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Correlation Between Thyroid Levels and Adverse Pregnancy Outcomes in Women: A Review

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Abstract

The second most prevalent endocrine diseases during pregnancy are thyroid Disorders, which include hyperthyroidism, Maternal thyroid hormones severe essential roles in fetal brain development (gestational week 1-20). Thyroid diseases curing pregnancy several affect subclinical hyperthyroidism, hypothyroidism, and subthyroxinemia. Pregnancy outcomes and neuropsychological development of the offspring**.** The result is either an increase in serum T4level or an amplification of TSH secretion. Ealy detection and intervention can help lower the chance of unfavorable pregnancy outcomes and enhance the m other's and the child's health. To completely comprehend the mechanisms underlying the link between thyroid disease ad pregnancy problems. Nonlinear associations were observed between preconceptionally TSH levels and pregnancy outcomes. Subclinical thyroid apparent was associated with an increased risk of adverse pregnancy outcomes prior to conception.

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العلاقة بين مستويات الغدة الدرقية ونتائج الحمل السلبية لدى النساء

حنين سعيد محسن، عتاب عبد الامير، سجى حيدر، كرار محمود شاكر

الخلاصة

ثاني أكثر الأمراض الغدد الصماء انتشارًا أثناء الحمل هي اضطرابات الغدة الدرقية، والتي تشمل فرط نشاط الغدة الدرقية، وهورمونات الغدة الدرقية الأمومية التي تلعب دورًا أساسيًا في نمو دماغ الجنين (الأسبوع الحملي 1-20). تؤثر أمراض الغدة الدرقية أثناء الحمل على فرط نشاط الغدة الدرقية دون السريري، وقصور الغدة الدرقية، ونقص هرمون الغدة الدرقية. نتائج الحمل والتطور النفسي العصبي للجنين. النتيجة هي إما زيادة في مستوى هرمون الغدة الدرقية في المصل أو تضخيم إفراز هرمون الغدة الدرقية. يمكن أن يساعد الاكتشاف المبكر والتدخل في تقليل فرصة حدوث نتائج حمل غير مواتية وتعزيز صحة الأم والطفل. لفهم الآليات الكامنة وراء الارتباط بين مرض الغدة الدرقية ومشاكل الحمل. لوحظت ارتباطات غير خطية بين مستويات هرمون TSH قبل الحمل ونتائج الحمل. ارتبط ضعف الغدة الدرقية دون السريري بزيادة خطر حدوث نتائج حمل سلبية قبل الحمل.

1. Introduction

Endocrinology, obstetrics, and gynecology have all examined thyroid disorders during pregnancy in great detail (Osuga *et al.*, 2019). Thyroid hormones were found in the umbilical blood of mothers who had a defect in thyroid hormone synthesis, indicating that the placenta is the route by which free thyroxine (also known as free T4 or fT4) is transferred. During the first 20 weeks of pregnancy, maternal thyroid hormones are crucial for the development of the fetus's brain (Pickard *et al.*, 1999; Moog *et al.*, 2017). Pregnancy-related thyroid disorders have a significant impact on the development of the offspring's neuropsychology and pregnancy outcomes (Pickard *et al.*, 1999; Moog *et al.*, 2017; Osuga *et al.*, 2019). Fetal neurodevelopmental abnormalities are caused by changes in thyroid stimulating hormone (TSH) secretion or an increase in serum T4 levels. Thyroid hormones appear to have a role in the regulation of early pregnancy and placentation (A. *et al.*, 2016; Alemu *et al.*, 2016). It could help to explain the correlation between preterm birth, gestational hypertension, and hypothyroidism. Maintaining normal energy and lipid metabolism requires adequate thyroid function, and weight gain or lipid abnormalities linked to hypothyroidism may further raise the risk of unfavorable pregnancy outcomes. The correlation between hypothyroidism and gestational diabetes may also be explained by variations in weight and energy metabolism. Due to the reduced sample size, we were able to observe higher risks of pregnancy outcomes even among women with hypothyroidism who were of normal weight, but less precisely. In unselected groups of pregnant women, Thyroperoxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) reported frequencies positive varies from 2% to 17%, contingent on a number of parameters (D Glinoer *et al.*, 1994; Chen *et al.*, 2023).

Research on thyroid autoimmunity in pregnant women from various ethnic backgrounds has shown inconsistent findings. While some studies have demonstrated that ethnicity has a role in thyroid autoimmune, others have not supported this conclusion (Ghassabian *et al.*, 2012; Medenica *et al.*, 2015; Unuane and Velkeniers, 2020).

The physiological decline in thyroid autoantibodies that occurs during pregnancy may help to explain the broad range in the prevalence of thyroid autoimmunity in the pregnant population, and varied antibody testing times during gestation. In fact, important research conducted in the 1990s by Glinoer et al (Balucan, Morshed and Davies, 2013). Thyroid antibody titers did, in fact, decline (on average, by 60%) during gestation and tended to become undetectable in the third trimester, according to critical investigations conducted by Glinoer et al. in the 1990s (Balucan, Morshed and Davies, 2013). Subsequent research has validated these results on multiple occasions, suggesting that the gestational age at which thyroid autoantibody measures are acquired has a direct bearing on their diagnostic accuracy. Since women whose TPOAbs are negative nevertheless have a higher risk of thyroid dysfunction, this idea is crucial for the diagnosis and treatment of thyroid disease during pregnancy and may call for closer monitoring.Dietary iodine consumption appears to be another factor contributing to the wide difference in thyroid antibody positive prevalence among pregnant women. Thyroid autoimmunity appears to be more common in areas with adequate or more than enough iodine intake than in areas with insufficient iodine, according to epidemiological research conducted on non-pregnant populations (De Leo and Pearce, 2018; Bogović Crnčić *et al.*, 2023; Joshi *et al.*, 2024). Furthermore, once iodine prophylactic measures were put into place, there was indications of increased thyroid autoimmunity (Bogović

Crnčić *et al.*, 2023). Some of the processes postulated to explain iodine-induced thyroid autoimmunity include the increased immunogenicity of a strongly iodinated thyroglobulin, the toxic impact of iodine on thyroid cells, and the direct stimulation of immune cells by iodine. Recent cross-sectional study on a large cohort of expecting moms regarding gestation from an area with sufficient iodine intake discovered that the incidence of TPOAb positive was considerably greater in women who consumed the most and least iodine relative to those who were pregnant and had access to enough iodine. Initiatives (Chen *et al.*, 2021, 2022).

2. Thyroid Physiology in Pregnancy

The thyroid gland secretes tetraiodothyronine (T4), or thyroxine, about 94% of thyroid hormones, and triiodothyronine (T3), or about 6% of thyroid hormones Fig.1. The plasma T4toT3 ratio is roughly4:1 due to the peripheral transformation of T4 toT3, wich is more biologically active, which is catalytically converted to T3 by means of deiodinases within peripheral tissues. Peripherally generated T3 also replenishes the bloodstream to some extent. The majority of T4 and T3 are attached to serum carrier proteins, primarily thyroxine-binding globulin (TBG). However, because free hormones are available for active transport, these are the ones that can enter cells and function, specifically free T4 (fT4) and free T3 (fT3) (Luongo *et al.*, 2013; Abdalla and Bianco, 2014).

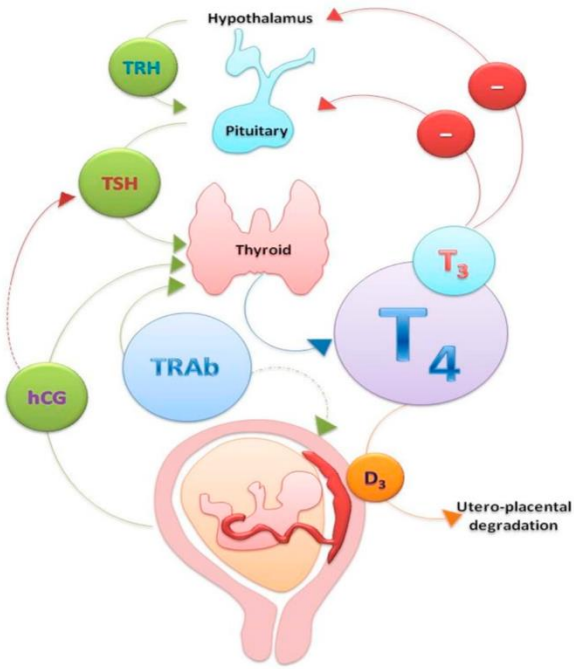

Figure 1: Hypothalamic-Pituitary-Thyroid Axis and Pregnancy (Luongo *et al.*, 2013; Abdalla and Bianco, 2014)

2.1.Thyroid Function Changes in Pregnant Women

Thyroid function changes in pregnant women are caused by a number of factors, including elevated metabolic demands, elevated serum TBG concentrations, stimulation of the TSH receptor by human chorionic gonadotropin (hCG), increased thyroxine transfer from mother to fetus, and increased intraplacental breakdown of T4 and T3 (due to placental expression of deiodinase 3). After circulatory TBG levels rise by 50% by 6–8 weeks of gestation, total T4 and T3 concentrations increase by 50% as well; their levels peak at about 16 weeks of gestation (Tingi *et al.*, 2016; Черенько and Черенько, 2019; Visser and Peeters, 2020).

During pregnancy, maternal TSH typically remains within normal ranges, but it may decrease in the first trimester due to elevated hCG levels and this hormone's cross-reactivity with TSH receptors. Both hCG and TSH are glycoprotein hormones that share an α subunit and have significant homology between their β subunits. As a result, hCG has a minimal ability to stimulate the thyroid (Lazarus, 2011; McNeil and Stanford, 2015). After fertilization, hCG levels rise and peak between 10 and 12 weeks of pregnancy. This causes a rise in total serum T4 and T3 concentrations, which in turn causes a decrease in TSH and thyrotropin-releasing hormone (TRH) levels due to negative feedback (Brown *et al.*, 2023). One physiological finding that arises from this hormonal interaction is a biochemical picture of subclinical hyperthyroidism. Later in pregnancy, a drop in hCG secretion causes a fall in fT4 and fT3 concentrations in the blood, which in turn causes TSH levels to return to normal. Usually between weeks 14 and 18 of pregnancy, thyroid hyperfunction and any associated symptoms disappear as hCG production declines. The assay-specific TSH reference ranges for each trimester should preferably be calculated from the local population in iodine-sufficient areas, and the pregnant women selected for these computations should be negative for thyroid and euthyroid antibodies (Cignini *et al.*, 2012; Franco-Herrera *et al.*, 2018; Petca *et al.*, 2023).

2.2.Thyroid Function Tests in Pregnancy

2.2.1. How Do Thyroid Function Tests Change During Pregnancy?

To meet the challenge of increased metabolic needs during pregnancy, the thyroid adapts through changes in thyroid hormone economy and in the regulation of the hypothalamic-pituitary-thyroid axis (Soldin, 2011; Stagnaro-Green *et al.*, 2011; Zhou *et al.*, 2019). Consequently, thyroid function test results of healthy pregnant women differ from those of healthy nonpregnant women. This calls for pregnancy-specific and ideally trimester-specific reference intervals for all thyroid function tests but in particular for the most widely applied tests, TSH and free T_4 (FT_4). Following conception, circulating total T_4 (TT_4) and T_4 binding globulin (TBG) concentrations increase by 6–8 weeks and remain high until delivery. Thyrotropic activity of hCG results in a decrease in serum TSH in the first trimester. Therefore, during pregnancy, women have lower serum TSH concentrations than before pregnancy, and frequently TSH is below the classical lower limit of 0.4 mIU/L.Most studies also report a substantial decrease in serum FT_4 concentrations with progression of gestation. Serum FT_4 measurements in pregnant women are complicated by increased TBG and decreased albumin concentrations that can cause immunoassays to be unreliable. Therefore, the analytical method

used for serum FT_4 analysis should be taken into consideration (Soldin, 2006; Zhou *et al.*, 2019; Bohn and Adeli, 2022).

2.2.2. What Is the Normal Range for TSH In Each Trimester?

There is strong evidence in the literature that the reference range for TSH is lower throughout pregnancy; i.e., both the lower normal limit and the upper normal limit of serum TSH are decreased by about 0.1–0.2 mIU/L and 1.0 mIU/L, respectively, compared with the customary TSH reference interval of 0.4–4.0 mIU/L of nonpregnant women. The largest decrease in serum TSH is observed during the first trimester and is transient, apparently related to hCG levels, which are highest early in gestation. Serum TSH and its reference range gradually rise in the second and third trimesters, but it is noteworthy that the TSH reference interval remains lower than in nonpregnant women (Soldin, 2011; Alexander *et al.*, 2017). Since hCG concentrations are higher in multiple pregnancies than in singleton pregnancies, the downward shift in the TSH reference interval is greater in twin pregnancies than in singleton pregnancies. In a study of 63 women with hCG concentrations >200,000 IU/L, TSH was suppressed (≤0.2 mIU/L) in 67% of women, and in 100% of women if hCG concentrations were >400,000 IU/L (Soldin, 2011; Stagnaro-Green *et al.*, 2011; Zhou *et al.*, 2019).

2.3.Thyroid Disorders in Pregnancy

Hypothyroidism: Discuss how low thyroid hormone levels affect pregnancy outcomes. Include complications such as preeclampsia, miscarriage, preterm birth, low birth weight, and cognitive impairments in children. Hyperthyroidism: Review the risks associated with elevated thyroid levels, including preterm delivery, fetal growth restriction, and stillbirth (A. *et al.,* 2016; Alemu *et al.,* 2016).

2.4. Thyroid - stimulating hormone receptor antibodies

The TSHR is a G-protein coupled receptor and the main regulator of the thyroid gland. Signaling through the TSHR via the stimulation of cytosolic second messengers promote the synthesis of thyroid hormones and the growth of the thyroid follicular cell (Chin, Jones and Kingham, 2007; Tagoe, Zezon and Khattri, 2012).The natural ligand of the TSHR is the TSH which binds to multiple sites in the extracellular domain. However, there are other hormones with the ability to bind to the receptor (e.g., luteinizing hormone and human chorionic gonadotropin). This receptor is expressed predominantly on the surface of thyroid cells. Nevertheless, TSHR mRNA is also found in other tissues, e.g., adipocytes, cardiac muscle cells, pituitary cells, bone cells, and fibroblasts, though its exact function on these cells is not fully understood.TRAb are usually part of the IgG1 subclass. The binding site of the TRAb is the region of the receptor to which TSH binds, which consists of a binding pocket-encompassing leucine-rich repeat region. They can be functionally classified into three categories: stimulating, blocking, and neutral (Chin, Jones and Kingham, 2007; Tagoe, Zezon and Khattri, 2012; Rayman, 2019; Vargas-Uricoechea, 2023).

2.5.Stimulating Autoantibodies

These antibodies were first identified by their prolonged thyroid – stimulating activity when serum from GD patients was transferred into animals. Initially, this finding was called long – acting thyroid stimulators. Stimulating antibodies

are those that bind to the TSHR and induce conformational changes that activate cytosolic second messengers and promote the synthesis of thyroid hormones and thyroid growth. By mimicking the action of the TSH, these autoantibodies compete with the hormone for the binding site on the receptor. Stimulating antibodies constitutes the hallmark of GD pathophysiology (Davies *et al.*, 2005; Arai *et al.*, 2017; Liang *et al.*, 2023). The development of the fetal brain and the early pregnancy thyroid hormones of the mother. Though there is still much to learn, our knowledge of the potential function of thyroid hormones in brain development has grown over the past few decades and helped to reconcile conflicting theories. Despite the highly effective uterine-placental "barrier," which is required to prevent potentially harmful amounts of free T4 and T3 from reaching fetal tissues before they are needed for development, thyroid hormones of maternal origin are present in the fetal compartment. While FT4 in fetal fluids quickly rises to adult levels and is influenced by the mother's supply of T4, T3 stays low during pregnancy. Four weeks after conception, FT4 is found in fetal fluids, and its levels gradually rise to biologically significant levels. T3, which is partially coupled to particular nuclear receptor isoforms, is produced from T4 in the cerebral cortex and reaches adult levels by mid-gestation. Since the needs of thyroid hormone-sensitive genes in various brain parts vary and change over time, iodothyronine deiodinases play a crucial role in the spatial and temporal regulation of T3 bioavailability (Sheila, 2011; Eng and Lam, 2020).

2.6. Relationship Between Early and Late Pregnancy Birth Weight and Maternal Thyroid Hormones

This was a big prospective study conducted at a hospital to examine the relationship between birth weight and maternal thyroid function. From early to late pregnancy, a considerably larger birth weight was linked to consistently poorer thyroid function in the mother. A 40% increased risk of LGA and a birth weight that was ≤0.7 SD greater were linked to low FT4 levels in the early stages of pregnancy that persisted in being low in the late stages. The relationship between maternal thyroid hormones in the first and third trimesters of pregnancy and the birth weight of female babies was also significantly influenced by fetal sex. We found that the prevalence of SGA and LGA in our study population was 3.6% and 13.3%, respectively. According to the INTERGROWTH-21st standard, which was established in a 10-country maternal population survey, this result is comparable to the variation in SGA or LGA rate (SGA, 4.7%; LGA, 13.2%) (Zhang *et al.*, 2019; Ding *et al.*, 2021). In this study, negative effects on birth weight were linked to both high and low maternal FT4 levels. These results are consistent with a prior study that found an inverted U-shaped relationship between maternal FT4 and gray matter volume and child IQ. This implies that rather than the periphery of the normal range, the ideal aim for levothyroxine treatment would be closer to the middle of the reference range. Although thyroid hormones are essential for fetal growth in the early stages of life, the availability of these hormones in the early stages of pregnancy is entirely dependent on placental transfer from mother to fetus. The fetus only partially depends on the thyroid hormones of the mother after the establishment of fetal thyroid function in the second half of pregnancy (Korevaar, Tiemeier and Peeters, 2018; Gui, Xu and Zhang, 2020; Ding *et al.*, 2021). With an effect estimate difference of about 0.4 SD, a lower FT4 concentration in late pregnancy was more strongly associated with birth weight than it was in early pregnancy. According to our findings, there was an L-shaped correlation between

birth weight and the FT4 concentrations in the early stages of pregnancy. However, the L-shaped connection vanished and changed to a linear shape when FT4 levels were assessed in late pregnancy, indicating that FT4 levels within the entire range have a sustained. Early pregnancy maternal FT4 concentrations more than 15 pmol/L are thought to have a negligible impact on birth weight. Thyroid hormones may be the cause since they are essential for fetal cell differentiation and for initiating early prenatal organ development processes. There is currently no proof that these women will benefit from treatment, despite the fact that we have shown that thyroid function, even when it is within the normal range, affects birth weight or has a negative impact on outcomes related to birth weight. However, in the case of high-normal FT4 levels, the possible benefits of antithyroid drug therapy probably outweigh the hazards. According to these results, pregnant patients on LT4 medication who have normal or suppressed TSH but high or low FT4 may benefit from a dosage adjustment. For values that are outside the normal range, it may also be helpful to follow up with at least one further thyroid function test. Lower FT4 levels may result in greater blood glucose levels under these circumstances, which raises the amount of glucose transferred to the fetus during the placenta and causes the fetus to gain weight. Another possible explanation is that hyperthyroidism speeds up the breakdown of proteins and lipids, causing pregnant women to experience a persistent shortage of energy, which has been linked to a lower birth weight (Korevaar, Tiemeier and Peeters, 2018; Gui, Xu and Zhang, 2020; Ding *et al.*, 2021).

Intriguingly, we discovered that fetal LGA and higher birth weight were associated with lower maternal FT4 levels (<10th percentile) in both the first and third trimesters of pregnancy. According to this research, the fetus receives maternal FT4 trans-placentally in order to sustain fetal development throughout the third trimester. Furthermore, it might have an impact on how the fetal hypothalamic-pituitary-thyroid axis develops in the early stages of pregnancy. Although the possible processes are still unknown, persistently reduced FT4 levels in late pregnancy may have a greater impact on the fetal hypothalamic-pituitary-thyroid axis, resulting in even higher birth weight and LGA. The effect of maternal TSH on fetal weight and growth, however, varied. Only in late pregnancy did we find a substantial correlation between TSH and SGA; in early pregnancy, there was none. We created an interactive heat map that demonstrated that there was no discernible effect of TSH on birth weight during the first or third trimester of pregnancy. In a similar vein, additional research found no connection between TSH and birth weight during the first or third trimester. The fact that TSH cannot directly contribute to fetal weight gain because it cannot cross the placenta may help to explain this outcome. More precise information for clinical recommendations might be available through future interactive analysis (Alvarez-Pedrerol *et al.*, 2009; Güdücü *et al.*, 2013; Zhou *et al.*, 2020; Lyu *et al.*, 2022).

This study demonstrates that during pregnancy, T3 affects birth weight. Whether maternal T3 truly reaches the placenta is still unknown. One thyroid hormone that has a direct biological impact is FT3. High FT4 to FT3 conversion rates brought on by activating deiodinases result in low serum FT4 levels and high FT3 levels. Elevated FT3 levels directly contribute to the growth of the fetus by stimulating the fetus's oxygen intake and having anabolic effects on its metabolism. According to a prior study, pregnant women's gestational weight increases and FT3 levels are positively correlated (Hoermann *et al.*, 2023).

Although it is unclear how T3 influences fetal weight, it has also been observed that increased FT3 levels are linked to neonatal obesity (Hoermann *et al.,* 2023). It's interesting to note that many women using levothyroxine have low FT3. According to the current study's findings, this amount may have a detrimental impact on the birth weight of the child. However, a modestly increased risk of LGA may be linked to maternal hypothyroidism that is appropriately treated during pregnancy. It runs counter to what the links for T3 in the current investigation would imply. But the latter is more likely to be mediated by gestational diabetes mellitus. There is typically no increased risk of adverse pregnancy outcomes for women who take levothyroxine to manage their hypothyroidism. However, the FT3 data from this study are inadequate for a number of women, and further investigation is needed to look at the relationship between FT3 during pregnancy and birth weight (Zhang *et al.,* 2022; Hoermann *et al.,* 2023; Huang *et al.,* 2024). With stronger interacting effects, sexual dimorphism seems to be compatible with the link between fetal growth and maternal thyroid metabolism. Given that maternal TSH levels were more strongly correlated with birth weight in female newborns than in male infants, we discovered a sex-specific variation in the relationship between TSH/FT4 levels and birth weight. High levels of human chorionic gonadotropin stimulated the thyroid in recent European investigations to guarantee sufficient thyroid hormone availability for the growing fetus. The current study also found that higher fetal growth in female fetuses, but not in male fetuses, was linked to high human chorionic gonadotropin concentrations in the late first trimester (Shields *et al.,* 2011; Korevaar *et al.,* 2016; Zhang *et al.,* 2022; Jiang *et al.,* 2023).

Thyroid function physiological changes in both the mother and the fetus during pregnancy.

In addition to many other aspects of pregnancy and fetal growth and development, thyroid hormones (TH) are crucial for the fetus's and the newborn's brain development. In humans, fetal illness, including a high rate of mental retardation, can result from thyroid gland dysfunctions such as hypothyroidism and thyrotoxicosis, which can also have an impact on the mother's health both before and after birth. After several months of pregnancy, the fetal thyroid gland starts to synthesize THs and concentrate iodine. Significant fetal brain growth occurs well beyond the first trimester, even though the mother is the only source of TH up to this point, which is crucial for fetal brain development. Preeclampsia, early labor, fetal death, low birth weight, and intellectual disability in the children are among the pregnancy issues that have been linked to the mother's obvious thyroid failure throughout the first half of her pregnancy(Shields *et al.,* 2011; Korevaar *et al.,* 2016) . The final phases of fetal brain differentiation and development, such as synaptogenesis, dendritic growth, axon myelination, and neuronal migration, are where THs most significantly impact the development. In the prenatal brain, TH receptors are widely distributed and present before the fetus can produce TH. Although significant progress has been achieved, evidence has shown that determining the molecular targets for TH action in the developing brain is difficult (Shields *et al.,* 2011; Stenzel and Huttner, 2013).

2.7.Mechanisms of Physiological Changes of Thyroid Function in Pregnancy

As early as the first trimester, the hormone β-HCG, which has some structural similarities to thyroid-stimulating hormone (TSH), begins to stimulate the thyroid. Additionally, thyroid-binding globulin (TBG) levels in the blood are increased by two to three times during pregnancy due to estrogen. A few weeks after conception, serum levels of TBG, one of the several proteins that carry TH in the blood with a high affinity for thyroxine (T4), rise and plateau throughout

the mid-gestational period. Increased hepatic synthesis of TBG and estrogen-mediated maintenance of TBG sialylation, which extends the half-life from 15 minutes to 3 days to fully sialylated TBG, are the two mechanisms underlying this rise in TBG (Cignini *et al.*, 2012). Because elevated TBG causes lower quantities of free T4, the pituitary secretes more TSH, which in turn causes greater production and TH secretion. Increased TBG synthesis ultimately results in a significant rise in total T4 and triiodothyronine (T3) levels by forcing a new equilibrium between free and bound THs. The increased need for THs is attained by around week 20 of pregnancy and continues until the baby is born (Alemu *et al.*, 2016). The fetus's draw off of maternal iodide and the kidney's notable rise in iodide clearance during pregnancy both contribute to the increased need for iodine, which reflects alterations in iodine metabolism, a crucial prerequisite for TH synthesis. Increased glomerular filtration and lower renal tubular absorption during pregnancy lead to an increase in iodine excretion in the urine. Relative iodine deficit is also a result of the active transfer of maternal iodine to the feto-placental unit. The impact of human placenta-secreted HCG is the other element. The hypothalamus pituitary thyroid feedback system's normal function is overridden by thyroid stimulation in response to the thyrotropic activity of HCG (Glinoer, 1997).

Increased glomerular filtration and lower renal tubular absorption during pregnancy lead to an increase in iodine excretion in the urine. Relative iodine deficit is also a result of the active transfer of maternal iodine to the feto-placental unit. The impact of human placenta-secreted HCG is the other element. The hypothalamus pituitary thyroid feedback system's normal function is overridden by thyroid stimulation in response to the thyrotropic activity of HCG. There is substantial maternal TH transfer across the placenta, according to recent data from multiple species, and the placenta contains deiodinases that can change T4 into T3. Because pregnant women and infants are the population groups most at risk for illness and death, protecting them is a top focus in health care. One of the most frequent pregnancy problems, thyroid dysfunction greatly increases the morbidity and death rates for both the mother and the fetus. Thyroid disorders and associated complications during pregnancy receive little attention or knowledge. Thus, evaluating the extent of thyroid dysfunction in both the mother and the fetus as well as the complications that result from it during pregnancy was the goal of this review (Shields *et al.*, 2011; Korevaar *et al.*, 2016; Zhang *et al.*, 2022; Jiang *et al.*, 2023).

2.8.Hyperthyroidism's Effects on The Health of The Mother and Fetus

It is uncommon for elevated TH levels to complicate pregnancy, but in roughly 2 out of 1000 pregnancies, a potentially serious problem arises. Congestive heart failure, preeclampsia, elevated blood pressure in the latter stages of pregnancy, thyroid storm, miscarriage, early birth, and low birth weight can all result from uncontrolled hyperthyroidism during pregnancy. Newborns with hyperthyroidism may have irritability, poor weight gain, early closure of the soft spot in the skull, an enlarged thyroid that can press on the windpipe and obstruct breathing, and a fast heartbeat, which can culminate in heart failure. Due to the trans-placental transfer of stimulatory TSHRAb, fetal and neonatal hyperthyroidism may arise from autonomous TH synthesis and untreated maternal hyperthyroidism (Zimmerman and Gan-Gaisano, 1990; Calabria, 2018). Approximately 1% of babies delivered to women with GD develop clinical neonatal hyperthyroidism. Infants of mothers with Graves' disease may also occasionally exhibit

neonatal hypothyroidism; this condition may be brought on by the pituitary-thyroid axis being suppressed by the transfer of maternal T4 or by the transplacental transfer of circulating maternal anti-thyroid medications. Untreated hyperthyroidism can lead to thyroid storm, the most severe form of the condition. It can be brought on by illness, trauma, surgery, or diabetic ketoacidosis (Fetene, Betts and Alati, 2017; Biondi, Kahaly and Robertson, 2018; Ahn and Yi, 2023). Another rare side effect of hyperthyroidism is thyrotoxic periodic paralysis. Acute muscular weakness and hypokalemia are two of its reversible symptoms. Hypokalemia, which results from a transcellular shift rather than a complete body loss of potassium, triggers episodes of periodic paralysis (Biondi, Kahaly and Robertson, 2018).

2.9. Changes in Thyroid Function During Pregnancy

From the start of pregnancy, the thyroid gland experiences physiological changes, including an increase in size and vascularity. Because it resembles thyroid-stimulating hormone (TSH), human chorionic gonadotropin beta (β-HCG) activates the thyroid gland from the first trimester. Pregnant women have lower TSH levels than non-pregnant patients, which can be explained by the thyrotropic activity of β-HCG, which also lowers TSH levels in the first trimester of pregnancy. Around the same time as the TSH value reaches its lowest point, the maximum level of hCG is reached between weeks 8 and 10 of pregnancy, after which it declines and plateaus until term (McNeil and Stanford, 2015).

Another factor contributing to the changes in thyroid hormones during pregnancy is the elevated levels of maternal estrogen, which cause a significant rise in the amount of thyroxine binding globulin (TBG) in the blood, increasing thyroxine (T4) by as much as 50%. The free form of T4 (fT4) is decreased by higher TBG levels because they enhance the binding capacity of T4 [91]. The fundamental process involves a decrease in TBG's plasma clearance and an increase in TBG production by hepatocytes [92]. During the first few weeks of pregnancy, the levels of thyroxine (T4) and triiodothyronine (T3) rise and plateau in the second trimester, when they are 30–100% greater than they were before conception (Cignini *et al.*, 2012).

variations in hCG and thyroid hormone plasma concentrations during pregnancy. Human chorionic gonadotrophin (hCG), thyroid-binding globulin (TBG), thyroxine (T4), and thyroid-stimulating hormone (TSH) are all within the typical reference range for non-pregnant women, which is represented by the orange surface.

A shift in the peripheral metabolism of thyroid hormones during pregnancy is another significant event that impacts the mother's thyroid function. The placental deiodination mechanism is the cause of these changes throughout pregnancy. The fetus is shielded against excessive exposure to maternal thyroid hormones by the uteroplacental deiodination enzymes' main form, D3, which inhibits the activation of T4 and inactivates T3. Early in pregnancy, the minority form of placental deiodinase, D2, is thought to be particularly crucial for preserving the intraplacental level of T3, which is necessary for trophoblast growth. A decrease in maternal iodine deposits is another alteration in thyroid function that happens during pregnancy. This is caused by three factors: increased iodine intake necessary for maternal thyroxine synthesis; increased clearance; and iodine transfer from mother to fetus (Silva, Ocarino and Serakides, 2018).

2.10. Treatment of Hyperthyroidism During Pregnancy

Controlling hyperthyroidism has a direct impact on the outcomes for both the mother and the fetus. Treatment is not necessary for moderate hyperthyroidism during pregnancy, if FT4 is normal but TSH is low. Anti-thyroid drugs are used to treat more severe high TH concentrations. To prevent hypothyroidism in the unborn child, the lowest dose of the drugs should be administered because they can reduce fetal TH synthesis and cross the placenta in trace amounts. Some people may experience negative side effects from the drugs, such as allergic reactions, leucopenia, which can reduce an individual's susceptibility to infection, and in rare instances, liver failure. Consideration should also be given to molar disease, which may result in fulminant hyperthyroidism, especially in women who already have autonomous nodular goiter. However, because it only lasts a few weeks or months and is quickly resolved by removing the diseased trophoblast 96, an uncomplicated hydatidiform mole is now easily detected in the early stages of gestation and will seldom result in severe hyperthyroidism (Özon *et al.*, 2018; Silva, Ocarino and Serakides, 2018; Guo *et al.*, 2022).

2.11. Hypothyroidism

It is the most prevalent pathological TH deficiency, affecting 0.1-0.2% of males and 2% of women. With a predicted frequency of 2-3% for subclinical hypothyroidism and 0.3-0.5% for overt hypothyroidism, it is prevalent throughout pregnancy. The majority of hypothyroidism in pregnant women globally is caused by endemic iodine (I-) deficiency, but in I-adequate regions of the world, Hashimoto's disease is the leading cause of hypothyroidism. Because thyroid disease screening is so common, hypothyroidism can present in a variety of ways, from asymptomatic subclinical detection to overt myxedema, which is infrequently observed. According to the general laboratory and globally accepted standards, the prevalence of subclinical hypothyroidism was 4.3% and 20.8%, respectively, in a cross-sectional investigation by Alkafajei et al (Daniel Glinoer *et al.*, 1994; Klubo-Gwiezdzinska and Wartofsky, 2022). Preterm birth, low birth weight, newborn respiratory distress, poor brain development, intrauterine death, and increased fetal distress are all common outcomes of hypothyroidism.Infants born to euthyroid pregnant women and mothers with thyroid peroxidase (TPO) antibody had significantly smaller head circumferences, lower brain weights, and a lower brain-to-body ratio than those born to mothers with TPO antibody negatives, which is linked to a higher risk of miscarriage and premature deliveries, according to a study also published by Renée et al. and Negro et al. (Daniel Glinoer *et al.*, 1994; Klubo-Gwiezdzinska and Wartofsky, 2022).

2.12. Risk of Hypothyroidism on Fetal and Maternal Well-Being

Hypothyroidism can create some of the same issues as hyperthyroidism. Preeclampsia, anemia, abruption, miscarriage, low birth weight, stillbirth, and infrequently, congestive heart failure can result from untreated hypothyroidism during pregnancy. According to a research by Casey et al., mothers with sub-clinical hypothyroidism had a twofold risk of preterm delivery and a threefold chance of placental abruption.Uncontrolled hypothyroidism, particularly during the first trimester, might impact the baby's growth and brain development because THs are essential for the development of the fetal brain and nervous system. Untreated hypothyroidism during pregnancy can significantly lower a child's IQ, according to a previous study by Haddow et al. (Alemu *et al.*, 2016). Two prospective studies demonstrated that

maternal FT4 was a significant predictor of orientation scores in the first trimester and that persistent hypothyroxinemia at 12 weeks of gestation was linked to an 8–10 point deficit in mental and motor function scores in infant offspring when compared to children of mothers with normal thyroid function. However, additional decreases in maternal FT4 at 24- and 32-weeks' gestation had no effect on the developmental scores (Kooistra *et al.*, 2006; Furnica *et al.*, 2017).

3.Conclusion

Thyroid abnormalities are known to be linked to issues for both the mother and the fetus during pregnancy as well as postpartum. sequelae. Though there is much discussion on the relationship between thyroid function during pregnancy and outcomes for both the mother and the fetus, there are still a few aspects that need to be made clear. In individuals with overt hyperthyroidism, ADT therapy is crucial, but in those with subclinical hyperthyroidism, it doesn't seem to be essential. Starting LT4 substitutive medication as soon as feasible is highly advised for pregnant women who have just been diagnosed with overt hypothyroidism. Thinks should be taken into account in cases of subclinical hypothyroidism; hypothyroid women who are currently receiving LT4 treatment need to start their pregnancies with a dosage increase of 30–50%. In this research, we attempted to assess potential preventative measures and appropriate care techniques to steer clear of an adverse outcome for mother and child. To elucidate the role of LT4 therapies in individuals with positive thyroid antibodies and subclinical hypothyroidism, more research is necessary. Different studies have showed that thyroid dysfunction is common in pregnancy. The major causes for this dysfunction is hormonal and metabolic changes during pregnancy leading to profound alterations of the biochemical parameters of the thyroid function. Understanding the normal physiological adaptation of the pituitary-thyroidal axis in pregnancy enables us to manage cases of thyroid dysfunction. Uncorrected thyroid function in pregnancy has adverse effects on fetal and maternal well-being. Thyroid disease usually affects females of the reproductive age group and caring for these women during pregnancy requires careful monitoring of both the mother and the fetus. Appropriate diagnosis, care and management of thyroid dysfunction in the pre-pregnancy, pregnancy and post-pregnancy periods are important to minimize the risk of complications, long-term effects of the mother and fetus.

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