2020

# Effects of Maternal Thyroid Hypofunction on Fetal Brain Development During Pregnancy: Possible Links to Autism Spectrum Disorder

Caroline R. Hobson
*University of Central Florida*

# EFFECTS OF MATERNAL THYROID HYPOFUNCTION ON FETAL BRAIN DEVELOPMENT DURING PREGNANCY: POSSIBLE LINKS TO AUTISM SPECTRUM DISORDER

by

CAROLINE R. HOBSON

A thesis submitted in partial fulfillment of the requirements
for the Honors in the Major Program in Biomedical Sciences
in the College of Medicine
and in The Burnett Honors College
at the University of Central Florida
Orlando, Florida

Summer Term, 2020

Thesis Chair: Raheleh Ahangari, M.D.

# ABSTRACT

Thyroid hormone regulates essential processes in brain development such as neural cell migration, differentiation, signaling, and myelination, particularly during the early stages of gestation. During this time, fetal thyroid hormone accessibility depends on the placental transfer of thyroid hormones. Deficiency of thyroid hormone during fetal and postnatal periods may lead to permanent mental retardation and neurological deficits. Clinical studies have been conducted demonstrating links between maternal hypothyroidism and numerous neurodevelopmental disorders such as Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder, lower IQ, behavioral disorders, and psychiatric disorders. To investigate the effects of thyroid hormone actions on perinatal brain development potentially present in ASD, a literature review was conducted using PubMed, UCF EBSCOhost, and Google Scholar to obtain relevant papers for analysis. Across the board, abnormal maternal thyroid function, especially suboptimal maternal free thyroxine hormone, was associated with increased risk for neurological disorders, including ASD. The implications of this study emphasize the importance of managing maternal hypothyroidism during pregnancy to possibly reduce the incidence of neurodevelopmental disorders such as ASD.

# DEDICATION

For my brother, who drives my intellectual curiosity and sparks compassion in me every day.

# ACKNOWLEDGEMENTS

I would like to thank my thesis chair, Dr. Ahangari, for her guidance and support throughout this process as well as my committee members, Dr. Bradshaw and Dr. Daly, for lending their expertise and suggestions. Together, we traversed most of the thesis process during the COVID-19 pandemic.

# TABLE OF CONTENTS

# INTRODUCTION

Autism Spectrum Disorder (ASD) is characterized by the Center for Disease Control and Prevention (CDC) as a developmental disability resulting in varying levels of social, communicative, and behavioral disorders (1). The prevalence of ASD has skyrocketed in recent years, with estimates currently lying around 1 in 54 children affected with a ratio of approximately 4:1 boys to girls (1). Signs and symptoms can include avoiding eye contact, not looking at objects when someone points to them, repeating actions, appearing unaware when being spoken to, and failing to show interest (1, 2). Diagnosis of ASD can occur as young as 18 months of age and with great reliability after two years of age (1). Current diagnostic criteria from the DSM-V focus on deficits in social interaction, nonverbal communicative patterns, and development and understanding of relationships (3).

## Characteristics of ASD Brains

While the etiology of ASD remains unknown, numerous studies have highlighted deviations in neuroanatomical structures pointing towards a developmental pathology. One study of 277 ASD patient brains exhibiting deviation from neurotypical brains identified six areas of the brain with converging information in magnetic resonance images (MRI) including the lateral occipital lobe, the pericentral region, the medial temporal lobe, the basal ganglia, and proximate to the right parietal operculum (4). Multiple studies concur on the presence of abnormal connectivity present in ASD brains as well as alterations in grey and white matter (5, 6). Areas associated with social communication and repetitive behaviors such as the superior temporal gyrus and cingulate cortex have shown dysfunctional activation in functional MRI studies (5).

Potential early markers for ASD were suggested in a study analyzing the presymptomatic period of approximately zero to two years of age, including cortical surface area growth, increased volume of extra-axial cerebrospinal fluid, and abnormal white matter connectivity in the genu of the corpus callosum (6). This study also identifies regions of the brain prominently associated with the pathology of ASD, consistent with clinical presentation. These include the cerebellum, which functions in higher cognitive processes and language, the amygdala, which plays a role in emotional processing, and the frontal cortex that regulates numerous cognitive processes and executive brain functions such as planning, social behavior, and communication (6). Multiple studies confer that brain imaging within the first year of life could potentially lead to the prediction of ASD before visible diagnostic symptoms arise (7).

**Thyroid Hormones and Brain Development**

Fetal brain development during gestation is heavily influenced by thyroid hormones responsible for crucial functions such as neural cell migration, differentiation, and synaptogenesis (8). Before midgestation, the mother is the only source of thyroxine (T4); therefore, adequate concentrations of maternal serum T4 for placental transfer to the fetus is essential for typical neurodevelopment (9). Maternal thyroid dysfunction is strongly associated with poor outcomes for mother and child, such as pre-eclampsia, spontaneous abortion, premature birth, low birth weight, neurological cretinism, and other neurological deficits in the child (10, 11).

Given the implications of maternal thyroid hormone levels on fetal brain development, dysfunction of the maternal thyroid could point to the emerging etiopathological identification of impacted neurodevelopmental structures in ASD. The goal of this research is to conduct a

literature review on the association of maternal thyroid dysfunction with adverse neurological outcomes in the fetus that is potentially linked to ASD diagnosis as well as impacts of treating maternal thyroid disorders to reduce the risk of ASD.

Thyroid hormones thyroxine (T4) and 3,5,3'-triiodothyronine (T3) are crucial for the development of many fetal structures, especially the central nervous system (8, 12). Upon entering the brain, thyroid hormones act upon class II nuclear receptors to control the expression of specific genes. These receptors act as a corepressor when there is no binding of the hormone, but upon particular hormone binding, transcription is stimulated (12). In the brain, T3 binding to thyroid nuclear receptor isoforms stimulates transcription of genes influencing processes, including myelination, cell differentiation, signaling, and migration (8, 13). The specific genes that thyroid hormone bind to include integrin $\alpha_v\beta_3$ membrane receptor that stimulates neocortex expansion, the *Reln* gene that influences neuronal migration in the cerebral cortex, and the *Shh* gene that controls granular cell proliferation (14). Any conflict in these processes can lead to deficits in neuroontogenesis of various brain structures. For example, a study found that mutation of thyroid hormone receptor beta isoform leads to impairment in development of the cerebellum due to lack of granular cell proliferation and migration in the external granular layer (15). A plethora of evidence of similar detrimental effects to other neuroanatomical structures and functions as a result of varying levels of maternal thyroid hypofunction has been demonstrated including the rate of neurogenesis (16), neocortical neuronal migration (17), cortical morphology (18), spatial learning and synaptic nature (19), and hippocampus and memory (20). Furthermore, studies have pinpointed the timing of specific impairments to correspond to the period of thyroid hormone inadequacy during gestation (13, 21).

**Thyroid Physiology and Placental Transfer**

Thyroid physiology is regulated by the hypothalamic-pituitary axis. Thyroid-releasing hormone (TRH) is secreted by neurons in the hypothalamus and stimulates production of thyroid stimulating hormone (TSH) in the anterior pituitary by activating thyrotroph cells (22). TSH stimulates follicular cells of the thyroid to synthesize and release T3 and T4. T3 is the active form of the thyroid hormone but is secreted in lower quantity (20%) compared to T4 (80%) (22). Most T3 production results from conversion of T4 to T3 by deiodinases. In peripheral tissues like the liver and kidneys, T3 is converted to T4 by type 1 deiodinase while in the brain this conversion occurs via type 2 deiodinase produced by glial cells (23). Both T3 and T4 in high levels can cause negative feedback on the anterior pituitary release of TSH, ultimately decreasing stimulation of T3 and T4 production (22).

The fetus receives thyroid hormone after maternal T3 and T4 cross the placental barrier during the first trimester. Research suggests that the blood-brain-barrier (BBB) is not permeable to the T3 form of thyroid hormone; therefore, the source of T3 in the fetal brain is the conversion of T4 to T3 after T4 crosses the BBB (12). Administering T4 maintains adequate physiological levels of T3 in the brain (12).

Specific transporter proteins are required for thyroid hormones to cross plasma membranes. Thyroxine-binding globulin (TBG), transthyretin (TTR), and albumin (HSA) are the main serum proteins that bind thyroid hormone for transport (24). Transporter proteins for placental transfer of thyroid hormones remain up for debate. TTR is synthesized and secreted by placental trophoblast cells and could play a role in transport of T3 and T4 to fetus (25). Organic anion-transporting polypeptide, L-type amino acid, and monocarboxylate transporter are other

proteins identified that bind thyroid hormone for transport and are active in multiple cell types within the placenta (26).

**Thyroid Function During Pregnancy**

When a woman becomes pregnant, there is a notable change in her thyroid physiology to ensure adequate thyroid hormone for herself and the fetus. This change is crucial since the fetal thyroid does not develop enough to produce thyroid hormone until approximately the 20$^{th}$ week of gestation (10, 27). In a typical pregnancy, serum free T4 levels increase during the first and second trimesters through a mechanism of increased thyroid hormone binding globulin production in the liver due to higher estrogen levels, which increases synthesis of T3 and T4 (27). Serum human chorionic gonadotropin (hCG) glycoprotein is produced primarily in the first trimester of pregnancy by the placenta. It acts as a weak agonist to TSH, further increasing T3 and T4 synthesis while simultaneously suppressing TSH level (27).

Thyroid dysfunction is relatively common in pregnancy with an estimated prevalence of 2-4% (11). Some risk factors for thyroid dysfunction include age greater than 30 years, type I diabetes or other autoimmune disorder, multiple prior pregnancies, family history of thyroid disease, and morbid obesity (28). It is important to identify the different classifications of thyroid hypofunction in the context of this research. Overt hypothyroidism is characterized by low free T4 and high TSH concentrations with a prevalence estimated to be between 0.2-1.0% (29). Subclinical hypothyroidism has presence of standard free T4 with elevated TSH levels and represents the most common type of thyroid dysfunction in pregnancy with estimates between 1.5-4.0% (30). Hypothyroxinemia is an isolated condition in pregnancy in which free T4 is below the 2.5th percentile with a normal TSH concentration (31). Differentiating these three

classifications of thyroid hypofunction is essential when analyzing the effectiveness of diagnostic techniques and possible medication suggestions.

Considering the importance of thyroid hormone levels for fetal nervous system development discussed as well as the high prevalence of maternal thyroid hypofunction, the goal of this research is to analyze the literature available to evaluate the potential benefits of universal early maternal thyroid screening. This idea paired with subsequent medical intervention to standardize maternal thyroid levels could possibly reduce the risk of adverse fetal outcomes such as ASD.

# METHODS

- To investigate effects of thyroid hormone actions on perinatal brain development potentially present in ASD, a literature review was conducted using PubMed, UCF EBSCOhost, and Google Scholar.
- These databases were searched for articles pertaining to thyroid function on brain development in ASD pregnancy by inputting keywords such as: Autism, thyroid function, pregnancy, maternal, hypothyroidism, hypothyroxinemia, brain development, levothyroxine.
- Articles containing selected key words were analyzed and selected based on relevance.

# MATERNAL THYROID HYPOFUNCTION AND ASD DIAGNOSIS RATES

Numerous case-cohort studies have been conducted analyzing maternal thyroid hypofunctions of varying severity and subsequent diagnoses of neurological disorders in the child, especially involving ASD.

Levie et al. conducted a meta-analysis to assess impacts of low maternal free T4 levels during early pregnancy (less than 18 weeks) on IQ and autistic traits. They concluded that low maternal free T4 was associated with lower verbal and nonverbal IQ across all cohorts, hypothyroxinemia has a possible association with autistic traits, and confirmed the reliability of free T4 as an indicator of the fetal thyroid state (32).

A case-cohort study assessed free T4 and thyrotropin level at week 9 of pregnancy and subsequent diagnoses of neurodevelopmental disorders including seizures, ASD, and ADHD in the children. Abnormal maternal thyroid function was most prevalent in the ASD cases compared to the other disorders. Maternal overt hypothyroidism presented the most risk factors for ASD (33). This research group produced a follow-up study that reassessed the neuropsychological performance of the children at age five years and reaffirmed that maternal thyroid dysfunction caused deficits in neurological development. Additionally, after performing intelligence and function tests, the researchers were able to draw further conclusions that maternal overt hypothyroidism had a greater effect on intelligence in the child while maternal hypothyroxinemia mainly affected motor and executive functions as well as behavior problems (34).

A retrospective cohort study showed that women diagnosed with hypothyroidism both before and during pregnancy had children with higher rates of ASD diagnosis. The association was seen in ASD diagnosis in both boy and girl children (35). Fetene et al. conducted a systematic review regarding maternal thyroid dysfunction and neurological disorders in the child and concluded that particularly maternal overt hypothyroidism displayed the highest rates of behavior and psychiatric disorders including ASD (36).

**A Focus on Hypothyroxinemia**

Another case-cohort study found an association between women with severe hypothyroxinemia (free T4 < $5^{th}$ percentile and normal TSH) and a four-fold increased risk of having a child with probable ASD based on a Pervasive Developmental Problem subscale (37). Thompson et al. conducted a large scale meta-analysis of 39 studies showing association of maternal hypothyroxinemia and subclinical hypothyroidism with intellectual disabilities and neurodevelopmental disorders in children (38).

A 3-year follow-up study after collection of maternal free T4 levels at 12 weeks of gestation demonstrated that maternal hypothyroxinemia leads to a higher rate of deficits in mental and motor function in children. This study also showed that an increase to standard levels of free T4 in women with hypothyroxinemia in weeks 24-32 of gestation did not have better fetal outcomes (39). This data reflects the crucial function of thyroid hormone in early gestation for fetal brain development before the fetus is able to synthesize T3 and T4 independently. Similarly, Kooistra et al. assessed neurobehavioral function of infants born to mothers with maternal hypothyroxinemia at 12 weeks gestation. Neonates of women with low free T4 levels in

early pregnancy scored significantly lower on the Neonatal Behavior Assessment Scale which assesses motor behavior, response to stress, adaptive behavior, and state organization at 3 weeks of age. The results also established that only first-trimester maternal hypothyroxinemia acted as a predicting factor for the assessment score, once more aligning with the timeline of fetal neurodevelopment (40).

# CLINICAL INTERVENTIONS FOR MATERNAL THYROID HYPOFUNCTION AND FETAL OUTCOMES

Considering the well-documented adverse maternal and fetal outcomes of various levels of maternal thyroid hypofunction including pre-eclampsia, spontaneous abortion, premature birth, low birth weight, neurological cretinism, and other neurological deficits (10, 11), clinical interventions for affected women planning pregnancy is encouraged.

Treatment options for hypothyroidism primarily include synthetic hormone replacement. Synthetic T4, levothyroxine (LT4), is the most common medication administered to patients with low T4 levels (41). LT4 and liothyronine (synthetic T3) combination therapies have also been developed; however, recent research confers that LT4 should remain standard of care for suboptimal thyroid hormone levels including hypothyroxinemia as clinical studies have shown inconclusive results that LT4-liothryonine combination therapies are superior to LT4 monotherapy (42, 43).

Duntas and Jonklaas identified factors that may require adjustment of a patient's LT4 dose including weight and hormonal changes, aging, and pregnancy citing that up to 85% of pregnant women require an increase of their LT4 dose (44). The 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum recommends LT4 treatment for women with overt hypothyroidism and encourages consideration of LT4 treatment for women with subclinical hypothyroidism to avoid possible progression of hypothyroidism upon becoming pregnant. The guidelines emphasize monitoring of TSH levels every 4 weeks and encourage LT4 treatment

when TSH is above 2.5 mU/L. It is recommended that women receiving LT4 treatment for hypothyroidism increase their dose by 20-30% upon confirmation of pregnancy (45).

**Case Studies: Levothyroxine Treatment During Pregnancy**

Case studies analyzing maternal and fetal outcomes when the mother is treated with LT4 during pregnancy are in relative abundance. The Thyroid Hormone Early Adjustment in Pregnancy (THERAPY) trial concluded that increasing LT4 dose by two tablets upon confirmation of pregnancy successfully mirrors typical pregnancy physiology and reduces hypothyroidism in the mother in the first trimester (46).

A 2019 meta-analysis conducted supports the benefits of LT4 medication in women with subclinical hypothyroidism during pregnancy citing lower risk of miscarriage and preterm birth (47). Meta-analyses of randomized controlled trials also show evidence for higher delivery rates and lower miscarriage rates with LT4 supplementation during pregancy. These studies have also demonstrated reduced gestational diabetes and hypertension in mothers, higher birth weights, and fewer congenital malformations with LT4 intervention (48, 49).

One clinical study analyzed the effects of LT4 supplementation in pregnant women with subclinical hypothyroidism compared to pregnant women with hypothyroxinemia. The significant findings were reduced premature birth and low birth rate risks in both groups and additionally decreased gestational hypertension in the subclinical hypothyroidism group (50).

Clinical research regarding LT4 intervention for maternal hypofunction during pregnancy and subsequent analysis of neurological outcomes in the fetus is few and far between. The results tend to not support the hypothesis of this research.

Casey et al., found that women treated for subclinical hypothyroidism and hypothyroxinemia at means of 16.7 and 17.8 weeks of gestation respectively did not have children with significantly better neurocognitive outcomes than untreated women (51). Another study analyzed randomized controlled trials and found lacking data for evidence of less risk for neurosensory disability in the child after the mother was treated with LT4 for thyroid hypofunction. One trial included women screened before 11 weeks gestation and the other trial included women screened before 15 weeks gestation (52). A solo randomized control trial analyzed children at 3 years of age and did not find improvement in cognitive function in children born to mothers treated for hypothyroidism at 12 weeks 3 days median gestation (53).

# DISCUSSION

## Implications

### Gaps in the Research

While conducting this literature review, it became apparent that a gap in the research exists in assessing the effectiveness of LT4 treatment for maternal hypofunction and subsequent neurological outcomes, ASD traits, and ASD diagnosis of offspring. A multitude of studies suggest that adverse maternal and fetal outcomes such as pre-eclampsia, gestational diabetes and hypertension, early delivery, miscarriage, low birth weight, and congenital malformations are reduced by adequate LT4 intervention (44-50). The few studies that do include assessment of neurological outcomes in children only consider IQ scores as a comparison benchmark to the control individuals (51-53). In order to better understand the possibility of reducing ASD in children with LT4 treatment for hypothyroid mothers, researchers should conduct studies including more in depth neurological follow-up including ASD diagnosis as well as evaluation of ASD traits such as social, communicative, and behavioral deficits.

### Timing of LT4 Treatment

A crucial factor to consider when analyzing the effects of LT4 intervention on neurological outcomes is the gestational age of the embryo or fetus when the treatment begins. The mother is the only source of thyroid hormone for the fetus up to midway through the pregnancy (9). Key neurological structures and begin their development as early as week three of gestation

including: medulla, pons, cerebellum, thalamus, hypothalamus, amygdala, neocortex, and hippocampus (50, 51). Additionally, essential brain functions synaptogenesis, myelinogenesis, and gliogenesis occur in the fetus as early as week five (54, 55).

The current clinical studies analyzing the effect of LT4 treatment during pregnancy on fetal neurodevelopmental outcomes show concerning gestational age for the start of the treatments. The studies averaged a median gestation ranging from 12-18 weeks as the starting point for implementation of thyroxine replacement (51-53). Other studies have demonstrated that the specific time of insufficient thyroid hormone during gestation corresponds to deficits in the typical development at the same point in time (13, 21). This creates questions about the efficacy of LT4 supplementation on nervous system development after the first trimester.

**Necessity for Universal Early Thyroid Screening**

It is evident that adequate thyroid hormone levels are necessary to ensure a typical development of numerous vital organs, especially in the central nervous system. For this reason, debates on the application of universal thyroid screening has been an emerging topic in prenatal care as well as for those trying to conceive. Current protocol used by most healthcare providers only seeks to target pregnant women with overt hypothyroidism (56). An analysis of cost-effectiveness of universal screening for subclinical hypothyroidism in pregnancy found that universal screening of all pregnant women is cost-effective in both financial as well as quality of life considerations (57). Taylor et al. highlight the importance to recruit women pre-conception for clinical studies to further confirm the efficacy of immediate T4 replacement as necessary

(53). For this reason, many researchers and clinicians are now urging the universality of thyroid screening to prevent neurological malformations (58-60).

Universal thyroid screening could allow the execution of effective and timely treatment for overt and subclinical levels of maternal thyroid hypofunction that could show promise in ameliorating risk for adverse neurological outcomes in the fetus, especially the risk of ASD.

# REFERENCES


1. "What Is Autism Spectrum Disorder?" *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 27 Aug. 2019, www.cdc.gov/ncbddd/autism/facts.html.
2. Dover, C. J, and A. Le Couteur. "How to Diagnose Autism." *Archives of Disease in Childhood*, vol. 92, no. 6, 2007, pp. 540–545., doi:10.1136/adc.2005.086280.
3. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. American Psychiatric Association, 2017.
4. Nickl-Jockschat, Thomas, et al. "Brain Structure Anomalies in Autism Spectrum Disorder-a Meta-Analysis of VBM Studies Using Anatomic Likelihood Estimation." *Human Brain Mapping*, vol. 33, no. 6, 2011, pp. 1470–1489., doi:10.1002/hbm.21299.
5. Ha, Sungji, et al. "Characteristics of Brains in Autism Spectrum Disorder: Structure, Function and Connectivity across the Lifespan." *Experimental Neurobiology*, vol. 24, no. 4, 2015, pp. 273–284., doi:10.5607/en.2015.24.4.273.
6. Donovan, Alex P. A., and M. Albert Basson. "The Neuroanatomy of Autism - a Developmental Perspective." *Journal of Anatomy*, vol. 230, no. 1, 2016, pp. 4–15., doi:10.1111/joa.12542.
7. Shen, Mark D. "Brain and Behavior Development in Autism from Birth through Infancy." *Dialogues in Clinical Neuroscience*, 19 Dec. 2017, pp. 325–333.
8. Bernal, Juan. "Thyroid Hormones and Brain Development." *Vitamins & Hormones*, 2005, pp. 95–122., doi:10.1016/s0083-6729(05)71004-9.

9. Escobar, G Morreale De, et al. “Role of Thyroid Hormone during Early Brain Development.” *European Journal of Endocrinology*, 2004, doi:10.1530/eje.0.151u025.
10. Medici, Marco, et al. “Thyroid Function in Pregnancy: What Is Normal?” *Clinical Chemistry*, vol. 61, no. 5, 2015, pp. 704–713., doi:10.1373/clinchem.2014.236646.
11. Krassas, G. E., et al. “Thyroid Function and Human Reproductive Health.” *Endocrine Reviews*, vol. 31, no. 5, 2010, pp. 702–755., doi:10.1210/er.2009-0041.
12. Bernal, Juan. “Thyroid Hormone Receptors in Brain Development and Function.” *Nature Clinical Practice Endocrinology & Metabolism*, vol. 3, no. 3, 2007, pp. 249–259., doi:10.1038/ncpendmet0424.
13. Rovet, Joanne F. “The Role of Thyroid Hormones for Brain Development and Cognitive Function.” *Paediatric Thyroidology Endocrine Development*, 2014, pp. 26–43., doi:10.1159/000363153.
14. Bernal, Juan. “Thyroid Hormones and Brain Development.” *Hormones, Brain and Behavior*, 2017, pp. 159–184., doi:10.1016/b978-0-12-803592-4.00100-0.
15. Portella, Aline Cristina, et al. “Thyroid Hormone Receptor β Mutation Causes Severe Impairment of Cerebellar Development.” *Molecular and Cellular Neuroscience*, vol. 44, no. 1, 2010, pp. 68–77., doi:10.1016/j.mcn.2010.02.004.
16. Mohan, Vishwa, et al. “Maternal Thyroid Hormone Deficiency Affects the Fetal Neocorticogenesis by Reducing the Proliferating Pool, Rate of Neurogenesis and Indirect Neurogenesis.” *Experimental Neurology*, vol. 237, no. 2, 2012, pp. 477–488., doi:10.1016/j.expneurol.2012.07.019.
17. Pathak, Amrita, et al. “Maternal Thyroid Hormone before the Onset of Fetal Thyroid Function Regulates Reelin and Downstream Signaling Cascade Affecting Neocortical

Neuronal Migration." *Cerebral Cortex*, vol. 21, no. 1, 2010, pp. 11–21., doi:10.1093/cercor/bhq052.

18. Lischinsky, Julieta E., et al. "Preliminary Findings Show Maternal Hypothyroidism May Contribute to Abnormal Cortical Morphology in Offspring." *Frontiers in Endocrinology*, vol. 7, 2016, doi:10.3389/fendo.2016.00016.
19. Opazo, M. C., et al. "Maternal Hypothyroxinemia Impairs Spatial Learning and Synaptic Nature and Function in the Offspring." *Endocrinology*, vol. 149, no. 10, 2008, pp. 5097–5106., doi:10.1210/en.2008-0560.
20. Willoughby, Karen A., et al. "Effects of Maternal Hypothyroidism on Offspring Hippocampus and Memory." *Thyroid*, vol. 24, no. 3, 2014, pp. 576–584., doi:10.1089/thy.2013.0215.
21. Chan, Shiao, and Joanne Rovet. "Thyroid Hormones In Fetal Central Nervous System Development." *Fetal and Maternal Medicine Review*, vol. 14, no. 3, 2003, pp. 177–208., doi:10.1017/s0965539503001086.
22. Pirahanchi, Yasaman, et al. "Physiology, Thyroid Stimulating Hormone (TSH)." *StatPearls*, June 2020.
23. Armstrong, Maggie, et al. "Physiology, Thyroid Function." *StatPearls*, 2020.
24. Pappa, T., and S. Refetoff. "Thyroid Hormone Transport Proteins: Thyroxine-Binding Globulin, Transthyretin, and Albumin ☆." *Reference Module in Neuroscience and Biobehavioral Psychology*, 2017, doi:10.1016/b978-0-12-809324-5.03494-5.
25. Landers, K.a., et al. "Transthyretin-Thyroid Hormone Internalization by Trophoblasts." *Placenta*, vol. 34, no. 8, 2013, pp. 716–718., doi:10.1016/j.placenta.2013.05.005.

26. James, Sally R., et al. “Placental Transport of Thyroid Hormone.” *Best Practice & Research Clinical Endocrinology & Metabolism*, vol. 21, no. 2, 2007, pp. 253–264., doi:10.1016/j.beem.2007.03.001.

27. Mladenovic, Violeta, et al. “Thyroid Function during Pregnancy.” *Endocrine Abstracts*, 2014, doi:10.1530/endoabs.35.p997.

28. Negro, Robert. “Thyroid Disease in Pregnancy.” *Best Practice & Research Clinical Endocrinology & Metabolism*, vol. 25, no. 6, Dec. 2011, pp. 927–943., doi:https://doi.org/10.1016/j.beem.2011.07.010.

29. Vaidya, Bijay, et al. “Detection of Thyroid Dysfunction in Early Pregnancy: Universal Screening or Targeted High-Risk Case Finding?” *The Journal of Clinical Endocrinology & Metabolism*, vol. 92, no. 1, 2007, pp. 203–207., doi:10.1210/jc.2006-1748.

30. Haddow, James E. “Subclinical Hypothyroidism and Pregnancy Outcomes.” *Obstetrics & Gynecology*, vol. 106, no. 1, 2005, p. 198., doi:10.1097/01.aog.0000169596.53498.7a.

31. Negro, Roberto, et al. “Hypothyroxinemia and Pregnancy.” *Endocrine Practice*, vol. 17, no. 3, 2011, pp. 422–429., doi:10.4158/ep10309.ra.

32. Levie, Deborah, et al. “Thyroid Function in Early Pregnancy, Child IQ, and Autistic Traits: A Meta-Analysis of Individual Participant Data.” *The Journal of Clinical Endocrinology & Metabolism*, vol. 103, no. 8, 2018, pp. 2967–2979., doi:10.1210/jc.2018-00224.

33. Andersen, Stine Linding, et al. “Maternal Thyroid Function in Early Pregnancy and Child Neurodevelopmental Disorders: A Danish Nationwide Case-Cohort Study.” *Thyroid*, vol. 28, no. 4, 2018, pp. 537–546., doi:10.1089/thy.2017.0425.

34. Andersen, Stine Linding, et al. “Maternal Thyroid Function in Early Pregnancy and Neuropsychological Performance of the Child at 5 Years of Age.” *The Journal of Clinical Endocrinology & Metabolism*, vol. 103, no. 2, 2017, pp. 660–670., doi:10.1210/jc.2017-02171.

35. Getahun, Darios, et al. “Association between Maternal Hypothyroidism and Autism Spectrum Disorders in Children.” *Pediatric Research*, vol. 83, no. 3, 2018, pp. 580–588., doi:10.1038/pr.2017.308.

36. Fetene, Dagnachew Muluye, et al. “MECHANISMS IN ENDOCRINOLOGY: Maternal Thyroid Dysfunction during Pregnancy and Behavioural and Psychiatric Disorders of Children: a Systematic Review.” *European Journal of Endocrinology*, vol. 177, no. 5, 2017, doi:10.1530/eje-16-0860.

37. Chang, Kathleen, and Jae Il Shin. “Association of Gestational Maternal Hypothyroxinemia and Increased Autism Risk.” *Annals of Neurology*, vol. 75, no. 6, 2014, pp. 971–971., doi:10.1002/ana.24143.

38. Thompson, William, et al. “Maternal Thyroid Hormone Insufficiency during Pregnancy and Risk of Neurodevelopmental Disorders in Offspring: A Systematic Review and Meta-Analysis.” *Clinical Endocrinology*, vol. 88, no. 4, 2018, pp. 575–584., doi:10.1111/cen.13550.

39. Pop, Victor J., et al. “Maternal Hypothyroxinaemia during Early Pregnancy and Subsequent Child Development: a 3-Year Follow-up Study.” *Clinical Endocrinology*, vol. 59, no. 3, 2003, pp. 282–288., doi:10.1046/j.1365-2265.2003.01822.x.

40. Kooistra, L. “Neonatal Effects of Maternal Hypothyroxinemia During Early Pregnancy.” *Pediatrics*, vol. 117, no. 1, 2006, pp. 161–167., doi:10.1542/peds.2005-0227.

41. Hennessey, James V. “The Emergence of Levothyroxine as a Treatment for Hypothyroidism.” *Endocrine*, vol. 55, no. 1, 2016, pp. 6–18., doi:10.1007/s12020-016-1199-8.

42. Jonklaas, Jacqueline, et al. “Guidelines for the Treatment of Hypothyroidism: Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement.” *Thyroid*, vol. 24, no. 12, 2014, pp. 1670–1751., doi:10.1089/thy.2014.0028.

43. Clyde, Patrick W., et al. “Combined Levothyroxine Plus Liothyronine Compared With Levothyroxine Alone in Primary Hypothyroidism.” *Jama*, vol. 290, no. 22, 2003, p. 2952., doi:10.1001/jama.290.22.2952.

44. Duntas, Leonidas H., and Jacqueline Jonklaas. “Levothyroxine Dose Adjustment to Optimise Therapy Throughout a Patient’s Lifetime.” *Advances in Therapy*, vol. 36, no. S2, 2019, pp. 30–46., doi:10.1007/s12325-019-01078-2.

45. Alexander, Erik K., et al. “2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum.” *Thyroid*, vol. 27, no. 3, 2017, pp. 315–389., doi:10.1089/thy.2016.0457.

46. Yassa, Leila, et al. “Thyroid Hormone Early Adjustment in Pregnancy (The THERAPY) Trial.” *Obstetrical & Gynecological Survey*, vol. 65, no. 11, 2010, pp. 687–688., doi:10.1097/ogx.0b013e3182022046.

47. Rao, Meng, et al. “Effect of Levothyroxine Supplementation on Pregnancy Loss and Preterm Birth in Women with Subclinical Hypothyroidism and Thyroid Autoimmunity: a Systematic Review and Meta-Analysis.” *Human Reproduction Update*, vol. 25, no. 3, 2019, pp. 344–361., doi:10.1093/humupd/dmz003.

48. Li, Jia, et al. “Effects of Levothyroxine on Pregnancy Outcomes in Women With Thyroid Dysfunction: A Meta-Analysis of Randomized Controlled Trials.” *Alternative Therapies in Health and Medicine*, vol. 23, no. 2, Mar. 2017, pp. 48–58.
49. Velkeniers, B., et al. “Levothyroxine Treatment and Pregnancy Outcome in Women with Subclinical Hypothyroidism Undergoing Assisted Reproduction Technologies: Systematic Review and Meta-Analysis of RCTs.” *Human Reproduction Update*, vol. 19, no. 3, 2013, pp. 251–258., doi:10.1093/humupd/dms052.
50. Zhou, Min, et al. “Effects of Thyroid Diseases on Pregnancy Outcomes.” *Experimental and Therapeutic Medicine*, 2019, doi:10.3892/etm.2019.7739.
51. Casey, B M, et al. “Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy.” *New England Journal of Medicine*, vol. 377, no. 7, 2017, pp. 700–701., doi:10.1056/nejmc1707415.
52. Spencer, Laura, et al. “Screening and Subsequent Management for Thyroid Dysfunction Pre-Pregnancy and during Pregnancy for Improving Maternal and Infant Health.” *Cochrane Database of Systematic Reviews*, 2015, doi:10.1002/14651858.cd011263.pub2.
53. Lazarus, John H, et al. “Antenatal Thyroid Screening and Childhood Cognitive Function.” *New England Journal of Medicine*, vol. 366, no. 17, 2012, pp. 1640–1641., doi:10.1056/nejmc1202720.
54. Howdeshell, Kembra L. “A Model of the Development of the Brain as a Construct of the Thyroid System.” *Environmental Health Perspectives*, vol. 110, no. suppl 3, 2002, pp. 337–348., doi:10.1289/ehp.02110s3337.

55. Bayer, S A, et al. “Timetables of Neurogenesis in the Human Brain Based on Experimentally Determined Patterns in the Rat.” *Neurotoxicology*, vol. 14, no. 1, 1993, pp. 83–144.

56. Negro, Roberto, and Alex Stagnaro-Green. “Clinical Aspects of Hyperthyroidism, Hypothyroidism, and Thyroid Screening in Pregnancy.” *Endocrine Practice*, vol. 20, no. 6, 2014, pp. 597–607., doi:10.4158/ep13350.ra.

57. Thung, S.f., et al. “The Cost-Effectiveness of Universal Screening in Pregnancy for Subclinical Hypothyroidism.” *Obstetric Anesthesia Digest*, vol. 30, no. 4, 2010, pp. 236–237., doi:10.1097/01.aoa.0000389616.01628.33.

58. Taylor, Peter N., et al. “Thyroid Screening in Early Pregnancy: Pros and Cons.” *Frontiers in Endocrinology*, vol. 9, 2018, doi:10.3389/fendo.2018.00626.

59. Stagnaro-Green, Alex, et al. “Universal Screening for Thyroid Disease during Pregnancy Should Be Performed.” *Best Practice & Research Clinical Endocrinology & Metabolism*, 2019, p. 101320., doi:10.1016/j.beem.2019.101320.

60. Taylor, Peter N, et al. “Should All Women Be Screened for Thyroid Dysfunction in Pregnancy?” *Women's Health*, vol. 11, no. 3, 2015, pp. 295–307., doi:10.2217/whe.15.7.