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REVIEW ON EFFECT OF MATERNAL HYPOTHYROIDISM ON FETAL DEVELOPMENT AND NEURODEGENARATIVE DISEASE

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ABSTRACT

The two primary thyroid hormones, thyroxine (T4) and triiodothyronine (T3), are essential in growth, metabolism as well as neurodevelopment. Their influence extends from early embryonic life through adulthood, impacting nearly all organ systems. Maternal thyroid activity is particularly vital during pregnancy, since the foetus depends on maternal T4 during early gestation for optimal brain maturation and neuronal differentiation. Hypothyroidism, characterized by inadequate thyroid hormone production, remains a common endocrine condition, particularly among women of reproductive age. Even subclinical Unhealthy thyroid function has been connected to adverse consequences for the mother and the fetus during pregnancy, such as miscarriage, premature birth, birth defects, and delayed neurocognitive development in the progeny. This review consolidates current knowledge regarding thyroid hormone physiology, mechanisms of action, and the pathophysiological implications of hypothyroidism, emphasizing maternal and fetal interdependence. Furthermore, it explores the relationship between hypothyroidism and neurodevelopmental and neurological disorders such autism spectrum disorder (ASD), Parkinson's disease, and Alzheimer's disease, elucidating the possible mechanisms linking thyroid dysfunction with altered brain development and function. Congenital hypothyroidism (CH) is one of the primary preventable causes of intellectual impairment, underscores the necessity for early detection and intervention through neonatal screening programs and maternal thyroid assessment. The review also highlights the healing significance of levothyroxine (L-T4) as the therapy of choice for hypothyroidism during pregnancy, ensuring adequate fetal neurodevelopment. Universal screening strategies for thyroid dysfunction remain an area of ongoing debate; however, the evidence strongly supports targeted screening and timely management to mitigate long-term neurodevelopmental deficits. Overall, understanding thyroid-related hormones dynamics during pregnancy and early life is critical for optimizing maternal health and preventing lifelong neurocognitive impairment in offspring**.**

Keywords: Thyroid hormone, Hypothyroidism, Maternal, Neurosensory disorder, congenital hypothyroidism.

I.INTRODUCTION

Thyroid hormone is essential for normal brain development and growth, and possesses a significant impact on practically every organ system (1). Numerous body processes depend on thyroid hormones (TH) procedures, from prenatal development, including memory and focus, metabolic rate maintenance, reactive oxygen species (ROS) balance, cardiovascular function, eating, and thermogenesis (2). The development and maturation of the foetus depend on thyroid hormone. The foetus depends on the T4 hormone until it can produce its own thyroid hormones that travels from the mother through the placenta (3). The thyroid gland's inability to produce enough thyroid hormone to meet the body's metabolic needs is known as hypothyroidism (4). The hypothyroid state is characterized by a deficiency of the thyroid hormones thyroxine (T4) and triiodothyronine (T3), which are generally brought on by an iodine shortage or an autoimmune response (2a). Thyroid disease is prevalent among women of reproductive age, and thyroid problems are frequently observed during pregnancy, A significant number of these women suffer from subclinical hypothyroidism, there have been reports linking maternal thyroid deficiencies, including those that are asymptomatic, to unfavourable pregnancy outcomes that may be enhanced by replacing thyroxine (T4) (5).

Pregnancy-induced hypertension, postpartum haemorrhage, congenital abnormalities, abortions, stillbirths, and foetal distress have all been linked to maternal hypothyroidism, according to numerous research (6). Throughout birth and youth, the growth and development of the brain depend on thyroid hormones, The first stage of the formation and maturity of the pituitary-

thyroid-hypothalamic axis is foetal dependence on it. the newborn's axis early pregnancy thyroid hormones in the mother (7). There are three primary circumstances where mental retardation and thyroid function abnormalities have been linked: Since the 16th century, the birth of deaf-mute and mentally challenged residents, known as cretins, has been linked to severe endemic goitre. Even before the fact that a goitre is an enlarged thyroid was known, this relationship was established. Since Curling reported two cases in the middle of the 19th century, congenital hypothyroidism has been linked to severe mental impairment. Since Man and Sirenian's research, maternal hypothyroxinaemia, with or without clinical hypothyroidism, has been linked to a lower mean I.Q. of the offspring (8).

II.MECHANISM 0F ACTIONs OF THYROID HORMONES

In species ranging from fish to mammals, L-thyroxine (T4) and L-triiodothyronine (T3), two thyroid hormones, have a wide range of actions and affect how most organs function. Thyroid hormones, for instance, raise both the basic metabolic rate and protein metabolism considerably, fats, and carbohydrates. These effects are often achieved by boosting the concentration of certain oxygen-consuming enzymes, such as the plasma cell membrane's Na + K+-ATPase, or by increasing the portion of enzyme isoforms that give higher activity (Vmax) but also consume more energy. One example of this kind of control is the thyroid hormone-induced change of the heart's myosin V3 to myosin VI isoenzyme. Thyroid hormones seem to speed up metabolic processes by acting as a kind of universal pacemaker. Thyroid hormones also significantly impact the body's metabolic environment by raising the levels of certain hormones, such as growth hormone, and changing how receptive the body is to other hormones. The transition in cardiac muscle from a euthyroid to a hyperthyroid state causes a drop in alpha-receptors and an increase in sympathetic beta-receptors, which may lead to heightened sympathetic reactivity. Additionally, thyroid hormones raise the number of adipocytes' glucagon receptors and fibroblasts' low-density lipoprotein receptors. On the other hand, thyroid hormones lower the amounts of muscarinic receptors in the heart and TRH receptors on pituitary cells. Thyroid hormones have a significant impact on cell formation and replication in addition to their effects on the mature organism. It has long been known that thyroid hormones are essential for the development of the brain. The decrease in the G1 phase of the cell cycle in GC cells caused by T3, which results in greater cell replication, is an illustration of how thyroid hormones affect cell replication. The various impacts of thyroid hormones, as demonstrated by the few instances above, have made it difficult to pinpoint the exact molecular processes that mediate thyroid hormone function. By working through entirely distinct and independent pathways for each of these activities, thyroid hormones may have an impact on this vast array of distinct biochemical processes. Another idea is that there is only one central initiating the activity of thyroid hormones, from which all subsequent influences originate. The particular T3 interaction to a cell nucleus receptor protein, which results in changes in the expression of particular genes, provides evidence for the latter theory. First, we'll talk about the traits of these T3 nuclear receptors. A later section will provide examples of how T3 action can be mediated by extranuclear processes. The goal of this succinct, albeit incomplete, review is to highlight some intriguing new findings in the field of thyroid hormone activity (9).

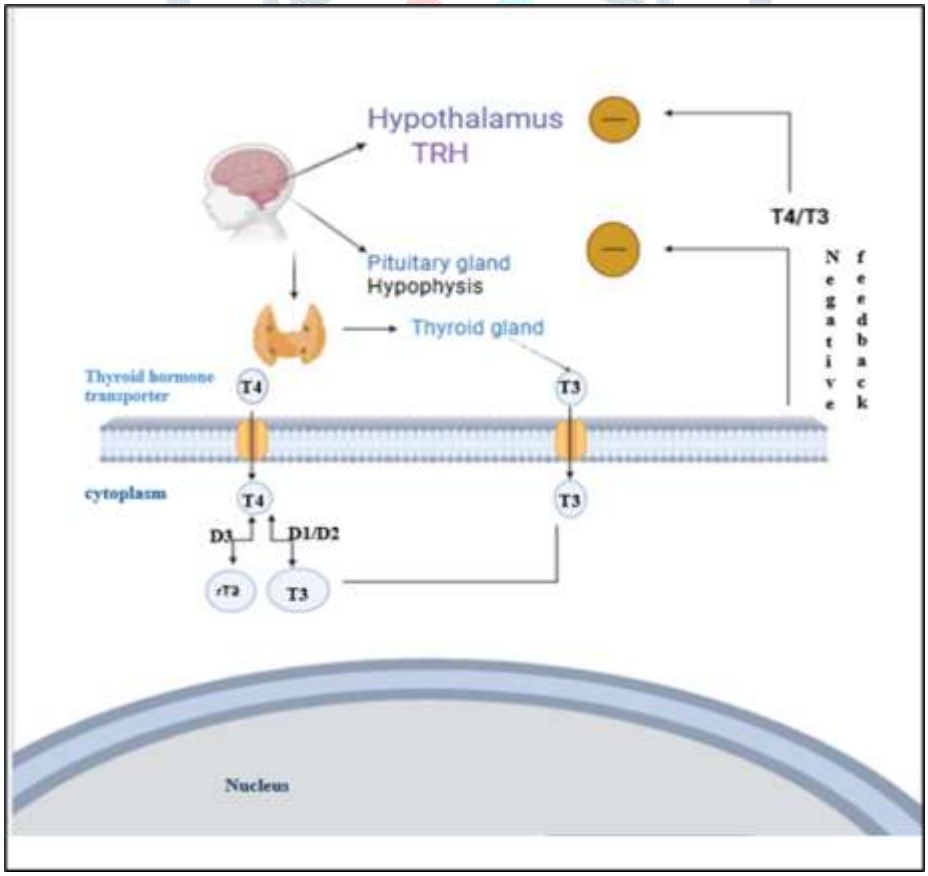

Figure 1. Mechanism of action of thyroid hormones

2.1 Functions of Thyroid Hormones

Hormones in the thyroid significantly raise both the metabolism of lipids, proteins, and carbohydrates as well as the basic metabolic rate (9a). TH regulates essential genes for basic brain functions, including myelination, synaptogenesis, cell migration and differentiation, and neurogenesis by activating or suppressing specific TH receptors in the neuronal nucleus (10). The development and maturation of the foetus depend on thyroid hormone. The foetus depends until it is able to generate its own thyroid hormones, on the mother's T4 hormone, which passes through the placenta (3a). Thyroid hormones (TH) are necessary for many body processes, from neural growth and differentiation during foetal development to adult functions like memory and concentration, metabolic rate

maintenance, reactive oxygen species (ROS) equilibrium, cardiovascular function, thermogenesis, and feeding (2b). The inhibitory effects of T3 and T4,1 create a negative feedback loop that controls TRH and TSH, while somatostatin from the anterior pituitary also inhibits TSH (16).

III.HYPOTHYROIDISM

The clinical state Thyroid stimulating hormone (TSH) levels rise when the thyroid gland produces insufficient amounts of the thyroid hormones T3 and T4. This condition is known as hypothyroidism. Delays in cell metabolism are among the primary consequences of hypothyroidism (2c). Among the developing organ systems that rely on thyroid hormones are the kidney, lung, and skeleton, thyroid hormones are very important, especially for the development of the fetal brain, the cytoarchitecture and radial distribution of specific neurons in the fetus's somatosensory cortex and hippocampus are impacted by the absence of maternal thyroid hormones, as demonstrated by experimental data in animals. According to other research, thyroid disease in pregnant women could negatively affect the child's behavior and cognitive development. We have discovered that children's cognitive delay is predicted by a low level of maternal free thyroxine-4 (FT4) during the first several months of pregnancy (11).

3.1 Hypothyroidism During Development

The most prevalent thyroid condition that occurs during pregnancy is hypothyroidism, which is a dangerous medical condition the possibility of low birthweight fetal death, premature delivery, miscarriage, or offspring with neurointellectual impairment is increased even in cases of mild gestational hypothyroidism (12).

3.1.1 Etiology Of Hypothyroidism in Pregnancy

It is believed that Subclinical hypothyroidism is found in 2-3% of pregnant women, whereas 0.3–0.5% of pregnant women have overt hypothyroidism. Autoimmune thyroiditis is the most common cause of hypothyroidism during pregnancy. Additional causes include surgery for thyroid tumours, Thyroid radioiodine ablation for the treatment of thyroid cancer or hyperthyroidism, and infrequently, central hypothyroidism, including lymphocytic hypophysis or ectopic thyroid, as well as medications that speed up thyroid metabolism, such as phenytoin and rifampicin. Nonetheless, iodine deficiency continues to rank among the primary causes of hypothyroidism worldwide, both overt and subclinical (13).

3.1.2 Clinical Epidemiology

Long-term Autoimmune thyroiditis is the most frequent cause of primary hypothyroidism in women who are of reproductive age. Both the atrophic and goitrous versions of the illness exhibit this. L-T4 is already given to 1% to 2% of pregnant women for hypothyroidism (14). Maternal FT4 levels were inversely correlated with birth weight in mothers whose FT4 and TSH levels were within the normal range [15.4 (3.6) g/pmol ~ liter, mean (SE); P 1.6 105]. This displays the mother's normal-range FT4 quintiles' birth weight (21). The prevalence of high blood TSH concentrations in the early stages of pregnancy in women without diagnosed hypothyroidism was carefully examined in two population-based studies: 2.5% overall TSH levels were higher among expectant mothers in a group who appeared healthy but were not chosen two thousand pregnant ladies had their levels of TPO-Ab, free T4, and serum TSH measured in one retrospective investigation. Six of these women additionally had low free T4, and 49 of them had raised TSH (2.5% of the population), resulting in a 0.3% prevalence of unreported overt hypothyroidism. Approximately 58% of women with increased TSH had positive thyroid antibody tests, compared to only 11% of pregnant controls who were euthyroid. Because of the study's design, the researchers were unable to ascertain if the women with elevated TSH had a known thyroid condition, in which case they might have been taking excessive amounts of antithyroid medications or an improperly low dose of L-T4 (14a).

3.1.3 Treatment Of Hypothyroidism in Pregnancy

As was previously mentioned, the development of the fetus's brain depends on maternal T4, not T3 throughout pregnancy. Therefore, LT4 is the recommended treatment for pregnancy-related hypothyroidism. It is not recommended to take desiccated thyroid pills, Levo triiodothyronine (LT3), or T3/T4 together (12a). Before becoming pregnant, hypothyroidism should be treated, early in pregnancy, replacement dosage should be increased, and euthyroidism should be maintained the entire time (20).

3.2 Maternal And Foetal Hypothyroidism

The majority of cases of combined maternal and foetal hypothyroidism occur in area where there is a dietary iodine deficit. Infants with neurologic cretinism, which is characterized by mental retardation (mean IQ of ;29), as well as poor locomotion and motor function, are the most severely afflicted (15). Thyroid enlargement and a rise in serum thyroglobulin are among the effects on the mother and foetus. Despite the mother's relative hypothyroxinaemia, the foetus's free T4 and TSH levels remain normal (15a).

3.2.1 Maternal And Foetal Thyroid Physiology

Thyroid function is affected by pregnancy in a number of ways.
The placenta actively participates in the transport and metabolism of iodide and T4, The HPT axis of the fetus grows on its own, and the mother's hypothalamic-pituitary-thyroid (HPT) axis goes through a number of changes. As a result, during pregnancy, there is an integrated three-compartment thyroid model (15b).

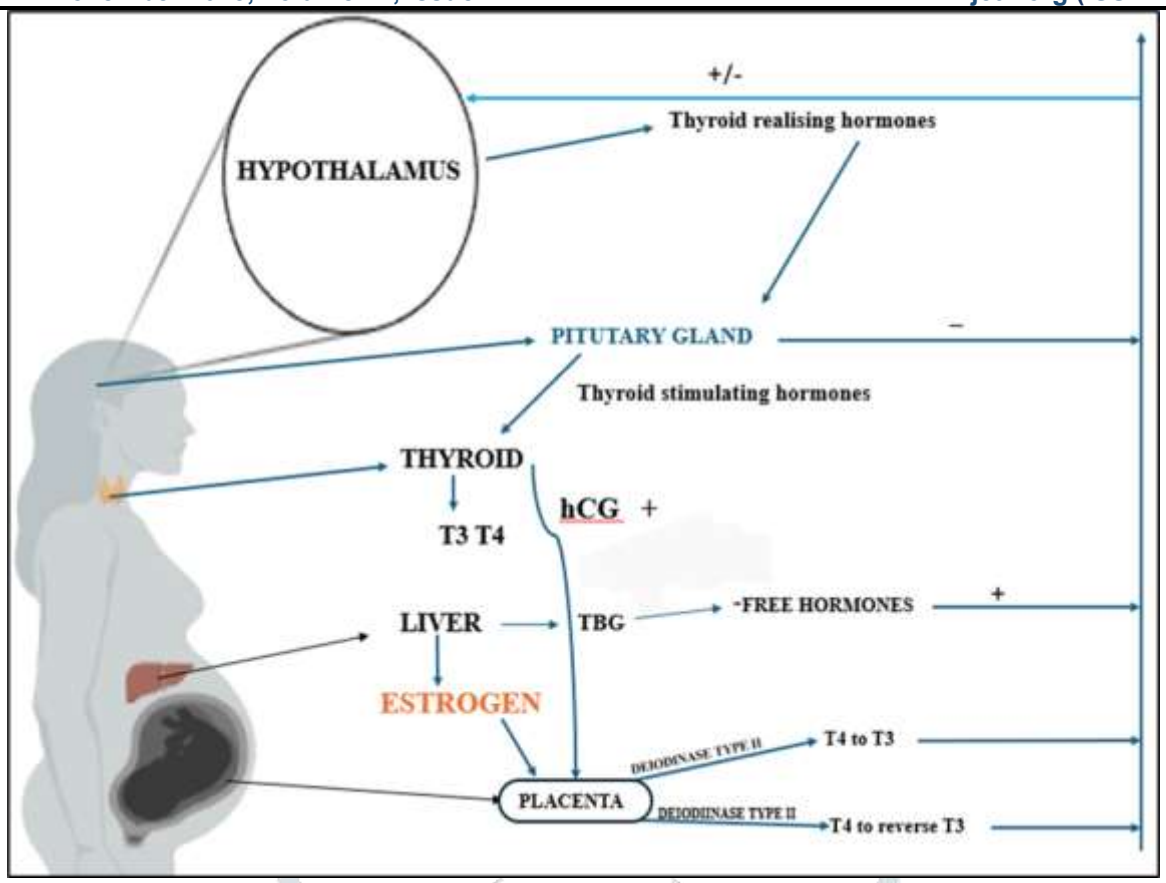

Figure. 2. An overview of positive and negative feedback from the hypothalamic-pituitary-thyroid axis explanation

Thyroid follicular cells are the most prevalent of the three layers of germ cells that make up the thyroid. Between the first and second branchial arches in the primordial pharynx, these follicular cells cause an enlargement. The first 60 days of pregnancy are when most important thyroid morphogenesis events occur. Therefore, the bulk of developing thyroid diseases are caused by morphogenetic errors at this time. These cells, which are close to the early heart, may be displaced by early morphogenic abnormalities. Iodine trapping can be detected by eight to ten weeks; foetal thyroglobulin production by four to six weeks; TRH synthesis by six to eight weeks; and TSH release with T4 synthesis by twelve weeks. Ectopic thyroid tissue can develop through aberrant follicular cell thickening buds, ventrally proliferate, laterally expand, and form the bilobed structure by seven weeks. These anomalies could be caused by improper thyroid migration, which is a secondary outcome of defective heart morphogenesis, or by interactions between the thyroid primordium and the heart (16a).

3.2.2 Causes Of Thyroid Dysfunction

The foetus, the expectant mother, or both may be the only ones with abnormal thyroid gland function. Both temporary and permanent foetal hypothyroidism are possible. Temporary causes include immaturity of the HPT axis in premature newborns or transplacental transfer of medications or autoantibodies. Iodine shortage is nearly always the cause of combined maternal and foetal hypothyroidism Thyroid-binding inhibitory immunoglobulin (TBII), however, has occasionally been linked. Both overt maternal hypothyroidism and extreme iodine shortage or birth defects in the thyroid has significant impacts on the foetus and baby during pregnancy. It is currently thought that foetal brain development may be impacted by even mild maternal hypothyroidism, which can result from thyroid autoimmunity, thyroid under-replacement, or minor iodine insufficiency. Although the ramifications of this discovery are yet unclear, they have brought up a number of issues that require attention (15).

3.2.3 Characteristics Of Infant with Congenital Hypothyroidism

A thyroid hormone deficit that is apparent from birth is known as congenital hypothyroidism (CH). Thyroid hormone insufficiency at birth is most frequently caused by disorders of thyroid gland development (dysgenesis) or thyroid hormone synthesis (dyshormonogenesis). The result of these situations is primary hypothyroidism. Secondary or central hypothyroidism is caused by insufficient thyroid stimulating hormone (TSH) from birth. Congenital TSH deficit, which results from mutations in the TSH b subunit gene, is rarely a stand-alone issue and is typically linked to other pituitary hormone shortages as part of congenital hypothyroidism (17).

A. Symptoms

Congenital hypothyroidism symptoms are initially unremarkable, although the history of Some clues could come from the mother's pregnancy. Twenty percent of pregnancies last longer than forty-two weeks (17a). Additionally, there can be signs of an iodine-deficient diet or maternal autoimmune thyroid illness. It is uncommon for pregnant women to have unintentional radioactive iodine treatment. After they come home, these calm newborns might sleep through the night. Constipation and A savage scream are further signs. It is typical for newborns to have hyperbilirubinemia for longer than three weeks. This results from hepatic glutaryl transferase's immaturity (17b).

B. Signs

The most typical initial examination findings include chilly or mottled skin, macroglossia, and umbilical hernia. Additionally, Thyroid hormone is necessary for bone development and maturation. A broad posterior fontanel of more than 5 mm may result from this. The most noticeable clinical characteristics are this, accompanied with ongoing jaundice and inadequate eating (17c).

3.2.4 Relationship Between Neonatal TSH and Maternal

The creation of thyroid hormones, which are vital for the body's and the brain's ideal development, depends on iodine. Negative outcomes like the chance of goitre, miscarriage, stillbirth, and congenital defects such creatinism are linked to iodine shortage during pregnancy (18). The placenta carries maternal iodide and iodothyronines to the developing fetus throughout pregnancy (19). Because the newborn thyroid is extremely sensitive to changes in the mother's iodine diet, the neonatal TSH concentration may be a good indication of pregnant mothers' iodine levels in the latter stages of pregnancy (18a). Pregnancy-related iodine insufficiency causes neurological dysfunction and lowers the infant's IQ (19a). Monitoring iodine levels during the examination of TSH percentage is done in nations that screen for congenital hypothyroidism. The results of newborn screening allow for routine monitoring at no further expense. A population's iodine status is indicated by the percentage of newborn TSH concentrations higher than 5mlU/L as follows: Iodine sufficiency is indicated by a frequency of less than 3%, mild iodine deficiency (MID) is indicated by a frequency of3% to 19.9 %, moderate Lack of iodine is indicated by a frequency of 20% to 39.9%, and severe iodine shortage is indicated by a frequency of more than 40% (18b).

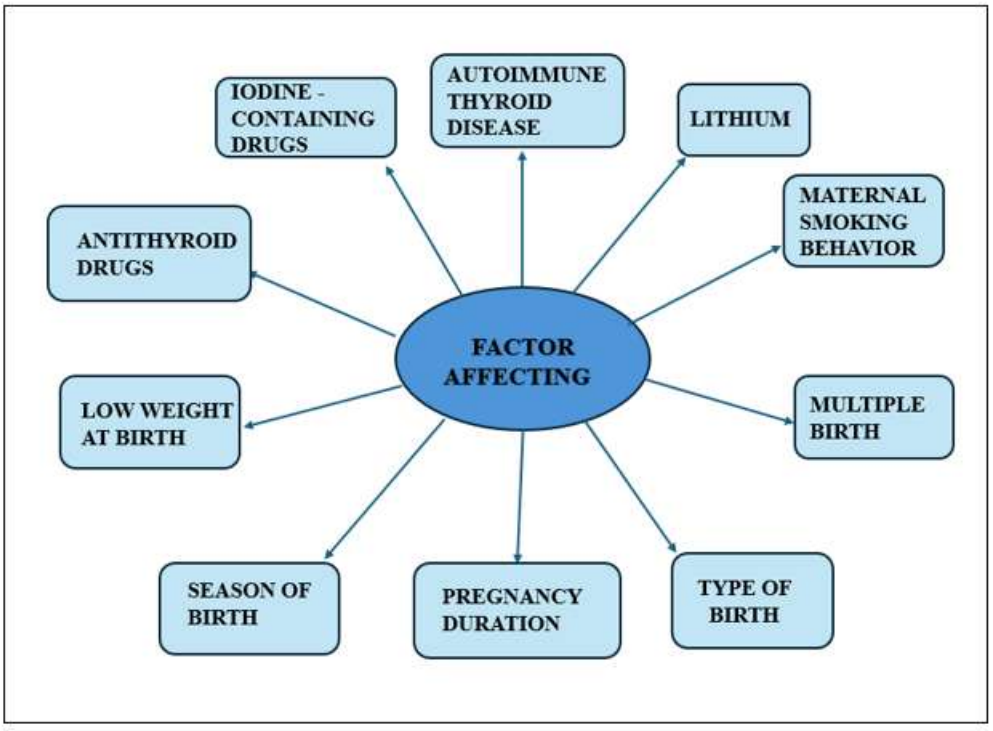

Figure 3. Factors affecting to neonatal TSH

3.2.5 Neonatal Thyroid Function According to Maternal Diagnosis

Normal brain development depends on thyroid hormone. Motor and cognitive development issues can result from either an excess or absence of thyroid hormones during such are congenital hypothyroidism and brain development thyrotoxicosis, respectively. Thyroid disorders in mothers can also affect the thyroid condition of the fetus, which could disrupt normal brain development. Impaired thyroid hormone contribution to the fetus in cases of maternal hypothyroidism may be detrimental, at least until the fetal thyroid system begins to operate in mid gestation. Fetal thyroid dysfunction in maternal autoimmune thyroid illness can be brought on by placental transit of TSH-binding inhibitory immunoglobulins (TBII) and antithyroid medications after fetal thyroid function has begun (22).

3.2.6 Treatment Of Hypotyroidism in Maternal

Similar to hyperthyroidism, hypothyroidism may potentially negatively impact the health of the fetus and the outcome of the pregnancy. When Hashimoto's thyroiditis, a previous thyroidectomy, or radioactive iodine treatment is present, maternal hypothyroidism is seen. Overuse of antithyroid medications can also cause maternal hypothyroidism (23). To identify Serum levels of thyroid-stimulating hormone (TSH), free thyroxine (FT4), total thyroxine (TT4), and TPO-Ab are evaluated early in pregnancy in cases of hypothyroidism (24).

IV.RELATIONSHIP BETWEEN HYPOTHYROIDISM WITH BRAIN DISORDER

Hypothyroidism damages many pathways in conditions such as autism and congenital hypothyroidism in children as well as in older diseases like Parkinson's and Alzheimer's because it affects multiple brain activities during development and maturity (2d).

4.1 Autism and Thyroid Dysfunction

The diverse set of neurodevelopmental diseases known as autism spectrum disorders (ASD) is characterized by unusual behaviours, sensory abnormalities, and deficits in social communication abilities (25). Neurodevelopmental disorders known as autism spectrum

disorders (ASDs) are typified by limited, stereotyped behaviours as well as a significant impairment in reciprocal social interactions and communication skills. ASDs are extremely disabling, start in early life, and have a chronic course. Even though ASDs have a significant personal and communal cost, they have not gotten much attention in the field of global public health (26). The specific cause It is thought that a mix of genes and environment may contribute to the severity of Asperger's syndrome and autism are included in autism spectrum disorder (ASD). One in 132 persons have ASD, which is more common in men and has a developmental communication disorder that hinders social interaction and communication. The symptoms can range in severity from seizures to intellectual and linguistic disabilities (2e). Although Since TH is necessary for cellular growth, metabolism, and brain development, and differentiation, a TH shortage during embryonic or early postnatal periods would probably result in developmental problems, including autistic pathology, several clinical studies have not yet found any evidence of thyroid dysfunction or TH blood level deficiency in autism (27).

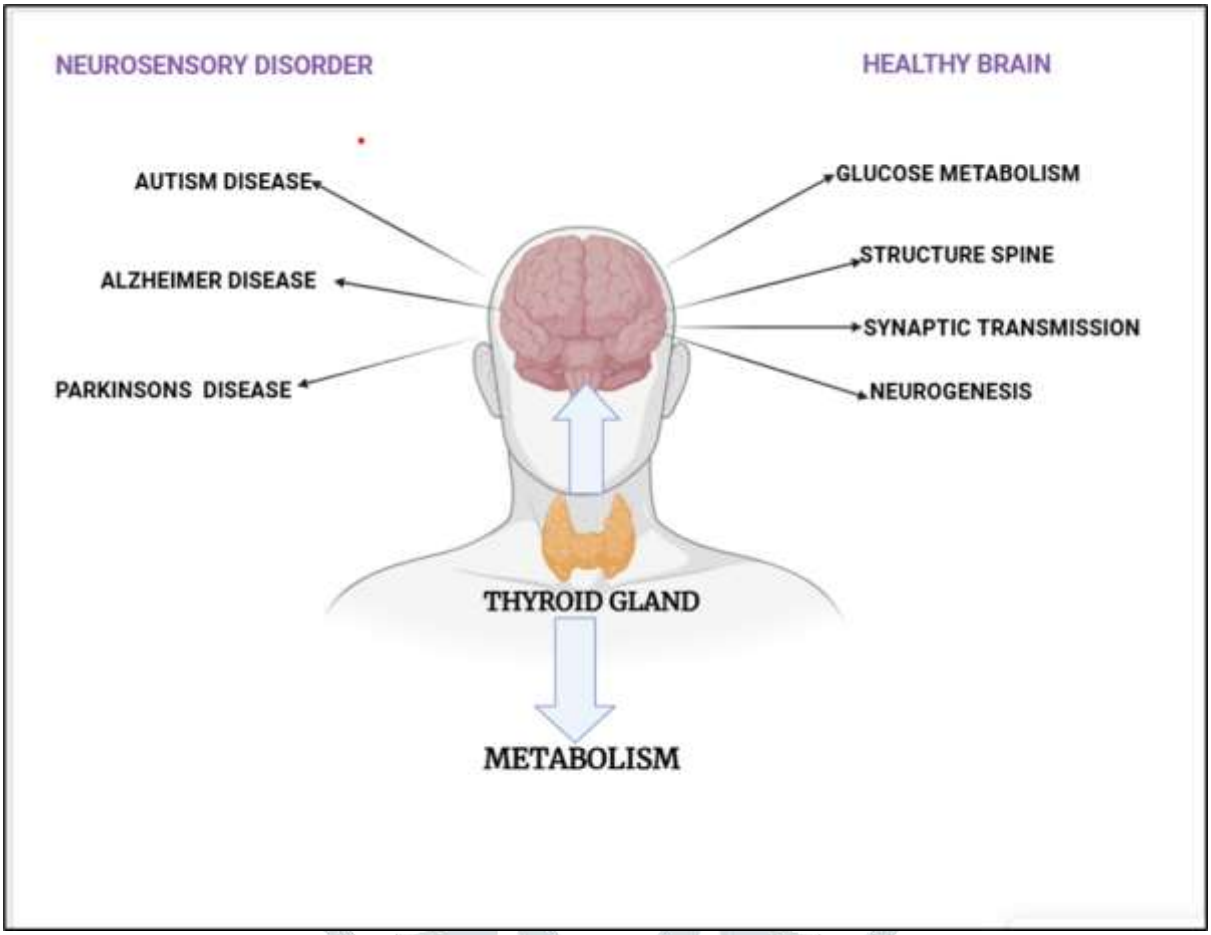

Figure 4. Relationship between neurosensory disorder and healthy brain

4.2 Parkinson's Disease and Hypothyroidism

Cardiovascular, neurosensory, musculoskeletal, gastrointestinal, and Parkinson's disease (PD) and other neurodegenerative illnesses have all been connected to hypothyroidism. The majority of the research that is currently available focuses on the prevalence of hypothyroidism in Parkinsons Disease patients, but epidemiological evidence has also suggested a connection between hypothyroidism and Parkinson Disease (28). One to three percent of adults over fifty suffer from Parkinson's disease (PD), a heterogeneous neurological disorder caused by the progressive degradation of dopamine-containing the substantia nigra's neurons pars compacta within the midbrain. The second most prevalent neurodegenerative disease is Parkinson's disease. The primary clinical manifestations of Parkinson's disease (PD) include bradykinesia, rigidity, resting tremor, disruption of gait, and postural instability absence of loss of substantia nigra neurons causes dopaminergic neurons in the striatum. The precise mechanisms underlying dopaminergic cell loss remain ambiguous in the substantia nigra notwithstanding significant advancements in our understanding of Parkinson's illness pathology. People with hypothyroidism typically have Parkinson's disease (PD) symptoms such as vocal problems, facial hypomimia, hypokinesia, and rigidity. Additionally, hyperthyroidism exhibits clinical symptoms that are typical of Parkinson's disease (PD) patients, such as tremor, sweating, and weight loss. It can even make symptoms like dyskinesia and tremor worse (29). The findings of our investigation primary goal were to compare an age-matched control group to a sample of PD patients in order to examine the most widely utilized measures for thyroid function screening. Characterizing hypothyroidism in PD patients and its potential implications to the clinical findings in these specific cases were our secondary objectives (30).

4.3 Hypothyroidism And Alzheimer Disease

Alzheimer's disease, or AD, is the most prevalent long-term neurological condition in older adults is referred to as senile dementia. It is mainly characterized by cognitive impairment, behavioral abnormalities, and personality abnormalities and is brought on by extensive cerebral cortical atrophy and degenerative lesions (31). The most prevalent form the most prevalent form of dementia in the elderly is Alzheimer's disease (AD), a progressive neurological illness that gradually impairs cognitive function before leading to death (32). Alzheimer's disease (AD), which mostly affects those 65 and older, is the most common irreversible neurological ailment

in the world. Its prevalence is rising exponentially over time, doubling roughly every five years (33). The three main neuropathological characteristics of AD are as follows: extracellular β-amyloid protein plaques (Amyloid-based plaques), intracellular NFTs or neurofibrillary tangles, Neurodegeneration. Depending on the stage of AD, these markers occur at significantly higher amounts in certain brain regions, yet all of them are visible during normal aging (33 a).

4.3.1. Amyloid Cascade Hypothesis

The pathophysiology of AD has involved the interaction of tau and Aβ proteins.

A. A ß Proteins

It is believed that Aβ has a role in the pathophysiology of AD. An amyloid precursor protein (APP) of 695 amino acids was recovered from the cerebral cortex of AD patients. It is mostly found at neuronal synapses and is essential for the innate immune system, synaptic plasticity, and brain development. Proteases have the ability to break down APP once neurons have created it. The α-decomposition pathway and the β-catabolic pathway are the two primary breakdown pathways. The β-catabolic pathway, which is controlled by the enzyme β-secretase (BACE1), is the only mechanism that can produce Aβ. According to human genetics, either presenilin or the APP gene (the γ-secretase catalytic subunit) are usually where mutations in early-onset familial AD cluster. These mutations may change the proteolytic processing of APP, altering the Aβ peptides' propensity to self-aggregate or the ratio of Aβ42 to Aβ40 (31a).

B. Tau

Tau is a component of the protein class known as microtubule-associated proteins (MAP), Tau has been demonstrated to be a typical example of a "naturally unfolded" protein. Tau proteins are crucial for neurogenesis, ion transport, neuronal activity, axonal transport, and microtubule stability in healthy neurons. However, neurodegenerative disorders such as tau proteinopathies emerge as a result of any harmful mutation that causes aberrant folding and aggregation. Normal tau function can be disrupted by mutations in the tau gene. For instance, the ΔK280 mutation can increase tau's propensity to self-aggregate, decrease tau's capacity to interact with microtubules, and thereby encourage the development of PHF and NFT. In addition to AD, this mutation has been found in other neurodegenerative illnesses like Parkinson's disease and chromosome 17-associated hereditary frontotemporal dementia (FTDP-17) (31b).

4.4 Neurosensory Development

The process of neurosensory development in late pregnancy and early infancy is intricate yet predictable. In the infant's brain and body, neural pathways are growing quickly in tandem with endogenous stimulation and external stimuli. The physical and neurological structures that direct the operations of the visual, auditory, chemosensory, somatosensory, and limbic systems are influenced by both internal and external environments. These systems both influence and react to memory and other aspects of cognitive development (34). Significant mental abnormalities that occur throughout life are linked to hypothyroidism (35).

4.5. Congenital Hypothyroidism

Congenital hypothyroidism (CH) is the term used to describe a thyroid hormone deficit that manifests at birth, The most frequent causes of thyroid hormone insufficiency at birth are disorders of thyroid gland development (dysgenesis) or thyroid hormone production (dyshormonogenesis), Hypothyroidism in primary is the outcome of these conditions (36). The most prevalent congenital endocrine condition in children is Congenital hypothyroidism, or CH, is a major preventable cause of mental disability (37). If left untreated, congenital hypothyroidism, the most prevalent metabolic disease in newborns, causes severe neurodevelopmental damage and infertility. There are two types of congenital hypothyroidism: permanent and transitory CH. A persistent thyroid hormone deficit that need lifelong medication is known as permanent CH. A temporary thyroid hormone deficit identified at birth that gradually returns to normal production is referred to as transitory CH. The initial years or months of life are usually when euthyroidism recovers (36a).

4.5.1. Epidemiology

A frequent endocrine condition in infants is congenital hypothyroidism (CH), affecting around 1 in 2000 to 4000 live births. Although the causes of this trend are unclear, some epidemiologic studies have demonstrated that the frequency of CH in Western nations is increasing. There could be a number of contributing factors, such as screening programs, environmental factors, birth and pregnancy characteristics, and ethnicity. According to findings from the majority of screening programs, For CH, the female-to-male ratio is around 2:1.

Intelligence quotient (IQ) and brain development may suffer if CH is not diagnosed and treated promptly. Infants with CH may exhibit hoarse crying, dry skin, constipation, anterior fontanels, jaundice, constipation, feeding problems, hypotonia, and voice hoarseness. CH is the most common avoidable and treatable cause of intellectual disability in children. The lack of the thyroid gland causes dwarfism, mental impairment, and developmental delay, which plays a significant role in both physiological and mental development. As a result, in CH, proper diagnosis and therapy are crucial. The main objectives of treatment for CH are to guarantee proper growth, development, and intellect. The most popular medication for bringing thyroid hormone levels in CH patients back to normal is oral levothyroxine (L-T4) (39).

4.5.2. Causes

Inappropriately normal or low TSH levels in relation to insufficient thyroid hormone are hallmarks of central causes of hypothyroidism, which usually exhibit with other signs of hypothalamic or pituitary dysfunction. Tyrosine kinase inhibitors, lithium, amiodarone, interleukin-2, and interferon alfa are among the medications that are traditionally linked to thyroid dysfunction. 6, 7 Inappropriately normal or low TSH levels in relation to insufficient thyroid hormone are hallmarks of central causes of hypothyroidism, which usually exhibit with other signs of hypothalamic or pituitary dysfunction. Tyrosine kinase inhibitors, lithium, amiodarone, interleukin-2, and interferon alfa are among the medications that are traditionally linked to thyroid dysfunction (40).

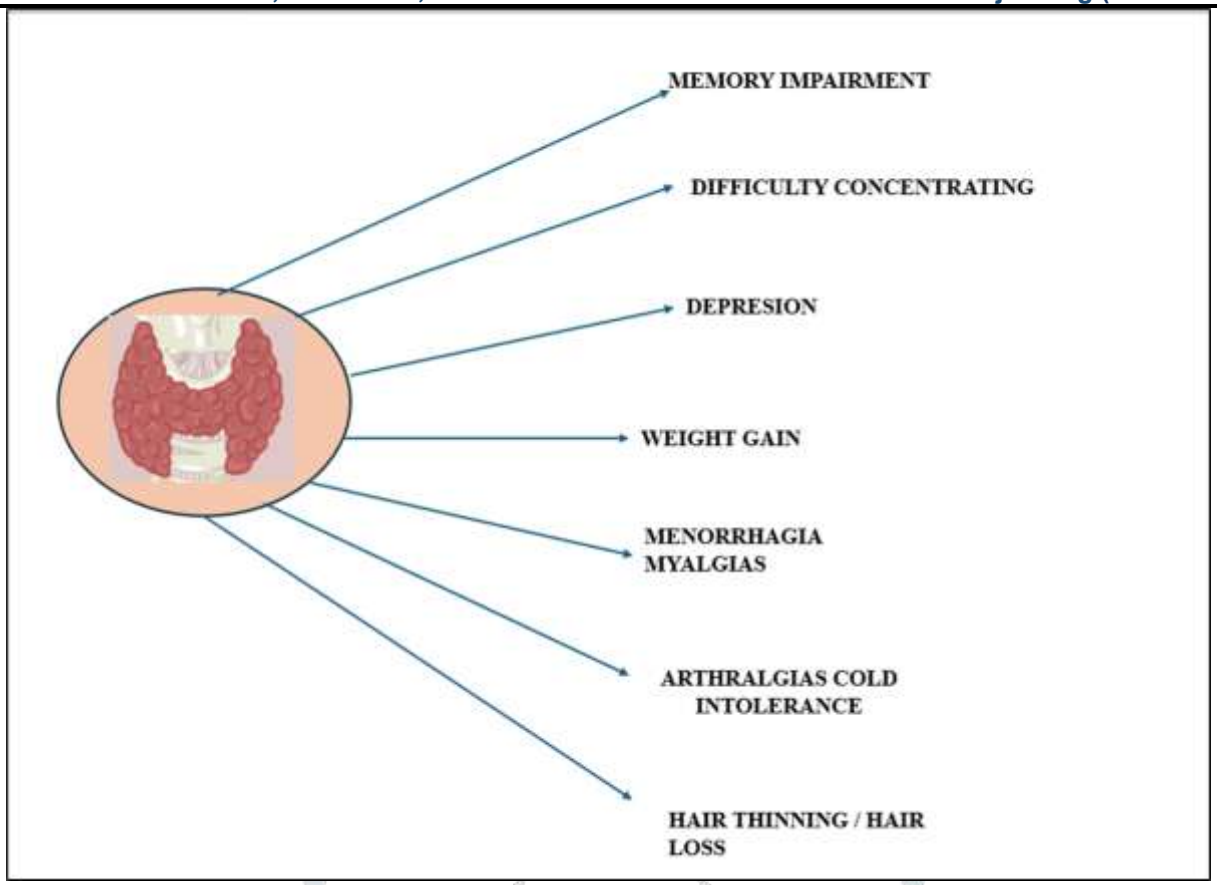

Figure 5. Symptoms in hypothyroidism

4.5.3. Central Congenital Hypothyroidism

According to early research, the prevalence of central congenital hypothyroidism in infants varied between 1 in 29,000 and 1 in 110,000. However, more recent Dutch research the prevalence of central congenital hypothyroidism may be as high as 1 in 16,000, according to a thorough newborn screening approach. 33, 32, The hypothalamus or pituitary's anatomical or developmental anomalies are typically the cause of inborn central thyroid axis problems. Growth hormone, prolactin, adrenocorticotropin, and gonadotropins are among the other pituitary hormone axes that are frequently impacted by such disorders, and around 75% of neonates with central hypothyroidism have shortages in numerous pituitary hormones. Genetic alterations in some of these situations are the cause of transcription factors include OTX2, SOX3, PROP1, HESX1, LHX3, LHX4, and POU1F1 that are involved in pituitary or hypothalamus development. Rarely, certain genetic abnormalities in TRH or TSH signaling may result in central congenital hypothyroidism. The most prevalent of them is an inactivating mutation in the recently identified X-linked gene IGSF1, which codes for a glycoprotein on the cell surface that appears to promote proper pituitary thyrotrope manufacture of TRH receptors. Mutations in the b-subunit of TSH (TSHB), the TRH receptor itself (TRHR), and another X-linked gene, TBL1X, are additional extremely uncommon genetic reasons. Infants exposed to maternal hyperthyroidism during pregnancy may also acquire central hypothyroidism, despite the fact that it is typically temporary (41).

4.5.4. Diagnosis Of Congenital Hypothyroidism

Congenital hypothyroidism is being identified through newborn screening programs and diagnose it. In the middle of the 1970s, hypothyroidism tests were introduced into already-existing screening programs (3). At the moment, screening programs are in place in all 50 US states, Western European countries, Israel, Japan, Australia, New Zealand, Puerto Rico, and Canada. There are programs in place in eastern Europe, Latin America, South America, and several Asian and African nations. In the US, about 4 million babies are checked, and 1000–1333 babies with hypothyroidism are found each year; globally, about 24 million babies are screened, and 6000–8000 instances of hypothyroidism are found annually (42). prenatal diagnosis when a history of dyshormonogenesis in the family, known mutations in genes linked to thyroid development or function, and a chance discovery of goitre during foetal ultrasound (43).

4.5.5. Treatments

Pregnancy-related hypothyroidism medication selection

Since maternal T4 (rather than T3) is important for It is not recommended to take desiccated thyroid tablets, T3/T4 in combination, or levo triiodothyronine (LT3) during pregnancy due to fetal brain development. Thyroid hormones can be transported across the placenta by the carrier proteins monocarboxylate transporter 8 (MCT8) and organic anion-transporting polypeptide 1c1 (Oatp1c1). According to Vulsma et al., maternal thyroxine does cross the placenta and reach the fetus. In order to ensure that the fetus receives the appropriate amounts of T3/T4 from the mother, placental deiodinases (D2, D3) are also present (44). The recommended medication for treating CH is L-T4. In newborns with CH identified by a second routine screening test, treatment should start as soon as feasible, but no later than two weeks after delivery or right after confirmation serum test results. Start with 10–15 g/kg of L-T4 each day. The highest initial dose should be given to infants who are severely unwell, as indicated by a very low baseline TT4 or FT4 concentration. It is best to take L-T4 orally. The dose should not exceed 80% of the oral dose if intravenous therapy is necessary. The dosage should then be adjusted in accordance with FT4 and TSH (43a).

V.UNIVERSAL SCREENING

The frequency of overt hypothyroidism, which is defined by low free thyroxine and elevated TSH, is thought to be between 0.2% and 0.3 percent. Offspring of mothers with untreated overt and subclinical hypothyroidism have been found to have higher levels of intellectual disability. Pop et al. discovered that children aged 1 to 2 who had moms with mild hypothyroxinaemia had lower Bayley motor and cognition sub scores. According to Haddow et al., Offspring of mothers with untreated overt and subclinical hypothyroidism had a full-scale IQ that was seven points lower than that of control people. It's interesting to note that in that same study, the IQs of babies born to women who had treated their hypothyroidism were similar to those of euthyroid women. However, it's still unclear if treating subclinical hypothyroidism will actually lessen these cognitive abnormalities given the observational nature of these investigations (45). Currently, only women who are checked for CH at high risk in Spain. Thus, recommendations for thyroid dysfunction screening in the general population are provided by the Spanish Society of gynaecology and Obstetrics and the Working Group on Iodine Deficiency Disorders and Thyroid Dysfunction of the Spanish Society of Endocrinology and Nutrition (46). Only women with a personal history or symptoms of thyroid disease are advised to get tested, according to the American College of Obstetricians and gynaecologists. To ascertain the circumstances under which routine screening for subclinical hypothyroidism during pregnancy might be financially beneficial, the study's authors developed a decision-analysis model (47).

VI.CLINICAL STUDY TRIAL

Chemiluminescent tests for free thyroxine and TSH were used to study thyroid function. In particular, Los Angeles-based Diagnostic Products Corporation, California, manufactures the Immulite 2000 Analyzer was used to conduct these tests. The test had an analytical sensitivity of 0.002 mU/L for TSH. Using specimens in the normal range, the coefficient of variance was 4.6% between runs and 3.8% within a run. For free thyroxine, the sensitivity limit was 0.18 mg/mL. Within runs, the coefficient of variance was 7.1%, while between runs, it was 6.4%. Our obstetric group's TSH (uncorrected for gestational age) 95th percentile value was 3.0 mU/L was estimated by analysing serum samples from women who were examined during a time frame of one month (October 2000). Women whose TSH levels were higher than 3.0mU/L had their serum tested prospectively for free thyroxine. A special obstetric difficulties clinic was contacted to refer women who had both an excessively low free thyroxine level (~0.9 ng/dL) and elevated TSH for evaluation and treatment. The identification and referral of women with clinical hypothyroidism was approved by the institutional review boards at Parkland Hospital and the University of Texas Southwestern. Analysis was done on women who were assessed at 20 weeks or less and had a singleton baby weighing 500 g or more during that time. In this study, women with free thyroxine levels greater than 0.680 ng/dL and TSH levels at or above the 97.5th percentile for gestational age at screening were retrospectively classified with subclinical hypothyroidism. The 2nd percentile of the study cohort's female participants' accessible free thyroxine levels was used to calculate the 0.680 ng/dL free thyroxine threshold TSH corrected for gestational age varied from 2.74 mU/L to 5.09 mU/L in the 97.5th percentile. Women with subclinical hypothyroidism had different pregnancy outcomes and those with TSH levels in the 5th to 95th percentiles. At Parkland Hospital, particular obstetric and neonatal outcomes for each woman giving birth are routinely updated in an electronic perinatal database. The nurses who attend each delivery complete an obstetric data sheet, which is then checked for accuracy and consistency by research nurses prior to being stored electronically. Data on baby outcomes is extracted from discharge records. The electronically stored thyroid function test results (free thyroxine and TSH) were connected to the neonatal and perinatal databases (48).

VII.CONCLUSION

The proper operation of the brain depends on thyroid hormones, which regulate vital processes like neurogenesis, cognitive function, and energy metabolism. When this hypothyroidism is identified early in life, it causes changes in the brain that may impact patients throughout adulthood. Maternal hypothyroidism is associated with several different conditions that may potentially affect the health of both the mother and the foetus, in addition to having a high potential to adversely affect both maternal and foetal outcomes. Thyroid hormones, which control essential functions like neurogenesis, cognitive function, and energy metabolism, are essential for the brain to function properly. Early detection of this hypothyroidism results in brain alterations that may affect patients well into adulthood. Thus far, thyroid hormone function has been connected to several neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, and autism. Early detection, rapid treatment initiation, appropriate follow-up, and—most importantly—adequate patient and physician education on these objectives, the importance of the illness, and the advantages and convenience of timely therapy are all necessary for this condition. Congenital hypothyroidism (CH) is one of the most common preventable causes of mental disability. The best way to find infants with CH is through widespread neonatal screening. If the diagnosis is made and treatment is started within a few weeks of birth, the neurodevelopmental result is typically typical. The pathogenesis of thyroid dysgenesis, the most prevalent cause of CH, is poorly understood despite the rising incidence of CH. Up until now, a number of studies have linked thyroid hormone function to a number of neurological disorders, including autism, Parkinson's, and Alzheimer's. In addition to having a high potential to negatively impact both maternal and fetal outcomes, maternal hypothyroidism is linked to a number of other disorders that may potentially have an influence on the fetus's and mother's health.

VIII.REFERANCE

1. Hulbert, A. J. "Thyroid hormones and their effects: a new perspective." *Biological Reviews* 75.4 (2000): 519-631.

2. Salazar, Paulina, et al. "Hypothyroidism and cognitive disorders during development and adulthood: implications in the central nervous system." *Molecular Neurobiology* 56.4 (2019): 2952-2963.

3. Dulek, Hatice, et al. "The prevalence of thyroid dysfunction and its relationship with perinatal outcomes in pregnant women in the third trimester." *Northern Clinics of Istanbul* 6.3 (2019): 267.

4. Shahid, Muhammad A., Muhammad A. Ashraf, and Sandeep Sharma. "Physiology, thyroid hormone." (2018).

5. VOL. 102, NO. 2, AUGUST 2003 0029-7844/03/$30.00 © 2003 by The American College of Obstetricians and Gynaecologists. Published by Elsevier. doi:10.1016/S0029-7844(03)00513-1

6. Iskandar Idris, Ramalingam Srinivasan, Andrew Simm and Renee C. Page Department of Diabetes and Endocrinology, Nottingham City Hospital, Nottingham, UK doi: 10.1111/j.1365-2265.2005.02382x

7. Liane Eng, MD, * Leslie Lam, MD* *Division of Paediatric Endocrinology and Diabetes, The Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY

8. Morreale de Escobar, Gabriella, Maria Jesus Obregon, and Francisco Escobar del Rey. "Foetal and maternal thyroid hormones." Hormones 26.1-4 (1987): 12-27.

9. Dillmann, W. H. "Mechanism of action of thyroid hormones." *Medical Clinics of North America* 69.5 (1985): 849-861.

10. Rivet, Joanne F. "The role of thyroid hormones for brain development and cognitive function." *Endocr Dev* 26.26 (2014): 26-43.

11. van Mil, Nina H., et al. "Maternal hypothyroxinemia during pregnancy and growth of the fetal and infant head." *Reproductive Sciences* 19.12 (2012): 1315-1322.

12. Shan, Zhongyan, and Weiping Teng. "Thyroid hormone therapy of hypothyroidism in pregnancy." *Endocrine* 66.1 (2019): 35-42.

13. Teng, Weiping, et al. "Hypothyroidism in pregnancy." *The lancet Diabetes & endocrinology* 1.3 (2013): 228-237.

14. Poppe, Kris, and Daniel Glinoer. "Thyroid autoimmunity and hypothyroidism before and during pregnancy." *Human reproduction update* 9.2 (2003): 149-161.

15. Smallridge, Robert Christian, and P. W. Ladenson. "Hypothyroidism in pregnancy: consequences to neonatal health." *The Journal of Clinical Endocrinology & Metabolism* 86.6 (2001): 2349-2353.

16. Sterrett, Mary. "Maternal and fetal thyroid physiology." *Clinical Obstetrics and Gynaecology* 62.2 (2019): 302-307.

17. Rastogi, Maynika V., and Stephen H. LaFranchi. "Congenital hypothyroidism." Orphanet journal of rare diseases 5.1 (2010): 17.

18. Trumpff, Caroline, et al. "Neonatal thyroid-stimulating hormone level is influenced by neonatal, maternal, and pregnancy factors." Nutrition research 35.11 (2015): 975-981.c

19. Effect of maternal and neonatal factors on neonatal thyroid stimulating hormone: Results from a population-based prospective cohort study in China.

20. Ozdemir, Hulya, et al. "Maternal thyroid dysfunction and neonatal thyroid problems." *International journal of endocrinology* 2013.1 (2013): 987843.

21. Medici, Marco, et al. "Maternal thyroid hormone parameters during early pregnancy and birth weight: the Generation R Study." The Journal of Clinical Endocrinology & Metabolism 98.1 (2013): 59-66.

22. Smit, B. J., et al. "Neurologic development of the newborn and young child in relation to maternal thyroid function." Acta Paediatrica 89.3 (2000): 291-295.

23. Casey, Brian M., and Kenneth J. Leveno. "Thyroid disease in pregnancy." Obstetrics & Gynecology 108.5 (2006): 1283-1292.

24. Ghanbari, Mahboubeh, and Asghar Ghasemi. "Maternal hypothyroidism: An overview of current experimental models." Life sciences 187 (2017): 1-8.

25. Ames, Jennifer L., et al. "Neonatal thyroid stimulating hormone and subsequent diagnosis of autism spectrum disorders and intellectual disability." Autism Research 13.3 (2020): 444-455.

26. Baxter, Amanda J., et al. "The epidemiology and global burden of autism spectrum disorders." Psychological medicine 45.3 (2015): 601-613.

27. Khan, A., et al. "Disrupted brain thyroid hormone homeostasis and altered thyroid hormone-dependent brain gene expression in autism spectrum disorders." J Physiol Pharmacol 65.2 (2014): 257-272.

28. Chen, Shih-Fen, et al. "Risk of Parkinson's disease in patients with hypothyroidism: A nationwide population-based cohort study." Parkinsonism & Related Disorders 74 (2020): 28-32.

29. Kim, Ji Hee, et al. "Association between thyroid diseases and Parkinson's disease: a nested case-control study using a national health screening cohort." Journal of Parkinson's Disease 11.1 (2021): 211-220.

30. Munhoz, Renato P., et al. "Parkinson's disease and thyroid dysfunction." Parkinsonism & related disorders 10.6 (2004): 381-383.

31. Chen, Jiahui, Zhongying Zhu, and Yuanyuan Xu. "Signs of Alzheimer's Disease: Tied to Aging." *International Journal of Molecular Sciences* 26.11 (2025): 4974.

32. Knopman, David S., et al. "Alzheimer disease." Nature reviews Disease primers 7.1 (2021): 33.

33. Reddi Sree, Radhakrishna, et al. "Newer Therapeutic Approaches in Treating Alzheimer's Disease: A Comprehensive Review." *ACS omega* 10.6 (2025): 5148-5171.

34. Marshall, Jennifer. "Infant neurosensory development: considerations for infant child care." *Early Childhood Education Journal* 39.3 (2011): 175-181.

35. Dugbartey, Anthony T. "Neurocognitive aspects of hypothyroidism." *Archives of internal medicine* 158.13 (1998): 1413-1418.

36. Rastogi, Maynika V., and Stephen H. LaFranchi. "Congenital hypothyroidism." *Orphanet journal of rare diseases* 5.1 (2010): 17.

37. Agrawal, Pankaj, et al. "Congenital hypothyroidism." *Indian journal of endocrinology and metabolism* 19.2 (2015): 221-227.

38. Park, S. M., and V. K. K. Chatterjee. "Genetics of congenital hypothyroidism." *Journal of medical genetics* 42.5 (2005): 379-389.

39. Chen, Chung-Yu, et al. "Epidemiology and clinical characteristics of congenital hypothyroidism in an Asian population: a nationwide population-based study." *Journal of epidemiology* 23.2 (2013): 85-94.

40. Gaitonde, David Y., Kevin D. Rowley, and Lori B. Sweeney. "Hypothyroidism: an update." South African Family Practice 54.5 (2012): 384-390.

41. Shan, Zhongyan, and Weiping Teng. "Thyroid hormone therapy of hypothyroidism in pregnancy." *Endocrine* 66.1 (2019): 35-42.

42. LaFRANCHI, S. T. E. P. H. E. N. "Congenital hypothyroidism: etiologies, diagnosis, and management." *thyroid* 9.7 (1999): 735-740.

43. Léger, Juliane, et al. "European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism." *The Journal of Clinical Endocrinology & Metabolism* 99.2 (2014): 363-384.

44. Wassner, Ari J. "Congenital hypothyroidism." *Clinics in perinatology* 45.1 (2018): 1-18.

45. Dosiou, Chrysoula, et al. "Cost-effectiveness of universal and risk-based screening for autoimmune thyroid disease in pregnant women." *The Journal of Clinical Endocrinology* 97.5 (2012): 1536-1546.

46. Candil, Sergio Donnay, et al. "Cost-effectiveness analysis of universal screening for thyroid disease in pregnant women in Spain." *Endocrinología y Nutrición (English Edition)* 62.7 (2015): 322-330.

47. Licciardone, John C., et al. "Osteopathic manipulative treatment of back pain and related symptoms during pregnancy: a randomized controlled trial." *American journal of obstetrics and gynecology* 202.1 (2010): 43-e1.

48. Casey, Brian M., et al. "Subclinical hypothyroidism and pregnancy outcomes." *Obstetrics & Gynecology* 106.1 (2005): 198-199.