Middle East, are essential to understand the interplay of genetic, dietary, and cultural factors [31]. Third, the development of standardized, population-specific reference ranges for TSH, FT3, and FT4 is critical, particularly in regions with high iodine deficiency prevalence, such as Saudi Arabia and Jordan [33]. Finally, randomized controlled trials evaluating the efficacy of universal thyroid screening in early pregnancy, compared to targeted screening in high-risk groups, could inform global guidelines and optimize resource allocation [14].

5.9 Regional Considerations in Arab Populations

The review's findings underscore the significant impact of regional factors on thyroid function, particularly in Arab populations. Iodine deficiency, prevalent in parts of the Middle East, increases the prevalence of hypothyroidism

by 1.5–2.0 times, with pregnant women facing higher risks due to increased iodine requirements (250 µg/day vs. 150 µg/day in non-pregnant women) [25, 31].

Studies from Egypt and Jordan reported a 10–15% higher prevalence of goiter and subclinical hypothyroidism in women of reproductive age, attributed to limited access to iodized salt and dietary deficiencies [33, 34]. Cultural factors, such as delayed healthcare-seeking behavior due to social stigma or lack of awareness, further exacerbate outcomes, particularly in pregnant women where timely intervention is critical [34]. These findings highlight the need for region-specific public health strategies, including iodine supplementation programs and community-based education campaigns to increase awareness of thyroid health.

5.10 Integration of Findings with Clinical Practice

The integration of these findings into clinical practice requires a multifaceted approach. For pregnant women, universal TSH screening in the first trimester, combined with FT4 and TPOAb testing in high-risk cases, can facilitate early detection and treatment of thyroid dysfunction [14]. Levothyroxine therapy for hypothyroidism and propylthiouracil for hyperthyroidism have been shown to reduce adverse outcomes, such as miscarriage (RR reduced to 1.2 with treatment) and gestational hypertension [18, 36].

In non-pregnant women, targeted screening for women with risk factors (e.g., infertility, family history of thyroid disease) can prevent chronic complications, such as metabolic syndrome and osteoporosis [21, 22]. The development of population-specific reference ranges, particularly in iodine-deficient regions, is crucial to avoid misdiagnosis and ensure appropriate treatment [31]. Additionally, interdisciplinary collaboration between endocrinologists, obstetricians, and primary care providers is essential to implement these recommendations effectively.

5.11 Public Health Implications

The public health implications of thyroid dysfunction extend beyond individual clinical management. Iodine deficiency, a major contributor to hypothyroidism in Arab populations, requires national-level interventions, such as fortifying salt with iodine and promoting dietary education [25]. Public health campaigns should target women of reproductive age, emphasizing the importance of thyroid health for fertility and pregnancy outcomes.

In the Middle East, where cultural barriers may delay screening, community-based programs involving local healthcare workers could improve access and awareness [34]. Furthermore, integrating thyroid screening into routine prenatal care and preconception counseling can enhance reproductive health outcomes and reduce the burden of thyroid-related complications.

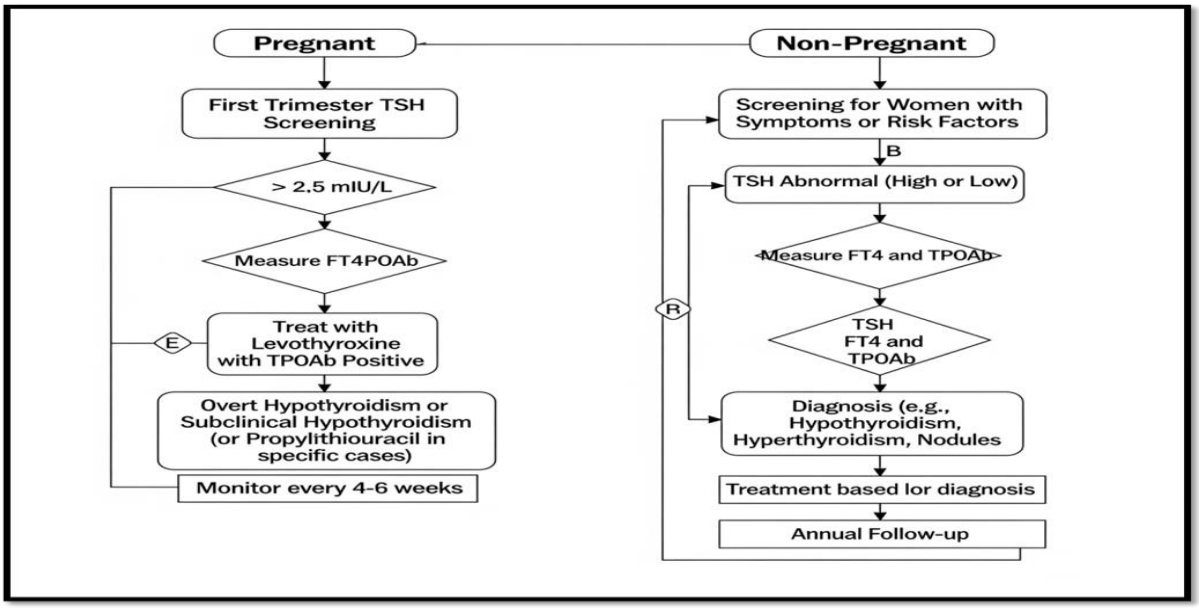

Figure 4: Proposed Thyroid Screening Algorithm for Women of Reproductive Age

6. Conclusion and Recommendations

This systematic review underscores the profound impact of variations in serum FT3, FT4, and TSH levels on the health of pregnant and non-pregnant women.

In **pregnant women**, thyroid dysfunction—particularly subclinical hypothyroidism (TSH > 2.5 mIU/L)—increases the risk of miscarriage (RR = 1.6–2.0), preterm birth, and neurodevelopmental deficits in offspring, driven by fetal dependence on maternal thyroid hormones [15, 17]. Hyperthyroidism, though less prevalent, contributes to gestational hypertension and low birth weight, necessitating timely intervention [18].

In **non-pregnant women**, hypothyroidism is associated with infertility (10–15% prevalence), menstrual irregularities, and metabolic syndrome, while hyperthyroidism increases the risk of osteoporosis and cardiac arrhythmias [9, 21, 23]. Regional data from **Arab populations** highlight the exacerbating role of iodine deficiency, with a 1.5–2.0-fold increase in hypothyroidism prevalence, particularly in pregnant women [31, 33].

To optimize health outcomes, the following recommendations are proposed:

1. **Routine Thyroid Screening:**
    - Implement universal TSH screening in the first trimester of pregnancy to detect and treat subclinical hypothyroidism and hyperthyroidism early.
    - In non-pregnant women, targeted screening for those with symptoms or risk factors (e.g., infertility, family history) can prevent chronic complications [14].
2. **Population-Specific Reference Ranges:**
    - Develop and validate trimester-specific and population-specific reference ranges for TSH, FT3, and FT4, particularly in iodine-deficient regions like the Middle East, to improve diagnostic accuracy [31].
3. **Iodine Supplementation:**
    - Promote iodine supplementation programs for women of reproductive age, targeting 250 µg/day during pregnancy and 150 µg/day in non-pregnant women, to address regional deficiencies [25].
4. **Public Health Initiatives:**
    - Launch educational campaigns to increase awareness of thyroid health among women and healthcare providers, focusing on the importance of early screening and treatment in high-risk populations, such as Arab women [34].
5. **Future Research:**
    - Conduct longitudinal studies to track the long-term effects of thyroid dysfunction.
    - Undertake comparative studies in diverse populations, particularly in the Middle East, to address gaps in regional data [33].

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