Review Article

Int Jou Hea Bio Sci, 6(4), 2025, 7-16

International Journal of Health care and Biological Sciences

Content available at www.saap.org.in Online ISSN: 2582-7499

Open Access

A REVIEW ON EXPLORING LINK BETWEEN MATERNAL TSH LEVELS DURING GESTATIONAL HYPOTHYROIDISM AND FOETAL DEVELOPMENTAL MILE STONES

Ravuri Venkata Suvarna[1], M. Sowjanya[2], Y Prapurna Chandra[3], Venugopalaiah Penabaka[4], Afroz Patan[5]

[1]B. Pharmacy, IV Year, Ratnam Institute of Pharmacy, Pidathapolur (V & P), Muthukur (M), SPSR Nellore District-524 346, Andhra Pradesh.

[2]Assistant Professor, Department of Pharmacy Practice , Ratnam Institute of Pharmacy, Pidathapolur (V & P), Muthukur (M), SPSR Nellore District-524 346, Andhra Pradesh.

[3]Principal and Professor, Department of Pharmacology, Ratnam Institute of Pharmacy, Pidathapolur (V & P), Muthukur (M), SPSR Nellore District-524 346, Andhra Pradesh.

[4]Professor, Department of Pharmaceutics, Ratnam Institute of Pharmacy, Pidathapolur (V & P), Muthukur (M), SPSR Nellore District-524 346, Andhra Pradesh.

[5]Professor & HOD, Department of Pharmacy Practice, Ratnam Institute of Pharmacy, Pidathapolur (V & P), Muthukur (M), SPSR Nellore District-524 346, Andhra Pradesh.

Article History

Received on: 24-07-2025
Revised on: 11-09-2025
Accepted on: 06-10-2025

Abstract

Pregnancy is a complex state with many endocrinological challenges to a woman's physiology. Gestational Hypothyroidism (GHT) is an emerging condition where insufficiency of the thyroid gland has developed during pregnancy in a previously euthyroid woman. It is different to overt hypothyroidism, where marked elevation of thyroid-stimulating hormone with corresponding reduction in free thyroxine levels, is well known to cause detrimental effects to both the mother and the baby. During the past couple of decades, it has been shown that GHT is associated with multiple adverse maternal and foetal outcomes such as miscarriage, pre-eclampsia, placental abruption, foetal loss, premature delivery, neurocognitive and neurobehavioral development. However, three randomized controlled trials and a prospective cohort study performed within the last decade; show that there is no neurodevelopmental improvement in the offspring of mothers who received levothyroxine treatment for GHT. Thus, the benefit of initiating treatment for GHT is highly debated within the clinical community as there may also be risks associated with over-treatment. In addition, regulatory mechanisms that could possibly lead to GHT during pregnancy are not well elucidated.

Keywords: Gestational hypothyroidism, subclinical hypothyroidism, pregnancy, thyroid disorders, placenta, oestrogen, iodine, levothyroxine.

***Corresponding Author**
M. Sowjanya

DOI: https://doi.org/10.46795/ijhcbs.v6i4.747

Introduction

Thyroid dysfunction during pregnancy is a well-researched area due to the detrimental effects of either profoundly low or high circulating thyroid hormones. On the lower end of the spectrum where there is an insufficiency in circulating thyroid hormones, exist three distinct conditions, namely; overt hypothyroidism (OH), subclinical hypothyroidism (SCH), and isolated hypothyroxinemia (IH). There is no doubt that overt hypothyroidism should be promptly diagnosed and treated with levothyroxine in order to prevent severe maternal and foetal consequences such as foetal loss, premature birth, neurocognitive impairment of the child [1]. Gestational hypothyroidism has been linked to a higher risk of premature delivery, intrauterine growth restriction (IUGR) foetuses, miscarriage, and risk of foetal death, particularly when hypothyroidism was untreated or inadequately managed [2]. The foetal thyroid gland reaches maturity by week 11–12, close to the end of the first trimester and begins to secrete thyroid hormones by

about week 16 [3]. Hypothyroid foetuses suffer various postnatal disorders including mental retardation, deafness, and spasticity. Severe iodine deficiency, which causes both maternal and foetal hypothyroidism, is, worldwide, the most common cause of mental retardation. [4]

Gestataional Hypothyroidism

Gestational hypothyroidism refers to an underactive thyroid gland diagnosed for the first time during pregnancy. It is characterized by inadequate production of thyroid hormones during pregnancy, which can affect both maternal health and foetal development.

Types

1. Overt Hypothyroidism

- >10 mIU/L or Elevated TSH (thyroid-stimulating hormone)
- Low free T4 (thyroxine)
- May present with symptoms like fatigue, weight gain, cold intolerance, or goiter.

2. Subclinical Hypothyroidism

- Normal for trimester
- Normal free T4
- Often asymptomatic, but still associated with risks during pregnancy.

Table 1: Causes of Hypothyroidism.

Category	Example
Autoimmune	Hashimoto's, TPO antibodies
Iodine deficiency	Low dietary iodine intake
Iatrogenic	Surgery, radioactive iodine, antithyroid drugs
Central causes	Pituitary/hypothalamic dysfunction
Drug-induced	Amiodarone, lithium, etc.
Previous thyroid disorders	Postpartum thyroiditis
Genetic	Congenital hypothyroid disorders

Risks in Pregnancy

- Miscarriage
- Preterm birth
- Preeclampsia
- Low birth weight
- Impaired neurocognitive development in the child (especially with overt hypothyroidism)

Treatment

Levothyroxine (synthetic T4) is the treatment of choice.

Regular monitoring of thyroid function is essential throughout pregnancy.

TSH (Thyroid stimulating hormone)

Thyroid dysfunction is the most common endocrinological disorder in pregnancy, only second to diabetes. In recent times, it is also the most sought-after area of research in clinical endocrinology [5].

TSH (thyroid-stimulating hormone), produced by the anterior pituitary gland, regulates the thyroid glands production of:

T3 (triiodothyronine)

T4 (thyroxine)

It works on a negative feedback loop:

If T3/T4 levels drop, TSH increases to stimulate the thyroid.

If T3/T4 levels rise, TSH decreases to reduce stimulation.

TSH Level Interpretation

0.4 – 4.0 mIU/L - Normal range (may vary slightly by lab)

< 0.4 mIU/L - Possible hyperthyroidism

> 4.0 mIU/L - Possible hypothyroidism

LEVELS:

Normal TSH Range (Non-pregnant adults):

0.4 – 4.0 mIU/L

Table 2: Trimester and TSH range levels.

Trimester	TSH range (mIU/L)
1st Trimester	0.1 – 2.5 mIU/L
2nd Trimester	0.2 – 3.0 mIU/L
3rd Trimester	0.3 – 3.5 mIU/L

TSH Monitoring in Pregnancy

In patients on levothyroxine

Monitor TSH every 4–6 weeks during pregnancy.

Dose often needs to be increased by 30–50% early in pregnancy.

Table 3: Specific levels of trimesters.

TRIMESTER	FT3	FT4	TSH
First trimester	1.91-3.5 pg/ml	0.86-1.77 pg/ml	0.1 to 2.5 µIU/ml
Second trimester	2.8-4.2 pg/ml	0.63-1.29 pg/ml	0.2 to 3.0 µIU/ml
Third trimester	2.4-4.1 pg/ml	0.66-1.12 pg/ml	0.3 to 3.0 µIU/ml

Hypothyroidism in Pregnancy

Hypothyroidism in pregnancy can be subclinical hypothyroidism, overt hypothyroidism, or isolated hypothyroxinemia. Subclinical hypothyroidism is more common than overt hypothyroidism. Other causes are hypothyroidism following surgery for multinodular goiter, Graves' disease or thyroid cancer, following radioactive iodine treatment of Graves' disease, overtreatment of hyperthyroidism with ATDs, medications that alter the absorption or metabolism of LT4 and central defects that inhibit the hypothalamic-pituitary-thyroid axis [6].

Subclinical Hypothyroidism (SCH)

Subclinical hypothyroidism is diagnosed based on elevated TSH concentration and normal free thyroxine

level. Risk factors for SCH include iodine deficiency, personal/family history of thyroid disease, positive thyroid antibodies, type 1 diabetes, autoimmune disorders, radiation exposure to head and neck area, and history of amiodarone and lithium use [7].

Overt Hypothyroidism

Hypothyroidism may present with nonspecific symptoms and signs that may be indistinguishable from common signs or symptoms of pregnancy, such as fatigue, constipation, cold intolerance, muscle cramps, and weight gain. Other features are edema, dry skin, hair loss, goiter and a prolonged relaxation phase of deep tendon reflexes.

Thyroid Autoimmunity

Thyroid autoimmunity is the most common autoimmune disease of the reproductive age group. Autoimmunity can occur in the presence or absence of thyroid dysfunction. Thyroid peroxidise antibodies (TPO), thymoglobulin antibodies, and TSH receptor antibodies (TR) are the antithyroid antibodies (ATAs) seen in autoimmune thyroid disease (ATD). The prevalence of TPO and thymoglobulin antibodies in pregnant women is 5–14% and 3–18%, respectively. [8] Antibodies to thyroid peroxidise and thymoglobulin are increased in both Graves disease and Hypothyroidism and both conditions have similar ultrasound picture.

Postpartum Thyroiditis (PPT)

Thyroid dysfunction within the first year postpartum is usually seen in those patients without a prior history of thyroid nodule or TSH receptor antibodies. It is an autoimmune process resulting from the increased release of thyroid antibodies after delivery following immune tolerance induced by pregnancy. The patients undergo a phase of transient thyrotoxic state lasting for 2–3 months followed by hypothyroidism lasting for 3–6 months, and the majority of them become euthyroid within a year. [9] The hypothyroid phase may persist in 20–30% of cases. PPT can be easily misdiagnosed as postpartum depression.

Influence of THs on Brain and Cognitive Development

The brain is an important target of thyroid hormones at all stages of life, however, the maximal vulnerability to an imbalance of thyroid hormone supply occurs during the earliest stages of brain development. The majority of human studies have been observational in nature, focusing on relatively broad cognitive outcome measures, whereas the mechanisms and molecular underpinnings of the behavioural changes have largely been studied in rodent models.

Physiological Changes of Thyroid Function in Mother and Foetus during Pregnancy

Thyroid hormones (TH) are very important for growth and development of brain for the foetus and neonate, in addition for many other aspects of pregnancy, foetal growth and development. The thyroid gland dysfunctions like hypothyroidism and thyrotoxicosis can affect the mother health as well as the child before and after delivery that can result in foetal disease; in humans, this includes a high incidence of mental retardation. The foetal thyroid gland begins concentrating iodine and synthesizing THs after months of gestation. Although the requirement for TH before this time is exclusively supplied by the mother which is most important to foetal brain development, significant foetal brain development continues considerably beyond the first trimester [10].

Characteristics of Various Types of Hypothyroidism

Hashimoto's disease (Chronic autoimmune thyroiditis):

It is the most common type of thyroiditis and the most common cause of primary hypothyroidism. In which the immune system attacks the thyroid, causing inflammation and interfering with its capacity to produce THs. Hashimoto's thyroiditis patients may develop a goiter or have thyroid atrophy. Chronic autoimmune thyroiditis is the most important cause of hypothyroidism in up to 90% of pregnant women with hypothyroidism during pregnancy test positive for thyroid antibodies. In its initial phase, Hashimoto's thyroiditis can cause hyperthyroidism that presents as a painless goiter caused by lymphocytic infiltration of the thyroid gland. Positive TPO antibody and/or TG antibody test results are found in approximately 5% of euthyroid pregnant women. However, a thyroid autoantibody prevalence of up to 15% has been found in pregnant women [11].

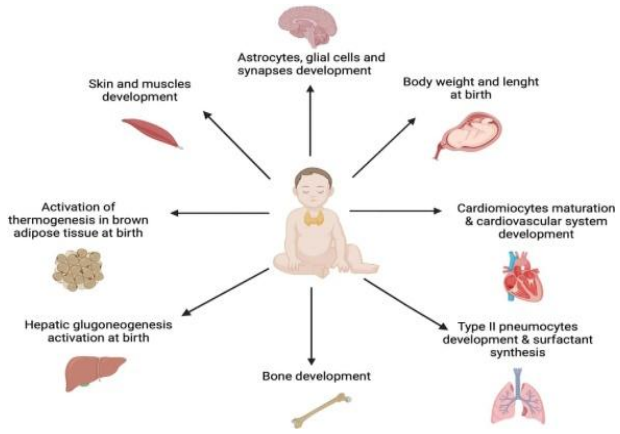

Figure 1: The role of thyroid hormones in foetal and infant development

Iatrogenic Hypothyroidism

Iatrogenic hypothyroidism is resulted from thyroid surgery, exposure of the thyroid to external radiation for neck carcinomas or from RAI to treat GD. Typically hypothyroidism occurs within 1 month following total thyroidectomy and within 1 year after RAI therapy for GD [11].

Iodine Deficiency, Thyroid Enzyme, Thyroid Hypoplasia and Goitrogens

Iodine deficiency or excess, and the ingestion of goitrogens may cause hypothyroidism on rare occasions by decreasing TH synthesis or release. Iodine deficiency,

thyroid enzyme defects, thyroid hypoplasia and goitrogens may cause TH deficiency in a developing foetus, resulting in cretinism [12].

Congenital Hypothyroidism (CH)

Congenital hypothyroidism (cretinism) is a TH deficiency at birth that occurs in 1/3000 newborns, as a result of the absence of thyroid tissue (thyroid dysgenesis) and hereditary defects in TH biosynthesis. Thyroid dysgenesis occurs more commonly in female infants and permanent abnormalities occur in 1 of every 4000 infants. It is one of the most common preventable causes of mental retardation. Most infants with CH do not show an obvious clinical manifestation of hypothyroidism at birth. This may result from remaining neonatal thyroid function, because of an over expression of deiodinases by compensatory mechanisms in target organs, or in the TH received from breast milk. [13]

Role of placenta

Effect of Thyroid Hormones on the Placenta:

It is important to identify that during pregnancy; placenta may play a central role in responding to and regulating maternal thyroid hormones. A recent review explains the available evidence on the effect of thyroid hormones on the placenta. Of interest, in established conditions which are due to abnormal placentation, such as pre-eclampsia, miscarriage, IUGR; studies have found that these women show abnormal levels of thyroid hormone as well. It is understood that optimal level of thyroid hormone is necessary for proliferation and differentiation of cytotrophoblasts [14].

Response of Maternal Thyroid Function to Placental Derived Factors

Strong evidence exists to show dysfunctional placentation due to overt hypothyroidism and hyperthyroidism in pregnant women [15]. The question remains whether any factors secreted by the placenta can alter the maternal thyroid function, perhaps lead to gestational hypothyroidism. Presence of GHT in turn could lead to associated maternal and fetal complications. Indeed, a promising set of studies within the last few years, attempt to clarify this notion.

Human Chorionic Gonadotropin (HCG)

Placenta produces hCG which shares molecular similarity with TSH. This homology between the beta subunit of hCG and TSH allows for stimulation of the thyroid gland by binding and activating the TSH receptors of thyroid follicular cells and exerting its effects via intracellular messengers, such as cAMP. It is believed that both the amplitude and duration of hCG peak plays a role in the degree of the stimulation of the thyroid gland. A transient suppression of TSH and elevation of serum fT4 is expected in those with high concentration of hCG lasting for a longer duration. This may be evident from studies that suggest hCG has a causative role in hyperemesis gravidarum, where excessive vomiting and associated 5% weight loss is considered to be due to transient mild gestational hyperthyroidism state [16].

Role of Iodine

Iodine is an essential micronutrient for the synthesis of thyroid hormone. Pregnancy, a state of many physiological changes, increases the demand for iodine around 50% [17]. This is due to increased renal clearance of iodine as the glomerular filtration rate increases, relative increase in production of maternal thyroid hormone and increased fetal requirements for iodine during second and third trimester for production of its own thyroid hormones. There is an active transport of iodine to the thyroid gland which is regulated by TSH and by the concentration of iodine in blood. According to guidelines by WHO/UNICEF/ICCIDD the recommended iodine intake for pregnant and lactating women was increased by 50ug/L from normal adult range of 100-199g/L.

Iodine Deficiency during Pregnancy

In pregnant women with moderate iodine deficiency, subclinical hypothyroidism, pre-eclampsia, anemia, fetal growth restrictions, congenital anomalies were observed while in pregnant women with severe iodine deficiency, eclampsia, placenta previa, cretinism, miscarriage, hemorrhage and fetal demise were observed. The review found that some authors suggest during light iodine deficiency there is an increased iodine uptake to increase thyroxine secretion, noted by the hyperplasia by the thyroid gland, thus reducing the damages. However, other studies suggest even during light iodine deficiency there is an increase in circulating TSH, which is associated with increased oxidative stress probably through antagonizing effects of insulin and thus inducing hyperglycemia [18]. Iodine intake is grouped according to WHO criteria by taking measurements of median urinary iodine concertation (UIC). This is because more than 90% of dietary iodine intake is excreted via urine.

Role of Estrogen

Changes to circulating estrogen during pregnancy could be another factor that might be contributing to development of GHT. It is known that there is relative increase in basal level of thymoglobulin in response to elevated estrogen levels. This decreases availability of free thyroid hormones, which in turn stimulates pituitary-thyroid axis. Thus, the thyroid gland is challenged to secrete more thyroid hormones to ensure a normal availability of free thyroid hormone. A study by De Geyter et al [19]. shows that women with SCH and on a fixed daily low dose (50 ug) supplementation with levothyroxine, still showed an increase in the TSH levels, reaching statistical significance compared to euthyroid women between gestational week 6-8. This closely parallels the pattern of rising estrogen levels during early pregnancy.

Ontogenesis of Thyroid Hormone Action in Fetal Development

There is growing evidence that thyroid hormones act on embryological and fetal tissues early in development.

Thyroid hormone and associated receptors are already found in human fetal tissues prior to the production and secretion of fetal thyroid hormones at 16–18 weeks of gestation, as evidenced by detection of T4 and T3 in the human cerebral cortex by week 12 gestation [20]. This is confirmation that active transport of maternal thyroid hormone across the placenta is occurring during this crucial period of gestation and highlights the need for maternal thyroid hormones to be at optimal levels at that time [21].

Thyroid Function Tests

Blood samples were collected in the morning after overnight fasting. Estimation of serum TSH, FT4, and thyroid peroxidise antibody (TPOAB) was performed in the institution's National Accreditation Board for Testing and Calibration Laboratories (NABL) accredited central laboratory. The methodologies used are described in the below table. The diagnostic criteria used for subclinical hypothyroidism were a serum TSH level of 4.0-10 mIU/mL with a normal FT4 level and a TSH of 0.1-2.5 mIU/mL with normal FT4 for euthyroid.

Table 4: Methods used for thyroid function tests.

Test	Method	Laboratory Reference Value
FT4	ECLIA method with cobas e 411 (Roche Diagnostics, Basel, Switzerland). Intra-assay CV: 1.3-4%; inter-assay	0.87-1.78 ng/dL
TSH	ECLIA method with cobas e 411 (Roche Diagnostics, Basel, Switzerland). Intra-assay CV: 1.8-8.6%; inter-assay CV: 3.3-8.7%	0.1-4.2 mIU/L
TPOAB	ELISA method using Euro immune kit (PerkinElmer, Inc., Waltham, USA). Intra-assay CV: 2.5-4.3%; inter-assay CV: 2.1-3.5%	<38 IU/mL

{ECLIA: electrochemiluminescence immunoassay; ELISA: enzyme-linked immunosorbent assay; CV: coefficient of variation; FT4: free thyroxine; TSH: thyrotropin; and TPOAB: thyroid peroxidise antibody.}

Maternal SCH in Pregnancy and Child Intellectual and Motor Development

Because child intelligence and motor ability develop as children mature, studies with children of similar age were included in this meta-analysis. In these three studies, the age range was 12 to 30 months. Intellectual and motor development was measured by Bayley Scales.

Fetal Thyroid Measurement

Measurements of the fetal thyroid were conducted with the fetus preferentially in the posterior dorsal position. Determine the fetal laryngeal level in a transverse view through the fetal neck, and then the probe is slid up and down to find the largest cross-section of the fetal thyroid gland. The fetal thyroid was visualized between both carotid arteries surrounding the trachea. In this plane, the transverse diameter of each lobe was measured by placing calipers on the outer borders of the thyroid lobes. Both the right and left lobes were separately measured in their three dimensions (longitudinal, anteroposterior, and transverse). Their volumes were calculated using the formula for an ellipsoid structure: vol=(π/6) *L*AP*T, where L, AP, and T are the longitudinal, anteroposterior, and transverse diameters, respectively. The isthmus was not included in these measurements because it is typically minimal in a normal fetus [22].

Maternal Outcome in Subclinical Hypothyroidism

The studies reported the adverse events associated with SCH are of poor quality. The reported prevalence of subclinical hypothyroidism in women with recurrent pregnancy loss is 12.9%. Based on current observational studies, there is no association between subclinical hypothyroidism and recurrent pregnancy loss, defined by nonconsecutive pregnancy losses. However, an association may exist between consecutive recurrent pregnancy loss and subclinical hypothyroidism [23]. SCH is associated with placental abruption (RR 2.14 [CI 1.23–3.70]), premature rupture of membranes (RR 1.43 [CI 1.04–1.95]), and neonatal death (RR 2.58 [CI 1.41–4.73]) [24]. A meta-analysis and systematic review of 19 cohort studies including 47045 women showed that the risk of preterm birth was higher for women with subclinical hypothyroidism than euthyroid women (6.1%vs 5.0%, respectively; absolute risk difference, 1.4% [95%CI, 0-3.2%].

Neonatal Outcomes

The neonatal outcomes, including birth weight, delivery weeks, preterm birth, stillbirth or miscarriage, and neonatal thyroid function, were obtained by extracting medical records or telephoning participants who delivered at other hospitals. Here, the neonatal thyroid function we use was the TSH value in dried blood collected routinely on filter paper on the third postnatal day of life for congenital hypothyroidism screening [25.]

Childhood Outcomes

The immediate neonatal and long-term adverse outcomes are rare and occur mainly in poorly controlled maternal hypothyroidism. In a large, nationwide cohort study from the United States, maternal hypothyroidism was associated with increased odds of respiratory distress syndrome, apnea, transient tachypnea of the newborn, large for gestational age infants, lower intelligence quotient, and poorer motor development in children [26]. Other associations reported include delays in the development of expressive language, decrement of orientation, vision abnormalities, and behavioural changes

in children born to women with hypothyroidism in pregnancy.

Outcome Measures

The pregnancy outcomes were miscarriage (defined as spontaneous pregnancy loss at <20 weeks of gestation) [27], placental abruption (separation of the placenta from the uterine lining at >20 weeks of gestation), gestational hypertension (high blood pressure of ≥140/90 mmHg at >20 weeks of gestation), pre-eclampsia (high blood pressure with proteinuria of ≥0.3 g/24 h),postpartum hemorrhage (blood loss of ≥500 ml within 24 h postpartum), preterm birth (birth at <37 weeks' gestation), intrauterine growth restriction (IUGR) (birth weight of <2 standard deviations for the gestational age), and low birth weight (LBW) (defined as ≤2500 g) [28].

Risk of Hypothyroidism on Foetal and Maternal Well Being

Some similar problems caused by hyperthyroidism can occur with hypothyroidism. Uncontrolled hypothyroidism during pregnancy can lead to preeclampsia, anaemia, abruption, miscarriage, low birth weight, stillbirth and rarely congestive heart failure. A study by Casey et al found that the three-fold risk of placental abruption and a two-fold risk of preterm delivery were reported in mother with sub-clinical hypothyroidism.

Previous study conducted by Haddow et al reported that untreated hypothyroidism during pregnancy can cause a significant decreased in the intelligence quotient of children [29]. Two prospective studies showed that persistent hypothyroxinemia at 12 week of gestation was associated with an 8-10 point deficit in mental and motor function scores in infant offspring compared to children of mothers with normal thyroid function and the first trimester maternal FT4 was a significant predictor of orientation scores. But the developmental scores were not influenced by further declines in maternal FT4 at 24 and 32 week gestation.

Epidemiology

- In India, the prevalence of hypothyroidism during pregnancy is significantly higher compared with Western countries.
- The data from Western countries indicate that the prevalence is to be estimated of subclinical hypothyroidism -- 2.5% overt hypothyroidism -- 0.3%-0.5%
- Hypothyroidism was found in 7 (4.12%) women with recurrent pregnancy loss and one in the control group.
- Majority of these hypothyroid pregnant women have subclinical hypothyroidism.

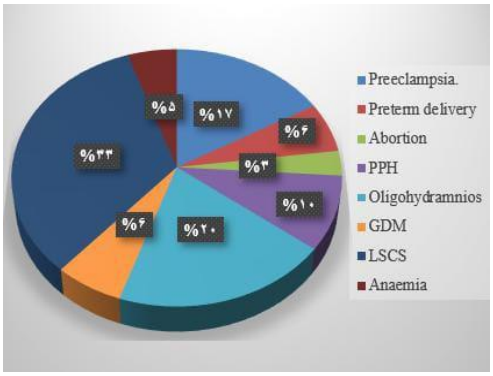

Figure 2: Maternal complications among 120 cases of hypothyroidism.

{Abbreviations: PPH- Post-Partum Haemorrhage; GDM-Gestational Diabetes Mellitus; LSCS- Lower Segment Caesarean Section.}

Mechanism of Physiological Changes of Thyroid Function in Pregnancy

Thyroid stimulation starts as early as the first trimester by β-HCG hormone, which shares some structural homology with thyroid stimulating hormone (TSH). There is also an estrogen-mediated increase in circulating levels of thyroid-binding globulin (TBG) during pregnancy by 2-3 times in serum TBG concentrations. TBG which is one of the numerous protein that transport TH in the blood with high affinity for thyroxine (T4) increases in serum a few weeks after conception and ranges a plateau during midgestational period. The mechanism for this increase in TBG involves both increased hepatic synthesis of TBG and estrogen mediated perpetuation in sialylation of TBG that increases the half-life from 15 min to 3 days to fully salivated TBG. [30]

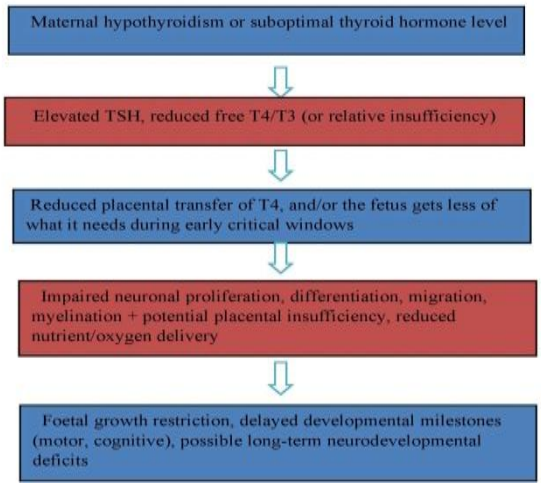

Figure 3: hypothyroid Hormonal Levels.

Reflecting changes in iodine metabolism, which is an essential requirement for TH synthesis, increased demand for iodine results from a significant pregnancy-associated increase in iodide clearance by the kidney and draw off

maternal iodide by the foetus. During pregnancy there is an increased iodine excretion in the urine as a result of increased glomerular filtration and decreased renal tubular absorption. In addition, maternal iodine is actively transported to the feto-placental unit, which contributes to a state of relative iodine deficiency [31].

Simple schematic presentation of the mechanism in maternal hypothyroidism:

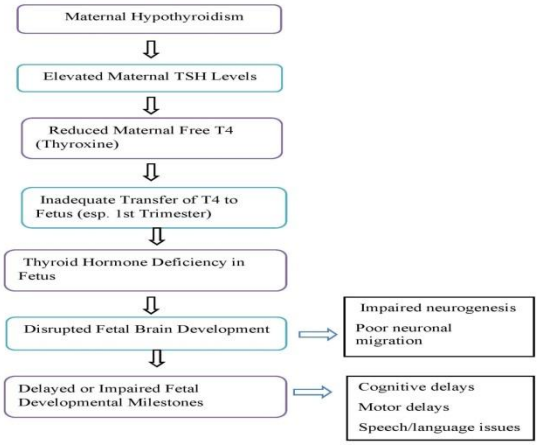

Figure 4: Maternal hypothyroid Levels.

Screening for Hypothyroidism

ACOG and the American Society of Reproductive Medicine do not recommend universal screening for thyroid disease in pregnant women. A prospective randomized trial in Italy involving 4562 women did not find adverse outcomes when universal screening was compared with 'case finding '(identify and test for high-risk women). The risk factors include women with a family history of autoimmune thyroid disease or hypothyroidism, goiter, thyroid antibodies, symptoms or clinical signs suggestive of thyroid hypofunction, type 1 DM or other autoimmune disorders, history of infertility, prior history of miscarriage or preterm delivery, prior therapeutic head or neck irradiation, prior thyroid surgery, those who are currently receiving levothyroxine replacement and women living in a region with presumed iodine deficiency [32].

Diagnosis and Differential of Hypothyroidism

Measurement of the TSH level is the only initial test necessary in a patient with a possible diagnosis of hyperthyroidism without evidence of pituitary disease. If the TSH level is low, then FT4 should be measured to evaluate for thyrotoxicosis. Measurement of FT3 is helpful in the clinical diagnosis of thyrotoxicosis when the FT4 values are unexpectedly normal. Thyroid-stimulating antibody levels can be used to monitor the effects of treatment with anti-thyroid drugs in patients with GD. High iodine uptake is seen in disease that cause increased T4 synthesis, including GD, toxic multinodular goiter, toxic adenoma and molar pregnancy. Low iodine uptake is seen disease that causes inflammation and release of T4 including subacute thyroiditis, thyrotoxicosis factitia, iodine ingestion and post-partum thyroiditis [33].

Clinical Manifestations

- Transient thyrotoxicosis (32%): Some patients with PPT experience a temporary phase of hyperthyroidism
- Transient hypothyroidism (43%): A significant proportion of patients go through a phase of temporary hypothyroidism
- Classic form of PPT (25%): This involves a sequence of transient thyrotoxicosis followed by hypothyroidism and then recovery. This is considered the classic pattern of PPT.

It is important to note that while the hyperthyroid phase is often temporary, some individuals may develop permanent hypothyroidism. PPT occurs when the immune system recovers after being suppressed during pregnancy. Asymptomatic women with PPT and a slightly elevated TSH above the reference range but below 10 mIU/L may not require immediate intervention but should be closely monitored. If the TSH elevation persists, treatment with levothyroxine may be necessary. However, symptomatic women with PPT or those with a TSH above normal who are planning pregnancy should be treated with levothyroxine. Pregnant women with a history of positive TPOabs should be closely monitored for the development of PPT [34].

Management of Hypothyroidism in Pregnancy

Hypothyroidism is treated with synthetic TH called thyroxine (LT4) which is identical to the natural T4. Pregnant women with pre-existing hypothyroidism will need to increase their pre-pregnancy dose of T4 to keep normal thyroid gland function. Thyroid gland function should be monitored every 6 to 8 weeks during pregnancy. Synthetic T4 is safe and necessary for the well-being of the fetus if the mother has hypothyroidism. Asymptomatic pregnant women should be routinely screened for hypothyroidism and patients with subclinical hypothyroidism should be treated to ensure a healthy pregnancy. A prospective intervention trial study found that treatment of hypothyroidism by LT4 reduces the risk of adverse maternal and fetal outcomes [35].

Dietary Supplements like iodine is an important mineral for a mother in pregnancy, because the thyroid uses iodine to make TH. During pregnancy, the baby gets iodine from the mother's diet. A woman requires more iodine when they are pregnant. A prospective study conducted by Murcia et al found that women took mean dose of 100-149 ug/day during pregnancy, and their children showed a two point decreased in PDI compared with the children of mother taking 150 ug/day with a decreased of 5.5 points [36].

Statistical Analysis

Qualitative and quantitative analyses were performed, and 95% confidence intervals (CI) (95% CI) were calculated. Heterogeneity analysis was performed with the I2 test. Meta-analysis was performed with a fixed effect model for studies without heterogeneity (I2<50%) and a random effect model for studies with heterogeneity (I2 ≥50%) after data combination. Descriptive analysis only was conducted for clinical trials with data not suitable for meta-analysis. Effect size was represented as relative risk (RR) for categorical variables and as standard mean difference for continuous variables, with 95% CI [37].

Conclusion

Gestational hypothyroidism, characterized by elevated maternal thyroid-stimulating hormone (TSH) levels, has emerged as a significant determinant of fetal growth and neurodevelopmental outcomes. The fetal brain is highly dependent on maternal thyroid hormones, especially during the first trimester when the fetal thyroid is not yet functional. Disruptions in maternal thyroid homeostasis-whether due to overt or subclinical hypothyroidism-have been consistently associated with a range of adverse outcomes, including impaired fetal growth, delayed developmental milestones, and long-term cognitive deficits in offspring.

Current evidence underscores a clear association between elevated maternal TSH levels and suboptimal neurocognitive development in children, though the extent of this impact varies with the severity, timing, and duration of the hormonal imbalance. While overt hypothyroidism during pregnancy is unequivocally linked to negative fetal and neonatal outcomes, the implications of subclinical hypothyroidism remain an area of active debate. Nevertheless, recent observational studies and clinical guidelines increasingly advocate for early identification and treatment of maternal thyroid dysfunction to optimize fetal developmental trajectories.

Timely intervention, most commonly with levothyroxine, has shown promise in mitigating the risks associated with maternal hypothyroidism. However, treatment efficacy appears highly dependent on the gestational age at initiation, with earlier correction of TSH levels offering the greatest potential for improved neurodevelopmental outcomes. Regular monitoring of thyroid function throughout pregnancy and adherence to trimester-specific TSH reference ranges are essential components of effective clinical management.

In conclusion, maintaining maternal TSH within optimal physiological ranges during pregnancy is vital for safeguarding fetal brain development and achieving favourable long-term developmental milestones. Further randomized controlled trials are warranted to delineate the precise benefits of treating subclinical hypothyroidism and to refine universal screening and treatment protocols. Until then, a proactive and individualized approach to maternal thyroid health remains a critical pillar of prenatal care.

Acknowledgement

Not Declared

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contribution

Both are contributed equally

Financial Support

None

Ethical Considerations and Inform Consent

Not Applicable

References

1. Shinohara DR, da Silva Santos T, de Carvalho HC, Lopes LCB, Günther LSA, Aristides SMA, et al. Pregnancy Complications Associated With Maternal Hypothyroidism: A Systematic Review. Obstetrical Gynecol Survey (2018) 73 (4):219–30. doi: 10.1097/OGX.0000000000000547
2. Taylor PN, Minassian C, Rehman A et al (2014) TSH levels and risk of miscarriage in women on long-term levothyroxine: a community-based study. J Clin Endocrinol Metab 99:3895–3902. https://doi.org/10.1210/JC.2014-1954
3. Obregon MJ, Calvo RM, Del Rey FE & de Escobar GM 2007 Ontogenesis of thyroid function and interactions with maternal function. Endocrine Development 10 86–98. (doi:10.1159/000106821)
4. Glinoer D 2001 Pregnancy and iodine. Thyroid 11 471–481. (doi:10.1089/ 105072501300176426)
5. S. Chunchaiah, N. Prasad, M. M, M. R, N. Rangaiah A prospective observational study of thyroid dysfunctions during pregnancy in a tertiary care hospital Int J Reprod Contracept Obstet Gynecol, 5 (11) (2016), pp. 3683-3689 View at publisherCrossrefGoogle Scholar
6. Nisha Nathan, Shannon D, Sullivan. Thyroid disorders during pregnancy. Endocrinol Metab. Clin North Am. 2014;43(2):573–97. https://doi.org/10.1016 /j.ecl.2014.02.008
7. Siobhan Deshauer MD, Ahraaz Wyne MD. Subclinical hypothyroidism in pregnancy. CMAJ 2017;17:189:E941. https://doi.org/10.1503/cmaj.161388
8. De Leo S, Pearce EN. Autoimmune thyroid disease during pregnancy. Lancet Diabetes Endocrinol. 2018;6(7):575–86. https://doi.org/10.1016/S2213-8587(1 7)30402-3

9. Riley Epp J, Malcolm K, Jolin-Dahel M, Clermont. Erin Keely. Postpartum thyroiditis. BMJ 2021;3:372. https://doi.org/10.1136/bmj.n495
10. Kilby MD. Thyroid hormones and fetal brain development. Clin Endocrinol 2003; 59: 280-281.
11. Cleary-Goldman J, Malone FD, Lambert-Messerlian G, Sullivan L, Canick J, Porter TF, et al. Maternal thyroid hypofunction and pregnancy outcome. Obstet Gynecol 2008; 112: 85-92.
12. DeRuiter J. Thyroid hormone tutorial: thyroid pathology. Endocrine Module (PYPP 5260), Thyroid Section, spring. Available at:
13. Raymond J, Lafranchi SH. Fetal 61Thttp://www.book.xlibx61T. info/bo-other/3556700-1-endocrine-module-pypp-526 0-thyroid-section-spring-2002-thyroid-h.php.and neonatal thyroid function: review and summary of significant new findings. Curr Opin Endocrinol Diabetes Obes 2010; 17: 1-7.
14. Adu-Gyamfi EA, Wang YX, Ding YB. The Interplay Between Thyroid Hormones and the Placenta: A Comprehensive Review. Biol Reprod (2020) 102(1):8–17. doi: 10.1093/biolre/ioz182
15. Delitala AP, Capobianco G, Cherchi PL, Dessole S, Delitala G. Thyroid Function and Thyroid Disorders During Pregnancy: A Review and Care Pathway. Arch Gynecol Obstetr (2019) 299(2):327–38. doi: 10.1007/s00404-018-5018-8
16. Rebagliato M, Murcia M, Espada M, Á lvarez-Pedrerol M, Bolúmar F , Vioque J, et al. Iodine Intake and Maternal Thyroid Function During Pregnancy. Epidemiology (2010) 21(3):62–9. doi: 10.1097/EDE.0b013e3181c1592b
17. Xiao Y, Sun H, Li C, Li Y, Peng S, Fan C, et al. Effect of Iodine Nutrition on Pregnancy Outcomes in an Iodine-Sufficient Area in China. Biol Trace Element Res (2018) 182(2):231–7. doi: 10.1007/s12011-017-1101-4
18. De Geyter C, Steimann S, Müller B, Kränzlin ME, Meier C. Pattern of Thyroid Function During Early Pregnancy in Women Diagnosed With Subclinical Hypothyroidism and Treated With L-Thyroxine is Similar to That in Euthyroid Controls. Thyroid (2009) 19(1):53–9. doi: 10.1089/thy.2007.0355
19. Calvo RM, Jauniaux E, Gulbis B, Asuncion M, Gervy C, Contempre B & Morreale de Escobar G 2002 Fetal tissues are exposed to biologically relevant free thyroxine concentrations during early phases of development. Journal of Clinical Endocrinology and Metabolism 87 1768–1777. (doi:10.1210/ jc.87.4.1768)
20. Bernal J 2007 Thyroid hormone receptors in brain development and function. Nature Clinical Practice. Endocrinology & Metabolism 3 249–259. (doi:10.1038/ ncpendmet0424)
21. Dorizzi RM, et al. Trimester-specific reference intervals for thyroid function parameters in pregnant caucasian women using Roche platforms: a prospective study. J Endocrinol Invest. 2023;46(12):2459–69. https://doi.org/10.1007/s 40618-023-02098-0
22. Dong AC, et al. Subclinical hypothyroidism and thyroid autoimmunity in recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril. 2020;113(3):587–e6001. https://doi.org/10.1016/j.fertnstert.2019.11.003
23. Maraka S, et al. Subclinical hypothyroidism in pregnancy: a systematic review and Meta-analysis. Thyroid. 2016;26(4):580–90. https://doi.org/10.1089/thy.20 15.0418. Epub 2016 Mar 3.
24. Mitchell ML, Larsen PR, Levy HL, Bennett AJ, Madoff MA. Screening for congenital hypothyroidism. Results in the newborn population of new England. JAMA, 239(22), 2348–51. https://doi.org/10.1001/jama.239.22.2348
25. Tuija Männistö P, Mendola U, Reddy. Katherine Laughon. Neonatal outcomes and Birth Weight in pregnancies complicated by maternal thyroid disease. Am J Epidemiol. 2013;178(5):731–40
26. Nguyen BT, Chang EJ, Bendikson KA: Advanced paternal age and the risk of spontaneous abortion: an analysis of the combined 2011-2013 and 2013-2015 National Survey of Family Growth. Am J Obstet Gynecol. 2019, 221:476.e1. 10.1016/j.ajog.2019.05.028
27. Franco B, Laura F, Sara N, Salvatore G: Thyroid function in small for gestational age newborns: a review . J Clin Res Pediatr Endocrinol. 2013, 5:2-7. 10.4274/jcrpe.846
28. Haddow JE, Palomaki GE, All an WC, Williams JR, Knight GJ, Gagnon J, et al. Maternal thyroid deficincy during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999; 341: 549-555.
29. Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol 2003; 59: 228-288.
30. Skjoldebrand L, Brundin J, Carlstrom A, Pettersson T. Thyroid associated components in serum during normal pregnancy. Acta Endocrinol 1982; 100: 504-511.
31. Okosieme OE, Marx H, Lazarus JH. Medical management of thyroid dysfunction in pregnancy and the postpartum. Expert Opin Pharmacother 2008; 9: 2281-2293.
32. De Groot L, et al. Management of thyroid dysfunction during pregnancy and postpartum: an endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(8):2543–65. https://doi.org/10.1210/jc.2011-2803

33. American Academy of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract 2002; 8: 457-469.
34. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid 2017;27:315–89.
35. Poppe K, Glinoer D. Thyroid autoimmunity and hypothyroidism before and during pregnancy. Hum Reprod Update 2003:9: 149-161.
36. Murcia M, Rebagliato M, Iniguez C, Lopez-Espinosa M, Estarlich M, Plaza B, et al. Effect of iodine supplementation during pregnancy on infant neurodevelopment at 1 Year of Age. Am J Epidemiol 2011; 173: 804-812.
37. Maraka S, Ospina NM, O'Keeffe DT, Espinosa De Ycaza AE, Gionfriddo MR, Erwin PJ, Coddington CC 3rd, Stan MN, Murad MH, Montori VM. Subclinical Hypothyroidism in Pregnancy: A Systematic Review and Meta-Analysis. Thyroid 2016;26:580-590. Epub 2016 Mar 3