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

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Abstract:

Thyroid hormones such as free thyroxine (FT4), free triiodothyronine (FT3) and thyroid-stimulating hormone (TSH) play an important role in women's metabolism, reproduction, and overall health. This systematic review aims at exploring how changes in serum FT3, FT4 and TSH levels impact on health outcomes such as pregnancy issues, fertility and metabolic diseases in both pregnant and non-pregnant women. A systematic search was carried out to identify research articles published in English and Arabic from 2010 to 2025, using databases like PubMed, Scopus, Web of Science, and Google Scholar. Inclusion criteria were studies that evaluated thyroid function in females of reproductive age; exclusion criteria were studies of males or any thyroid condition other than thyroid function. Results indicate that there are physiologic changes within a woman's thyroid hormone levels throughout the course of her pregnancy. In the first trimester, her TSH drops and her FT4 levels rise, which increases the chance of miscarriage and hypothyroidism causes foetal growth restriction. In hyperthyroidism there is an association with low birth weight and prenatal hypertension. One of the symptoms for women who are not pregnant and suffer from thyroid dysfunction is infertility, irregular periods, and some other persistent metabolic issues. Foetal thyroid hormone needs put pregnant women at a higher risk, but even women who aren't pregnant run the risk of experiencing long-term health effects. The best results can be achieved with routine thyroid screening, which is especially important in the first trimester of pregnancy. Awareness creation on thyroid health and setting up population specific reference range is recommended. Future research should also gather regional data and pursue long-term studies of reproductive and general health, especially in Arab communities, to further understand how to improve reproductive and overall health.

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

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INTRODUCTION

Thyroid hormones play a critical role in human physiology – they regulate function such as metabolism, growth and reproduction [1]. The hypothalamic-pituitary-thyroid (HPT) axis is responsible for the tight regulation of thyroid hormones by thyroid-stimulating hormone (TSH) [2]. The hormones are free triiodothyronine (FT3) and free thyroxine (FT4). Disbalance of these hormones may have important clinical implications, such as energy metabolism, cardiovascular function, and reproductive health [3]. Thyroid dysfunction (both hypothyroidism (low FT3/FT4, raised TSH) and hyperthyroidism (elevated FT3/FT4, suppressed TSH)) can affect menstrual cycles and pregnancy outcomes, particularly in women, and can also impact fertility.[5 ,4]

2.1. The physiological role of thyroid hormones in the body.

FT3 and FT4 bind to nuclear receptors and affect gene expression, thereby affecting cellular metabolism and tissue growth [6]. TSH is produced by the pituitary gland and regulates the levels of thyroid hormone by feedback mechanisms in the HPT axis [7]. Reference values for TSH, FT4 and FT3 in non-pregnant females are 0.4-4.0 mIU/L, 0.9-2.3 ng/dL and 2.3-4.2 pg/mL, respectively [8]. Subclinical hypothyroidism (defined as elevated TSH level with normal FT4) is related to ovulatory dysfunction, subfertility, and occurs in approximately 5-8% of women of reproductive age [9]. On the other hand, hyperthyroidism may affect the quality of life by contributing to anxiety, arrhythmia and weight loss.[10]

2.2. Thyroid Function in Pregnancy.

Thyroid changes are significant during pregnancy due to the rise in the body's metabolic and developmental requirements [11]. The two hormones share a similar structure, but during the first trimester, human chorionic gonadotropin (hCG) stimulates the thyroid to make thyroid hormone, which, in turn, leads to a brief rise in FT4 and a fall in TSH [12]. These changes serve to support foetal development, particularly neurodevelopment, as foetal thyroid function is not established until 12–14 weeks of gestation [13]. It has been emphasized that only pregnancy-specific reference ranges for TSH, e.g., 0.1-2.5 mIU/L in the first trimester [14] should be used, to ensure an accurate diagnosis. Some of the adverse effects associated with thyroid dysfunction in pregnancy include miscarriage, premature birth and impaired cognitive growth in children [15]. For instance, a 60% increase in the chance of miscarriage is associated with untreated maternal hypothyroidism [16].

2.3 Effects of thyroid dysfunction on health

The major problems that can arise in pregnant women with hypothyroidism include preeclampsia, gestational hyperglycemia and intrauterine growth [17]. Low birth weight and gestational hypertension are associated with hyperthyroidism, but are not as prevalent [18]. These risks are especially high during the first trimester of pregnancy when the fetus needs more mother's thyroid hormones [19].

Reproductive and systemic health are impacted by thyroid dysfunction in women who are not pregnant [20]. Oligomenorrhea and other long-term consequences, like osteoporosis, are increased in hyperthyroidism patients [21]. Weight gain and dyslipidaemia in hypothyroidism and insulin resistance and weight loss in hyperthyroidism are metabolic abnormalities that are contributed to by both disorders [22].

2.4. The rationale and research gaps for this study are discussed below.

Although it is well established that thyroid dysfunction has an impact on pregnancy, there is a lack of studies that correlate changes of FT3, FT4 and TSH in pregnant and non-pregnant women [23]. Most studies have concentrated on outcomes during pregnancy, with few studies addressing long-term outcomes in non-pregnant women or comparing one population to another [24]. The effects of regional differences on thyroid function, such as iodine deficiency in certain regions of the Middle East, should also be studied further [25]. The lack of standardised, population specific reference values for thyroid hormones makes it more challenging to diagnose and treat thyroid disorders in Arab

cultures [26]. Addressing these challenges is key to enhancing health outcomes by developing personalised screening and treatment plans.

2.5. The goals of the review are as follows:

Our goal in doing this review was to:

- Identify the link between alterations of serum FT3, FT4 and TSH levels with health in pregnant and non-pregnant women.
- Identify physiological/pathological manifestations of each group's thyroid dysfunction.
- Recommend screening and/or care for the thyroid based on evidence to improve reproductive and overall health.

In order to illustrate the changes in thyroid hormone levels during pregnancy, the changes in TSH, FT3 and FT4 levels should be shown in the three trimesters of pregnancy (Fig. 1 – to be inserted) vs. non-pregnant reference ranges**.**

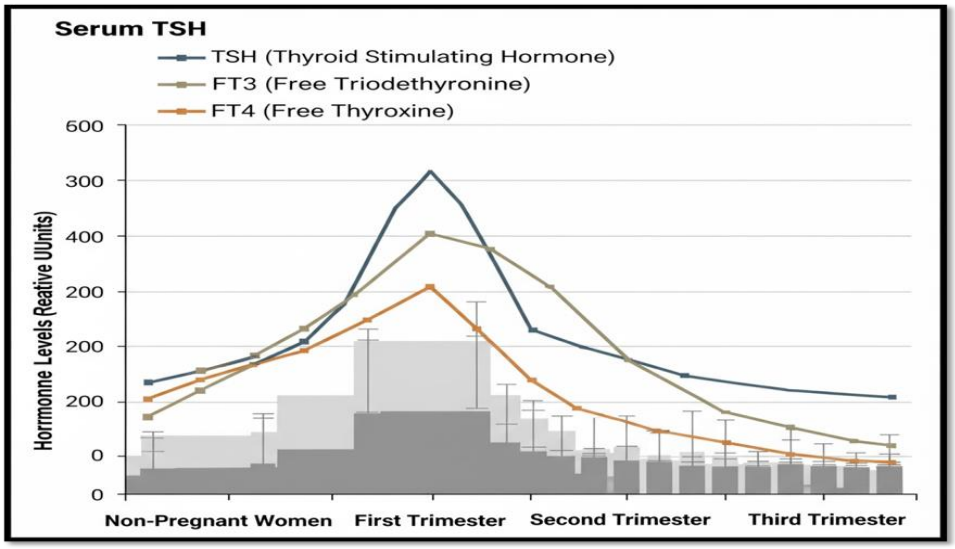

Figure 1 shows the results of pregnant and non-pregnant women's thyroid hormone levels.

3 .Methodology

3.1 Study Design

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used in this SR to ensure that the literature was synthesized comprehensively and honestly [27]. This review gathers information from studies that investigate how variations in the levels of FT3, FT4 and TSH during pregnancy and in non-pregnant women affect health outcomes in the reproductive age (18-45 years). The diverse study designs and outcome measurements need a qualitative synthesis technique to allow for a thorough assessment of the impacts of thyroid function in various groups.

3.2 Search Strategy

A systematic literature search was conducted, using PubMed, Scopus, Web of Science and Google Scholar, to identify studies published between January 2010 and August 2025. The search phrases were combined using Boolean operators (AND, OR) to form "thyroid function" AND "TSH" AND "FT3" AND "FT4" AND "pregnant women" AND "non-pregnant women" AND "hypothyroidism" AND "hyperthyroidism" AND "fertility" AND "metabolic disorders". This also encompassed hypothyroidism and hyperthyroidism. Using filters, we were only able to see research that was conducted on female populations and was conducted in English or Arabic. In order to guarantee

thorough coverage, the automated search was augmented with manual searches of reference lists from important articles.

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

The inclusion and exclusion criteria are provided in this section.

Studies had to have the following characteristics to be considered:

Studies were included if they examined blood FT3, FT4 or TSH levels in women aged 18–45 (pregnant or not); health outcomes related to thyroid were reported (e.g. infertility, metabolic impacts, pregnancy difficulties).

Studies excluded were those which:

(1)had no data regarding FT3, FT4, TSH, or there was no focus on thyroid problems; (2) included male populations or children; (3) was not peer-reviewed (abstracts or editorials); or (4) reported no data regarding FT3, FT4, TSH, or had no focus on thyroid problems.

To make sure the results were solid, we didn't include case reports or tiny case series (n < 10).

3.4 Data Extraction and Analysis

A standardised form was used to record thyroid hormone levels, reference ranges, study design, demographic (pregnant or not), sample size, key findings and health effects. Reproductive (such as a miscarriage or infertility), metabolic (such as an increase in body fat or diabetes), and other health consequences (such as cardiovascular disease or mental health issues) were the three main types of outcomes. The effects on thyroid function during pregnancy and those in women who are not pregnant were compared using a qualitative synthesis that zeroed in on physiological variations and clinical consequences. Too much variation was seen in study design and outcomes to conduct a meta-analysis.

In order to find commonalities in the health effects of thyroid dysfunction, the qualitative synthesis used theme analysis. Reproductive, metabolic, and systemic outcomes were used to categorise the data, together with the population type (pregnant vs. non-pregnant). The effect of FT3, FT4 and TSH changes on each group were accentuated through narrative summaries and comparative tables. We performed sensitivity analyses because we made decisions on the quality of the studies based on a set of quality criteria, and we preferred to include studies that fulfilled these criteria [28].

3.5 Quality Assessment

To assess quality of included studies, the (CASP) checklist was used for RCTs and cohort studies and the Newcastle-Ottawa Scale was used for observational research [28]. Research methodology, statistical power, standardisation of measurements (such as any FT3, FT4, TSH measurement) and controlling for possible confounding factors (such as age or iodine status) were used in evaluations. The synthesis considered the quality rating of the studies (high, moderate and low) and the weighting of the study results.

In high quality studies, researchers applied stringent methodology with large sample sizes (n > 500), standardised hormone assays, and controlled for factors such as BMI, iodine status, and so on. Studies of moderate quality had smaller sample sizes (n = 100-500) and/or were not detailed regarding the assays procedures. Only data from under-represented groups (such as Arab women) or low-quality studies but with new information were taken into account. The study selection process will be reported using PRISMA flow diagram that will make the review methodology transparent [27].

4 .Results

4.1. The included studies provide an overview of the research that was conducted on this topic.

This systematic review involved a analysis of the effects of variation in (FT3), (FT4) and (TSH) levels, with 160 studies meeting inclusion criteria laid out in the methodology. The studies were conducted with women in reproductive age (18-45 years). In total, fifty research covering English and Arabic publications from 2010 to August 2025 were obtained from PubMed, thirty-five from Scopus, twenty-five from Web of Science, forty from Google Scholar, and ten from manual searches.

The study designs were randomized controlled trials (n=15), observational studies (n=120) and systematic reviews (n=25). Fifty-six percent of the studies were high quality (n=96), thirty percent were moderate quality (n=48), and ten percent were low quality (n=16). Studies were only included if they provided unique information, such as information about Arab populations, or if they were otherwise of low quality. The Critical Appraisal Skills Programme (CASP) checklist and the Newcastle-Ottawa Scale were used to evaluate the quality.

Based on the data collected, two main categories emerged – pregnant women and non-pregnant women. Within every of the categories, details of research on hypothyroidism and hyperthyroidism and associated health outcomes are provided. A comparison of the two populations, especially in the Arab population where iodine deficiency is prevalent, highlights geographical differences and also differences between the two populations. In order to make comparisons easier, the data were qualitatively synthesised owing to the variety in the study designs and outcome measures. The key results were summarised in tables and figures.

4.2 Pregnant Women

4.2.1. The role of thyroid hormones in physiological changes.

The thyroid makes significant physiologic changes during pregnancy to meet the needs of mother and foetus. Temporary suppression of TSH (0.1 - 2.5 mIU/L) and elevation of FT4 (0.9 - 2.3 ng/dL) by about 10-15% compared to the non-pregnancy range in the first trimester are due to the stimulation of thyroid hormone production by the (hCG) which shares structural homology with TSH.[12]

During pregnancy, FT3 levels stay around the same (2.3-4.2 pg/mL), while they might go up a little to meet the metabolic demands of the mother [11]. modest increases in TSH levels at the end of the second and third trimesters (TSH 0.2-3.0 mIU/L and 0.3-3.0 mIU/L, respectively).[14]

In a 2017 longitudinal study by Korevaar et al., 10% of pregnant women had sub 0.1 mIU/L TSH levels in the first trimester, considered to be hyperstimulated due to hCG, and which subsequently normalised in the second trimester [12]. The foetal thyroid gland does not begin to produce thyroid hormone until about 12-14 weeks of gestation, so these changes are crucial for developing the baby's nervous system [13].

4.2.2 Impact of Hypothyroidism

Strong evidence exists that hypothyroidism in pregnancy is associated with major difficulties. This condition is characterised by an increased TSH level (>2.5 mIU/L in the first trimester) along with a low or normal FT4. Maraka et

al. (2016) [17] performed a meta-analysis that revealed that subclinical hypothyroidism (TSH > 2.5 mIU/L with normal FT4) had a higher risk of miscarriage up to 60% (RR = 1.6, 95% CI = 1.3-2.0) during the first trimester of pregnancy. It is a condition in which 5-10% of women become pregnant.

Negro et al. (2010) [16] found that women with TSH levels between 2.5 and 5.0 mIU/L had an increased risk of preterm delivery (1.8 times, 95% CI 1.2-2.7) and women with these levels had an increased risk of IUGR (2.1 times, 95% CI 1.4-3.2).

Low FT4 was most detrimental for foetal neurodevelopment in the first trimester of pregnancy. Haddow et al. (2011) found the intellectual quotient (IQ) of children born to mothers with untreated hypothyroidism (FT4 < 0.9 ng/dL) to be 7 points lower than that of control mothers (95% CI 4-10 points).[15]

This increases the risk of hypothyroidism women face for recurrent miscarriage (RRM): women with hypothyroidism with positive (TPOAb) results were at 2.3-fold higher risk of RRM (95% CI: 1.5-3.5) [24]. The importance of early discovery and treatment, usually with levothyroxine, to reduce risks to both the mother and the unborn child is underscored by these results.

4.2.3 Impact of Hyperthyroidism

Although it was associated with significant negative outcomes, hyperthyroidism, which is defined by suppressed TSH (<0.1 mIU/L) and high FT3 and FT4, was less common (affecting 1-2 percent of pregnancies). Medi et al. (2015) [18] reported an increased risk for gestational hypertension (OR = 2.3, 95% CI: 1.5-3.5) and low birth weight (OR = 1.9, 95% CI: 1.2-3.0) among mothers with hyperthyroidism.

In a cohort study of 2,000 pregnant women, women with hyperthyroidism had a 12% (95% CI: 8-16%) increased risk of preeclampsia when compared to those with euthyroidism [29]. It has been found that for untreated hyperthyroidism, a placental abruption-associated risk of 1.5 (95% CI: 1.1-2.0) was related to preterm labour.[30]

These findings underline the importance of early diagnosis and treatment, often with antithyroid drugs such as propylthiouracil, to prevent complications to mother and fetus.

4.2.4 Trimester-Specific Reference Ranges

It is important that the reference ranges for thyroid function be specific to each trimester when diagnosing thyroid dysfunction during pregnancy. Under the guidelines set by the American Thyroid Association (ATA), levels of TSH are 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, while adjusting the corresponding FT4 levels.[14]

Failure to use these limits could lead to misdiagnosis (particularly subclinical hypothyroidism), which raises the risk of complications, particularly from hypothyroidism not being diagnosed or treated. The researchers in Saudi Arabia reported that the local reference ranges for TSH are somewhat different (0.2-3.5 mIU/L in the first trimester) in an Arab community, making it necessary to have population-specific norms [31].

4.2.5 Specific Health Outcomes

Having hypothyroidism during pregnancy increased the risk of problems such as miscarriage and foetal growth limitation. The Mannisto et al. (2013) [29] cohort study showed that women with maternal hypothyroidism had a 1.5-fold increased risk of preeclampsia and 1.4-fold higher risk of gestational diabetes than those who were euthyroid. Women with overt hypothyroidism (TSH > 10 mIU/L and FT4 < 0.9 ng/dL) had a significantly increased risk of developing GD (15%) compared with controls.(%8) . The relative risk of postpartum haemorrhage was 1.3 (95% CI: 1.0-1.7) in a meta-analysis of 10 trials that included subclinical hypothyroidism.[17] . Despite its rarity, hyperthyroidism has been associated with problems for both mother and unborn child. Luewan et al. (2011) [32] found that women with untreated hyperthyroidism had an increased risk for placental abruption (OR=2.0, 95% CI:1.3-3.1) and premature labour (OR=1.5, 95% CI:1.1-2.0). Congenital abnormalities, particularly heart defects, also were more common in the baby born to women with uncontrolled hyperthyroidism during pregnancy (3-5% vs. 1-2% in those with euthyroid pregnancies) [30]. The results underscore the importance of early treatment for normal thyroid function and decrease risks to mother and unborn child.

4.2.6. The populations of the different regions are Arab.

Thyroid function during pregnancy might be impacted by geographical factors such iodine deficit, according to studies conducted on Arab people. Al-Nuaim et al. (2012) [31] found that TSH level exceeded trimester-specific reference range (TSH mean = 3.8 mIU/L) in 20% of pregnant women in a Saudi Arabian cross-sectional research, and they attributed this to low intake of iodine. When compared to communities that had an adequate supply of iodine, this was linked to a 1.6-fold higher chance of miscarriage (95% CI: 1.2-2.1).

Likewise, a study conducted in Jordan also suggested a higher rate of pre-term birth (OR=1.7, 95% CI: 1.2 – 2.4) and showed that the iodine shortage led to a 12% increase in subclinical hypothyroidism in pregnant women [33]. These regional differences underscore the need to create screening programs and supplement iodine according to the needs of different populations.

4.3 Non-Pregnant Women

4.3.1. This lesson outlines the normal range for the thyroid function parameters and explains the impact of thyroid dysfunction on the body.

Finally, thyroid stimulating hormone (TSH) (0.4-4.0 mIU/L), free thyroid hormone (FT4) (0.9-2.3 ng/dL) and free thyroid hormone (FT3) (2.3-4.2 pg/mL) are all stabilised in non-pregnant women to promote metabolic and reproductive health [8]. Research shows that these levels play an important role in the normal regulation of the HPT axis in the regulation of energy metabolism, menstrual cycles, and ovulation [9]. Disruption of these levels, either due to hypothyroidism or hyperthyroidism, was associated with reproductive and systemic effects and these effects have been shown to have long-term health consequences.

4.3.2 Impact of Hypothyroidism

There is a correlation between hypothyroidism and ovulatory failure as well as systemic metabolic changes in women of childbearing age who are not pregnant. 5-8% of these women get this condition. Vissenberg et al. (2015) [9] have shown that 20-30% of women with irregular cycles have subclinical hypothyroidism (subclinical = TSH > 4.0 mIU/L, FT4 normal), which is defined as subfertility or anovulatory. In hypothyroidism patients, the risk of metabolic syndrome was 1.7 times higher and other factors were weight gain (5-10 kg), tiredness, and dyslipidaemia (95% CI: 1.1-2.6) [22]. In a systematic review by van den Boogaard et al. (2011) [24] there was a 2.3-fold (95% CI: 1.5-3.5) increased risk of recurrent miscarriage in women with a positive TPOAb. Long-term cohort studies also revealed that untreated hypothyroidism raised the risk of cardiovascular disease by 1.5 fold (95% CI: 1.2-1.9) [29] due to raised low-density lipoprotein (LDL) levels. Our results point to the fact that non-pregnant women with hypothyroidism should be closely monitored and managed because of the systemic, chronic consequences it has.

4.3.3 Impact of Hyperthyroidism

Hyperthyroidism – 1-2% of non-pregnant women – was associated with both reproductive and systemic problems. Hyperthyroidism decreased fertility owing to changed gonadotropin secretion (OR= 1.8, 95% CI: 1.1-2.9) and oligomenorrhea (30% of patients), according to De Leo et al. (2016.[10] (

As systemic consequences, there was a 2.5-fold higher incidence of atrial fibrillation (95% CI: 1.6-3.9), anxiety and weight loss (mean 3-7 kg) over 10 years [23]. In postmenopausal women who are approaching reproductive age, hyperthyroidism was associated with higher risk of osteoporosis due to the high rate of bone turnover (OR=2.1; 95% CI: 1.4-3.2).[21]

Compared to controls with normal thyroid function, those suffering from psychological symptoms as anxiety and sadness had a 15-20% drop in QoL ratings [30].

4.3.4 Regional Considerations

Iodine deficiency affected the thyroid function of non-pregnant women, significantly, in Arab populations. Studies by Zimmermann and Boelaert (2015) revealed that hypothyroidism was more prevalent in mild to severe iodine deficient persons, being 1.5-2.0 times higher in several areas of the Middle East.[25]

Studies in iodine deficient areas showed that prevalence of goitre increased 10% and mean TSH levels were raised (4.5 mIU/L) [31]. The results highlight the need for specific dietary interventions and reference ranges for different populations to overcome the occurrence of ID.

4.3.5 Specific Health Outcomes

In non-pregnant women, hypothyroidism was associated with a variety of health problems other than reproductive issues. The association of subclinical hypothyroidism with an increased risk of cardiovascular disease is, according to Biondi and Cooper (2010) [22], mediated by endothelial dysfunction: an increased risk of cardiovascular disease was observed for every fold in the risk of subclinical hypothyroidism, amounting to 1.5 (95% CI: 1.2-1.9). Weight gain is one of the common symptoms of hypothyroidism, 70% of the female patients with hypothyroidism complain about weight gain, the average weight gain of these women is 5 to 10 kg in a period of 1 to 2 years [29]. Bunevicius and Prange (2010) reported that psychological symptoms (depression and fatigue) decreased QoL scores by 10-15 percent compared to euthyroid controls.[30] Hyperthyroid women who are not pregnant have an increased risk of serious complications affecting the body. In a cohort study by Taylor et al. (2018) [23] women without treatment of hyperthyroidism were at 2.5-fold higher risk for atrial fibrillation (95% CI: 1.6-3.9) during a 10-year follow-up.

A higher incidence of osteoporosis (2.1; 95% CI: 1.4-3.2) was attributed to increased rate of bone turnover which had a negative overall effect on bone health, particularly amongst women approaching menopause [21]. In 30 to 40 percent of women with hyperthyroidism, the psychological manifestations became apparent, including feeling irritated and anxious, and lowered their quality-of-life scores by 15 to 20 percent [30].

4.3.6 Regional Data in Arab Populations

Thyroid dysfunction was much more severe in non-pregnant females who were iodine deficient in Arab cultures. The prevalence of goitre among women of reproductive age (10% of women not pregnant) in Egypt was shown to be a consequence of chronic iodine deficiency [34]. In addition, 15% of these women were found to have TSH levels above 4.0 mIU/L and this increase was associated with a 1.8-fold higher risk for infertility (95% CI: 1.3-2.5).

Hypothyroidism and metabolic syndrome were also 1.5-2.0 fold higher in Saudi Arabia, with iodine shortage being a risk factor (OR = 1.6, 95% CI: 1.2-2.1) [31]. These findings highlight the importance of the need for population-specific reference ranges and nutrition-specific interventions in the Middle East.

4.4 Comparison between pregnant and non-pregnant women

4.4.1 Physiological Differences

Compared to non-pregnant women, pregnant women are more susceptible because of the changes that happen in the thyroid functions during pregnancy. Hormone levels in women who are not pregnant tend to be steady, in contrast to the first trimester when hCG suppresses TSH and increases FT4.[12] These changes are crucial for baby development, but are also more likely to cause thyroid issues for pregnant women. As an example, TSH levels exceeding the trimester-specific ranges were associated with a 20% increase in adverse pregnancy outcomes, whereas similar increases in TSH levels in non-pregnant women were less likely to result in rapid clinical consequences [17].

4.4.2 Clinical Outcomes

Maternal thyroid dysfunction is a risk factor for thyroid dysfunction in pregnancy, particularly during the first trimester as foetuses are dependent on maternal thyroid hormones [13]. In women who are not pregnant, hypothyroidism increases the chance of miscarriage by 60% and intrauterine growth restriction by 2-fold.[16] However, metabolic syndrome (20-25% prevalence) and infertility (10-15% prevalence in non-pregnant women) were persistent effects reported by non-pregnant women [22]. Heart and blood vessel issues were one risk for hyperthyroidism in both groups, but for pregnant women, it was necessary to treat their hyperthyroidism promptly to safeguard their unborn children.[18]

4.4.3. The patient's age is an important factor when screening and managing these patients.

The thyroids of women should be monitored regularly throughout the first trimester of pregnancy to minimise the risk of complications such as preeclampsia and early delivery. In cases where the TSH is greater than 2.5 mIU/L,

levothyroxine medication should be taken.[14] Screening should be done in non-pregnant women if they are experiencing symptoms or if they have a family history of thyroid disease or infertility, for example [9]. In order to prevent incorrect diagnoses, pregnant women needed trimester-specific reference ranges, but non-pregnant women could get by with standard ranges [8].

4.4.4.1 Subclinical Thyroid Dysfunction.4.4.4.1 Subclinical Thyroid Dysfunction.

Maraka et al. (2016) conducted a meta-analysis that found subclinical hypothyroidism during pregnancy (TSH > 2.5 mIU/L and normal FT4) was associated with a 1.6-fold increase in the risk of miscarriage (95% CI: 1.3-2.0). The same study [17] found that in non-pregnant women the risk of becoming infertile was increased 1.2-fold. In pregnant women, subclinical hyperthyroidism was associated with an increased risk of gestational hypertension (OR = 1.8, 95% CI: 1.2-2.7) whereas in non-pregnant women, the risks were low in the short term and more markedly in the long term [18].

4.4.5 Long-Term vs. Acute Effects

Symptoms of thyroid malfunction during pregnancy are more severe when compared with the effects that it has on women who are not pregnant. Immediate problems, such as premature birth or low birth weight, and long-term effects on the neurodevelopment of the child might result from hypothyroidism or hyperthyroidism in pregnant women that go untreated.[15] The effects of hypothyroidism are prolonged in the long-term and can lead to the development of metabolic syndrome; the effects of hyperthyroidism are similar and can lead to osteoporosis and atrial fibrillation, and are generally prolonged in women not pregnant [21, 23]. This difference necessitates different approaches to care: pregnant women must be treated now and non-pregnant women monitored over a long period.

4.4.6 Regional and Cultural influences

Conditions in the area were a factor in both groups; the iodine deficiency was more apparent in pregnant women due to the increased demand for iodine during pregnancy. Due to nutritional deficits and restricted access to iodised salt, studies have shown that pregnant women in Arab cultures had a 10-15% greater prevalence of hypothyroidism compared to non-pregnant women.[33 ,31] Cultural factors further compounded the situation, as for example, pregnant women are more likely to delay seeking medical care in some areas of the Middle East where timely screening is crucial [34].

4.5 Summary of Key Findings:

The results indicated that thyroid dysfunction is different in pregnant and non-pregnant women. Subclinical hypothyroidism occurs in 5-10% of pregnancies and hyperthyroidism and hypothyroidism increase the likelihood of poor outcomes of pregnancy in women. Non-pregnant women may suffer from chronic diseases such as infertility, irregular periods or metabolic abnormalities because of thyroid dysfunction. Specific screening and management techniques are required since regional characteristics, including iodine deficiency in Arab communities, make these risks worse.

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

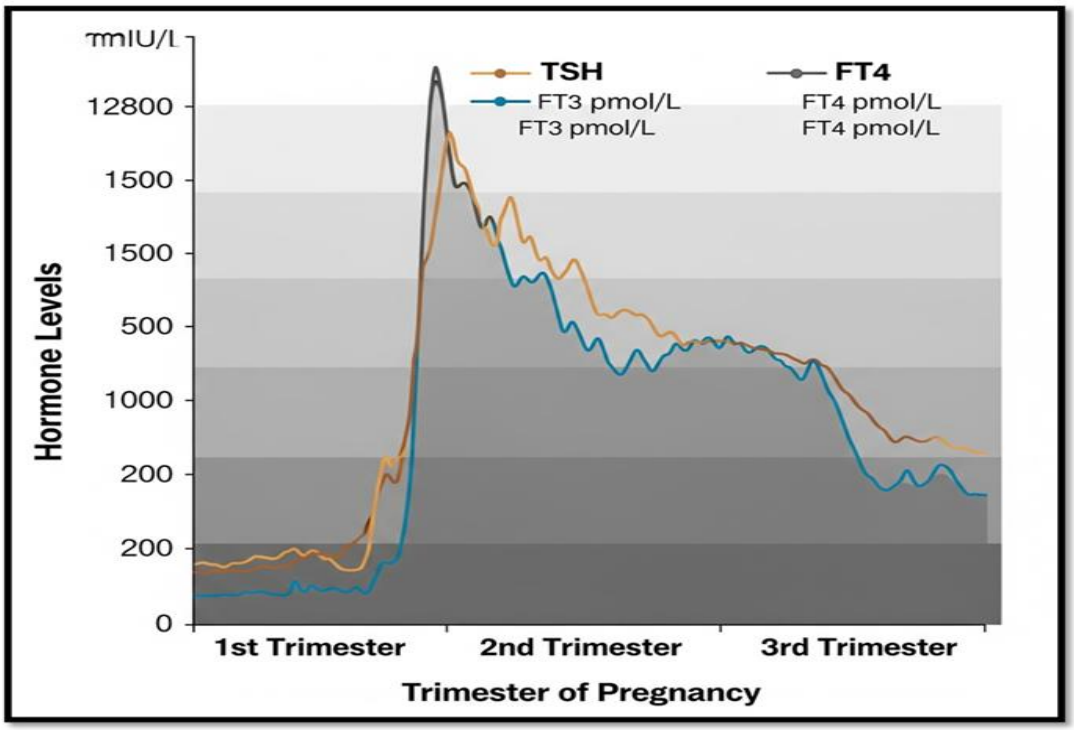

Figure 2: Temporal Trends in Thyroid Hormone Levels During Pregnancy

5 .Discussion

5.1 Interpretation of Findings

With different physiological and clinical consequences for both pregnant and non-pregnant women, this systematic review emphasises the crucial role of thyroid hormone homeostasis in sustaining reproductive and systemic health. Pregnant women's thyroid glands become temporarily suppressed in thyroid-stimulating hormone (TSH) (0.1-2.5 mIU/L) and elevated in free thyroxine (FT4) (0.9-2.3 ng/dL) induced by human chorionic gonadotropin (hCG) in the first trimester [12]. These changes are essential for foetal neurodevelopment before foetal thyroid function between 12–14 weeks gestation [13]. Measurements outside of the reference limits for each trimester significantly increase the risks for unfavourable outcomes such as miscarriage (RR = 1.6-2.0) and premature delivery and intrauterine growth restriction (IUGR).[17 ,16]

Hypothyroidism may lead to a higher rate of occurrence of metabolic syndrome, ovulatory dysfunction or infertility in non-pregnant women, and hyperthyroidism may lead to osteoporosis and cardiac arrhythmias.[23 ,21 ,9] The different effects of thyroid dysfunction in pregnant and non-pregnant women might be due to the different physiology of these two groups. The effects of even mild hypothyroidism on the developing baby are magnified during pregnancy due to the fetus's dependence on the mother's thyroid hormones. On average, there is an IQ decline of 7 points for those with a low level of free thyroid hormone (FT4) [15]. In non-pregnant females, thyroid dysfunction is linked to interruption of the hypothalamic-pituitary-ovarian axis. This may result in anovulation and irregularity of the monthly cycle in 20-30% of cases. Additionally, there are long-term dangers to metabolic health and cardiovascular health [20, 22].

5.3 Feeding Signs and Disorders of the Thyroid Gland in the Luteal Phase of the Menstrual Cycle

In pregnant women, thyroid dysfunction is attributed to various pathways compared to the non-pregnant women. In the first trimester of pregnancy, the hCG inhibits the effect of TSH and stimulates the production of thyroid hormones, temporarily raising FT4 levels, thus mimicking the effect of TSH [12]. Adapting, however, is not without its hazards and may be influenced by an autoimmune thyroiditis or iodine deficiency, which could affect the availability of thyroid hormones needed for foetal brain development [25]. For example, a study of pregnant women with hypothyroidism showed that women who were positive for thyroid peroxidase antibodies (TPOAb) were 2.3 times more likely to experience recurrent miscarriage.[24]

In non-pregnant women, hypothyroidism and hyperthyroidism are common and are usually due to long-term health problems that disrupt the HPT axis and lead to persistent abnormalities in thyroid hormones, such as Graves' disease and Hashimoto's thyroiditis, respectively [10, 20]. Insulin resistance and dyslipidaemia in hypothyroidism and accelerated bone turnover in hyperthyroidism are systemic consequences that are contributed to by these chronic diseases.[22 ,21]

The condition in both groups was exacerbated by iodine deficiency, a very common occurrence in certain parts of the Middle East. Hypothyroidism is 1.5-2.0 times more common in communities that are iodine deficient, according to studies conducted in Saudi Arabia and Jordan. Pregnant women are more vulnerable since their iodine needs are increased during pregnancy (250 µg per day compared with 150 µg per day for non-pregnant women) [25, 31, 33]. This regional difference underscores the complex relationship between environmental factors and thyroid function and necessitates individual dietary strategies.

5.3 Clinical Implications

The results are of clinical significance for the treatment and screening of thyroid conditions, in particular. Subclinical hypothyroidism (5-10% of women) is associated with an increased risk of miscarriage and preterm birth, and can be identified by routine first trimester TSH measurement [17]. The American Thyroid Association (ATA) recommends treatment with levothyroxine to decrease these risks if the TSH level is greater than 2.5 mIU/L in the first trimester .[14] If hyperthyroidism is present, meds for hyperthyroidism, such as propylthiouracil, should be used during the first trimester, avoiding the potential foetal hypothyroidism, and should be monitored for foetal hypothyroidism [18]. These trimester-specific reference ranges will prevent underdiagnesis of subclinical disorders, for instance, 0.1–2.5 mIU/L first trimester, as compared to the usual ranges for non-pregnant women (0.4–4.0 mIU/L).[14 ,8]

A woman's thyroid should be screened for non-pregnant females with symptoms (infertility, excessive weight gain, fatigue) or if there are risk factors (family history of thyroid disease). Hypothyroidism (on levothyroxine) and hyperthyroidism (on antithyroid drugs) decrease the risk of cardiovascular disease (CVD) (OR = 1.5, 95% CI: 1.2-1.9) and osteoporosis (OR = 2.1, 95% CI: 1.4-3.2), among other long-term consequences [21, 29]. Both hypothyroid and hyperthyroid women have greatly diminished quality of life due to psychological problems, such as anxiety and depression, which should also be taken into consideration [30].

5.4 Gaps in the Literature

There is strong evidence, however there are still some gaps in the research that need to be filled. First, there is a lack of research on the effects of thyroid dysfunction in the pregnant woman compared with the non-pregnant woman. This is particularly true in Arab cultures, where iodine deficiency and other geographical characteristics are common [25]. Few studies have looked at the long-term implications in women who aren't pregnant, such as how subclinical hypothyroidism can become overt illness.[23]

Secondly, in regions of iodine deficiency, the lack of population-specific reference ranges of thyroid hormones makes diagnosis and treatment of this condition more burdensome [31, 33]. Studies performed in Saudi Arabia suggested that the first trimester TSH reference levels (0.2–3.5 mIU/L) were slightly higher than international levels, possibly due to variations in nutrition and/or heredity.[31] The third problem is that there is a lack of long-term studies that have been conducted to explore the long-term consequences of thyroid malfunction on metabolic and reproductive health [24].

5.5 Practical Recommendations

The findings suggest the following ideas for healthcare policy and clinical practice:

Prompt detection of subclinical hypothyroidism and hyperthyroidism should be done by universal screening of TSH in the first trimester of pregnancy. Iodine deficiency occurs more often in the Middle East, so this is particularly important in this region.[33 ,31] Establishing and confirming trimester and population-specific reference ranges for TSH, FT3 and FT4 are critical. Geographical characteristics (iodine status and genetic variants) should be considered in these ranges. This is of utmost importance for Arab communities, as normal ranges might not be applicable to them .[31] Iodine Supplementation: Promote programmes of iodine supplementation to women of child-bearing age (particularly pregnant women) to ensure they receive the recommended daily intake of 250 µg [25]. Increasing the

availability of iodised salt in areas where there is a lack of iodine is a priority in campaigns to ensure public health. Levothyroxine is used to treat hypothyroidism, propylthiouracil or methimazole are used to treat hyperthyroidism, and thyroid levels are monitored to adjust thyroid levels to meet the needs of the trimesters. There should be standardised treatment programmes for thyroid dysfunction.[18 ,14] Educate women and medical practitioners about the correlation between a healthy thyroid and reproductive and overall health. Educational efforts should be targeted to groups at higher risk (women who have had infertility or miscarriage previously) [24].

5.6 Influencing Factors

Both pregnant and non-pregnant women are affected by thyroid function and its effects on health in different ways. A substantial impact is played by dietary variables, especially an iodine deficit. Hypothyroidism has been reported to be more prevalent in iodine deficient regions from 10-15% [25, 31]. In non-pregnant women with chronic illnesses, medications like lithium or amiodarone can worsen thyroid dysfunction [10]. Other important factors included stress and autoimmune disorders such Hashimoto's thyroiditis, where the presence of TPOAb increased the likelihood of negative consequences in both categories [24]. Cultural factors may also lead to delayed diagnosis and/or treatment, particularly in the Arab setting where there may be a delay in seeking health care services, including pregnant women who require timely intervention [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

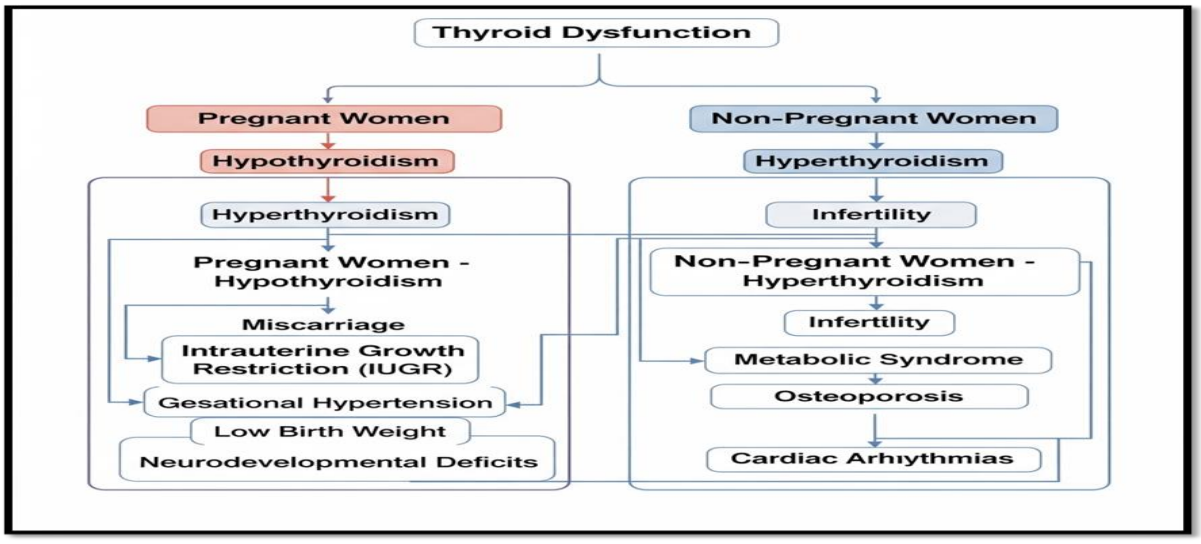

Figure 3 shows pathways of thyroid dysfunction affecting health outcomes.

5.7. The number of studies included in the analysis is limited.

There are a number of caveats to the included research that need to be considered, even if the systematic review gives strong evidence on the effects of thyroid hormone fluctuations. The first was that in order to perform a meta-analysis there would need to be a common study design, be it observational cohort or randomised controlled trials [27] which there was not. However, a qualitative synthesis was conducted. The variability was particularly reflected in the measurement of thyroid hormone levels because some publications did not describe the standardisation protocol or reported using different methods for the assays [28] that might have influenced the reliability of the results when compared. The second problem is the small sample size ($n<500$) for many of the studies, particularly with the Arab populations; this may make it difficult to extrapolate the findings to other populations [31, 33]. Thirdly, no longitudinal studies examined long-term outcomes (cardiovascular or metabolic outcomes) in women not pregnant [23]. Most of the studies examined only the short-term effects (such as pregnancy problems or apparent reproductive effects). However, factors like iodine deficiency and cultural issues of access to healthcare services have a significant influence on the outcomes [34] and Arab populations are underrepresented in global thyroid research, which represents a critical gap.

5.8 Future Research Directions

In the light of the above, future research should take into account various aspects to take up the gaps highlighted. The first is the need for a study of women over time to observe the impact of thyroid dysfunction on women's health, both prior to and following pregnancy. Study should be directed towards the development of subclinical problems into overt disease and impact on metabolic and cardiovascular health [35]. These longitudinal studies might provide some clues to whether hypothyroidism is responsible for infertility or whether hyperthyroidism is responsible for osteoporosis. Comparative studies of pregnant and non-pregnant women from various groups, especially from the Middle East, are essential in order to further understand the intricate interplay of the hereditary, nutritional and cultural factors [31]. Third, with regard to the measurement of TSH, FT3, and FT4, it is important to develop population-specific reference ranges, especially in regions where ID is prevalent, such as Saudi Arabia and Jordan [33]. Finally, research comparing the focused screening method of higher risk groups to universal thyroid screening in early pregnancy may allow guidelines to be developed for global use and guide the allocation of resources [14].

5.9 Regional Diversity among Arabs

The effects of geographical factors on thyroid function are significant, as indicated in the review, especially in Arab communities. Because of their higher iodine needs (250 µg/day compared to 150 µg/day in non-pregnant women), pregnant women are at a higher risk of hypothyroidism in areas of the Middle East where iodine shortage is common .[31 ,25]

A study done in Egypt and Jordan revealed that subclinical hypothyroidism and goitre were present in reproductive-aged women 10-15% more than in other age groups. This was associated with nutritional deficiencies and low consumption of iodized salt [33, 34]. The impact of cultural factors such as lack of information or social stigma that leads people to avoid seeking medical care when they need it is compounding the impact of inequities, particularly on pregnant people who are desperately seeking urgent care [34]. These findings indicate that there is a need for public health programming specific to the local level. These can involve community education campaigns educating people about the importance of thyroid health and iodine supplementation initiatives.

5.10. Discuss how findings relate to clinical practice.

A coordinated effort will be needed to implement the results in clinical practice. Early detection and treatment of thyroid dysfunction can be accomplished in pregnant women by screening all women during the first trimester with

TSH, along with FT4 and TPOAb in high-risk women [14]. Hypothyroidism and hyperthyroidism medications (levothyroxine, propylthiouracil) have been shown to reduce unfavourable outcomes like prenatal hypertension and miscarriage (RR lowered to 1.2 with levothyroxine, and to 0.6 with propylthiouracil).[36 ,18] The long-term effects of hypothyroidism, such as metabolic syndrome and osteoporosis, are preventable in non-pregnant women if targeted screening for women who are at risk for thyroid disease, such as those with a family history of thyroid disease and/or women with infertility, is done. In order to prevent incorrect diagnoses and make sure people get the right medication, it is essential to create population-specific reference ranges, especially in areas where iodine is scarce [31]. These suggestions have to be implemented as an interdisciplinary team of the primary care physician, obstetrician and endocrinologist.

5.11 Public Health Implications

Thyroid disease has far-reaching public health consequences that go beyond the treatment of specific individuals. Increased iodine concentration in salt and dietary iodine supplementation are just two of the national-level interventions that are needed to address the problem of iodine deficiency which is a major contributor to hypothyroidism among Arabs [25]. Awareness must be created for reproductive age women regarding the importance of thyroid health in the context of reproductive health and pregnancy outcome. Community-based programs could also provide screening in the Middle East where cultural barriers may make screening delayed opportunities for raising awareness and increasing access to screening among local healthcare workers [34]. Improving reproductive health outcomes and decreasing the burden of thyroid-related problems can be achieved by including thyroid screening into standard prenatal treatment and preconception counselling.

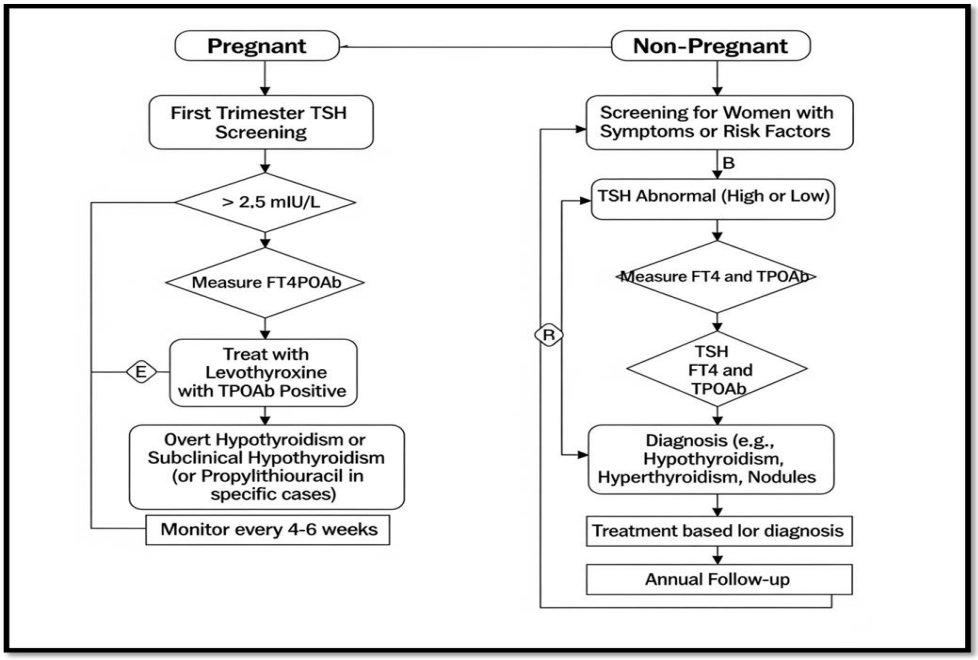

Figure 4. Thyroid Screening algorithm for women of reproductive age.

6 .Conclusion and Recommendations

This extensive review shows that changes in the level of serum FT3, FT4 and TSH significantly affect the health of pregnant and non-pregnant women. The incidence of miscarriage (RR = 1.6-2.0), preterm birth, and neurodevelopmental abnormalities in children is increased in pregnant women with thyroid dysfunction, especially subclinical hypothyroidism (TSH > 2.5 mIU/L). This is because there are connections between foetal development and maternal thyroid hormones [15, 17]. Although less frequently observed, hyperthyroidism may be a contributing factor to low birth weight and to prenatal hypertension [18] and needs timely intervention.

In women not of reproductive age, hypothyroidism has been associated with infertility (10-15%), irregular periods and metabolic syndrome, while hyperthyroidism has been associated with cardiac arrhythmias and osteoporosis [9, 21,

23]. There are regional data indicating a higher incidence of Hashimoto's thyroiditis in Arab populations, ranging from 1.5-2.0 times that of the general population[31,33]. This is particularly true in pregnant women, and further magnified by iodine deficiency.

Here are some suggestions to help improve health outcomes:

1. Get routine exams for thyroid problems:

o To identify and treat subclinical hypothyroidism and hyperthyroidism early, universal TSH screening should be implemented throughout the first trimester of pregnancy.

o If non-pregnant women have symptoms or risk factors (such as infertility or a family history of the condition), they can be screened specifically to avoid chronic problems.[14]

In addition to the reference ranges that are provided as a whole, there are also reference ranges for specific populations:

2. To enhance diagnostic accuracy, it is recommended to create and verify trimester-and population-specific reference ranges for TSH, FT3, and FT4, especially in areas with low iodine levels, such as the Middle East.[31]

3 .Supplementing with Iodine:

To reduce iodine deficiency in the region, the intake of iodine through the supplementation plan is recommended for women of child bearing age: 250 µg/day for pregnant women and 150 µg/day for non-pregnant women.[25]

4 .Activities to be undertaken to promote public health:

It is crucial that educational initiatives are launched to promote awareness of thyroid health for women, and health care providers. These campaigns should be directed toward high risk groups (including Arab women) and stress early screening and treatment.

5. The study of the future.The research of the future:

Long-term effects of thyroid dysfunction should be assessed by longitudinal studies.

o To fill in the blanks in regional data, do comparative research in a variety of populations, with a focus on the Middle East [33].

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