Review Article

iMedPub Journals
www.imedpub.com

Critical Care Obstetrics and Gynecology
ISSN 2471-9803

2021
Vol.7 No.7:44

Hypothyroidism and Pregnancy

Mario Enmanuel López Marenco*, José Antonio Hernández Pacheco and Ángel Nares Torices

Intensive Therapy Department, National Institute of Perinatology, Mexico

*Corresponding author:
Mario Enmanuel López Marenco

drlopez89@gmail.com

Intensive Therapy Department, National Institute of Perinatology, Mexico

Abstract

Pregnancy endocrine disorders during pregnancy. In this regard, maternal thyroid dysfunction can lead to serious complications for the mother and the fetus; such is the case of premature birth, preeclampsia, miscarriage and low birth weight. In addition, the development of the central nervous system of the product may be compromised.

Keywords: Thyroid; Hypothyroidism; Pregnancy; Lodo; Thyroid autoimmunity

Received: October 26, 2021; **Accepted:** November 11, 2021; **Published:** November 20, 2021

Citation: Marenco MEL, Pacheco JAH, Torices ÁN (2021) Hypothyroidism and Pregnancy. Crit Care Obst Gyne Vol.7 No.7:44

Introduction

Epidemiology hypothyroidism

The prevalence of overt maternal hypothyroidism, defined as the elevation of Thyroid Stimulating Hormone (TSH) and the decrease in serum levels of free thyroxine (TL4) outside the specific reference ranges for the trimester is estimated to be between 0-3 and 1.5% in different studies [1-4].

Maternal subclinical hypothyroidism is characterized by an increase in serum TSH levels in the presence of normal levels of thyroid hormone. This has a prevalence of 3.5% to 18%, according to the TSH values used [5-6].

The most frequent cause of primary hypothyroidism in women of reproductive age is chronic autoimmune thyroiditis. However, it can also occur as a result of previous thyroid surgery, goiter secondary to iodine deficiency, treatment with radioactive iodine due to hyperthyroidism, toxic multinodular goiter or thyroid cancer.

Thyroid physiology in the pregnancy and interpretation of the thyroid profile

Anatomy and physiology of the thyroid: The thyroid is constituted predominantly by follicular cells derived from the endoderm, which are responsible for the production of Thyroxine (T4) and 3,5,3'-triiodoThyronine (T3) in a percentage of 94% and 6%. Peripherally, T4 is catalytically converted to T3, the active biological form of thyroid hormones, by deiodinases and a peripherally produced portion of T3 returns to circulation.

Due to this peripheral conversion it is estimated that the plasma ratio of T4: T3 is 4: 1 [7]. It is considered that T4 is a reservoir for the production of T3, since the majority of T3 is produced by conversion of T4 by iodothyronine deiodinases type 1 (D1), which are distributed in all tissues [8].

Both Deiodinase2 (D2) and Deiodinase3 (D3) are expressed in the brain. D3 deactivates T4 by converting it to inverse T3, a metabolically inactive compound, in turn T3 changes in diiodothyronine (T2), while D2 functions to convert T4-T3.

D2 is expressed mainly in the glial cells of several regions of the Central Nervous System (CNS) and plays an important role in its development and function. In particular, deiodinase type 3 is localized in high amounts in the placenta, where it protects the fetus from toxic levels of thyroid hormones by converting T4 into biologically inactive reverse T3 [9,10].

The complex actions of thyroid hormones are initiated by the intracellular binding of T3 to the nuclear receptor after inducing or repressing the expression of target genes [11]. Likewise, they affect cell function through a non-genomic action, which is independent of the nuclear receptor. This action is exerted on the cell membrane with the generation of intracellular second messengers, such as calcium and cyclic Adenosine MonoPhosphate (cAMP). Thyroid hormones play a critical role in the regulation of many physiological processes such as heart rate, blood pressure, lipid metabolism and the progression of atherosclerosis and neural development [12-14].

The production of thyroid hormones is regulated by a negative feed-back circuit in which both the TSH, which is synthesized and secreted from the anterior pituitary gland, and the Thyrotropin-

Releasing Hormone (TRH) generated by the parvocellular neurons of the thyroid gland. Paraventricular nucleus of the hypothalamus. Like TRH, TSH responds, essentially, to the inhibitory actions of T3 and T4; and in a paracrine fashion, somatostatin exerts an effect on TSH secretion [15]. Both mechanisms are physiologically important to regulate cell differentiation and function.

Physiology of fetal thyroid: The thyroid gland contains elements of the three layers of germ cells. Its main components, the follicular cells which derive from a thickening of the endoderm in the midline of the primitive pharynx located between the first and the second branchial arch originated around day 20 to day 22 of the gestational process.

Most of the critical events in thyroid morphogenesis occur within the first 60 days of gestation. Consequently, a large part of the thyroid development anomalies are due to morphogenetic errors occurred in this period of time. The synthesis of fetal thyroglobulin can be detected in 4 weeks to 6 weeks; the synthesis of TRH from 6 weeks to 8 weeks; iodine uptake from 8 weeks to 10 weeks; and the release of TSH with the synthesis of T4 at week 12, being functionally mature until week 18 to week 20 of gestation [16]. This condition the period of organogenesis to the adequate placental transfer of maternal T4.

Thyroid and pregnancy: During pregnancy, an increase of 10% in the volume of the thyroid gland and up to 20% to 40% in populations with iodine deficiency is expected in populations with iodine deficiency. The production of total Thyroxine (T4) and Triiodothyronine (T3) increase by almost 50%, which can condition an increase in iodine needs.

TSH exhibits a decrease in secretion, especially during the first trimester, due to cross-stimulation by placental Human Chorionic Gonadotropin (HCG). Although suppressed TSH is expected, the upper limits of normal TSH during each trimester have not yet been firmly defined. With the increase in estrogen stimulation, serum levels of Thyroxine-Binding Globulin (TBG) increase rapidly in the first trimester, reaching a plateau around the middle of gestation, where TBG remains relatively unchanged until term [17].

Thyroid hormones, likewise, influence the development of the brain through modifications in the expression of participating genes in the coordinated and timely regulation of many development processes: cell proliferation, neurogenesis, differentiation of cell migration, synaptosis and myelination; as well as modifications in the neurochemical environment in the brain [18].

IODO: Due to increased hormone production, renal excretion and fetal consumption, dietary iodine requirements are higher in pregnancy, compared with those reported in non-pregnant women [19].

Women with iodine sufficiency in the pre-gestational period have an adequate body reserve and do not have difficulty adapting to the greater hormonal demand during pregnancy; so that iodine levels remain stable throughout pregnancy [20]. However, in women with deficiency of this element, from mild to moderate, there is a gradual decrease in the biosavailability of iodine from the first to the third trimester of pregnancy [21].

The consequences of maternal dietary deficiency of iodine directly impact the synthesis of maternal and fetal thyroid hormone. The low values of them produce increase in the secretion of TSH, which stimulates the growth of the thyroid, and can generate maternal and fetal goiter. In regions with severe iodine deficiency, this is observed in up to 30% of pregnant women. This deficiency can condition an important cognitive deterioration in the offspring. The maximum expression of these alterations is cretinism, characterized by a profound intellectual deterioration, sensorineural deafness and alterations in motor skills.

Regarding obstetric complications, it has also been associated with an increase in the rates of pregnancy loss, fetal death and increased perinatal and infant mortality. In this sense, there are several recommendations on adequate iodine supplementation in the gestational stage.

The Institute of Medicine of the United States recommends as dietetic targets the daily intake of 150 µg/d of iodine for women with pregnancy wishes; 220 µg/d for pregnant women; and 290 µg/d for lactating women [22]. The World Health Organization (WHO) recommends an intake of 250 µg/d for pregnant and lactating women; similarly, it suggests that a daily iodine intake >500 µg can be harmful [23].

Worldwide, iodine deficiency is the leading cause of preventable intellectual deficits. In this context, universal salt iodization has been the most cost-effective way to increase iodine intake and, therefore improves the prognosis of maternal and child health [24].

Thyroid autoimmunity: Anti-Thyroid Peroxidase (TPOAb) antibodies together with Anti-ThyroGlobulin Antibodies (TGAb) are markers of thyroid autoimmunity and other autoimmune disorders [25,26]. Although a genetic and environmental predisposition has been documented the etiology of these disorders is largely unknown [27]. Autoimmune thyroid disease can cause hypothyroidism and other diseases such as thyroid cancer, although the latter is still debatable [28].

The mechanisms by which antithyroid antibodies may increase the risk of adverse outcomes in pregnant women are unclear. Since TPOAb is a biochemical marker of chronic lymphocytic thyroiditis, pregnant women with positive antibodies may have an increased risk of thyroid dysfunction and complications during pregnancy.

Autoantibodies (TgAb) are present in 2% to 18% of all pregnant women and there is a proportion of women who have Tg antibodies in isolation; however, most studies on thyroid autoimmunity and complications during pregnancy use only TPOAb. The positivity of TPOAb has been linked to thyroid dysfunction during pregnancy and in the post-partum period.

In women with thyroid autoimmunity, hypothyroidism can occur because the ability of the thyroid to increase the production of

hormones is compromised by the stress of pregnancy [29]. In 1994, Glinoer showed that 16% of women with TPOAb positivity developed serum TSH>4 mU/L during pregnancy, despite normal TSH values before pregnancy [30].

Black in 2006 reported similar results [31]. The authors specify that in euthyroid women with positive TPOAb, TSH levels increased as the pregnancy progressed; This increase is established with average values of 1.7 mU/L (week 12) to 3.5 mU/L (term). 19% of women had a TSH value above normal at the end of pregnancy.

Due to the trend in the increase of TSH in this population, close monitoring should be maintained in euthyroid women with the presence of TPOAb. The guidelines of the American Thyroid Association (ATA) suggest the performance of thyroid function tests every 4 weeks, from confirmation of pregnancy to half of it.

TPO antibodies are able to cross the placenta. At the time of delivery, TPOAb levels in umbilical cord blood correlate strongly with maternal concentrations of TPOAb [32]. However, the maternal passage of TPOAb or TgAb is not associated with fetal thyroid dysfunction.

The group of antibodies against TSH receptors (TRAb) includes 2 types of autoantibodies: the thyroid-stimulating immunoglobulin and the thyroid-binding inhibitory immunoglobulin. Thyroid stimulating immunoglobulin binds to TSH receptors and promotes the production of thyroid hormones, which brings with it a state of hyperthyroidism. On the other hand, immunoglobulin inhibiting thyroid binding blocks the binding of TSH to its receptors and generates hypothyroidism. However, the determination of the function of these antibodies is not accessible in most hospital settings and their clinical importance has not been established in large population studies.

Placental barrier: Iodine, HRT, antithyroid drugs, most maternal thyroid hormones, and IgG antibodies cross the placenta; but there is no placental transport of TSH. In this sense, the placenta plays a key role in regulating the exchange of products between the mother and the fetus.

The amount of placental transfer of LT4 and the consequent effect on fetal thyroid function vary widely. Under normal circumstances, the human placenta has a moderate permeability for T4, due to the predominance of placental Deiodinase 3 (D3), which inactivates most of the maternal thyroid hormone. The iodide released by this process can be used as a substrate for the synthesis of fetal thyroid hormone. The placenta also expresses some D2 (an activating deiodinase), but the placental activity of D3 is approximately 200 times greater than that of D2. The placenta also expresses a range of transporters of thyroid hormones, binding proteins, sulfotransferases and sulfaases.

The balance of all these enzymatic processes determines the amount of transfer of the T4 produced [33]. This transport generates a maternal fetal transit of thyroid hormones that protects the neurological development of the product.

Iodine is actively transported through the placenta, from the maternal circulation to the fetus. The placenta actively protects the iodine through the expression of the sodium iodide transporter, whose concentration increases with gestational age [34].

Considerations for the interpretation of the thyroid profile in pregnancy

The increase in the production of thyroid hormone, serum levels of thyroxine-binding proteins, and renal iodine excretion, together with the stimulatory effect of hCG, cause changes in the levels of T4, T3 and TSH in the pregnant woman. The healthy thyroid adapts to these alterations through dynamic changes in the hypothalamic-pituitary-thyroid axis.

Following this premise, there are several modifications that should be considered when interpreting the thyroid profile.

Serum TSH levels: During the first trimester, maternal HGC stimulates the TSH receptor, which increases the production of thyroid hormone and suppresses the concentration of serum TSH. Therefore, during pregnancy, women have a lower serum TSH than before pregnancy. Up to 15% of pregnant women have a TSH below 0.4mU/L in the first trimester of pregnancy without this representing a pathological process. The fraction of women with suppressed TSH decreases to about 10% in the second trimester, and to 5% in the third trimester.

There is a readjustment in the TSH range during pregnancy, with a reduction in both the lower limit (from 0.1 mU/L to 0.2 mU/L) and in the upper limit (around 0.5 mU/L to 1.0 mU/L). This, in relation to the typical TSH reference range of 0.4 mU/L to 4.0 mU/L [24].

In the first trimester, the lower reference range of TSH can be reduced by approximately 0.4 mU/L, while the upper reference range decreases by 0.5 mU/L. As the hCG levels fall, the serum TSH and its Reference range increases gradually in the second and third quarters; however, it remains lower than in non-pregnant women [35].

It is necessary, as far as possible; to define the specific population reference ranges of the quarter for serum TSH, through the evaluation of data from the representative local population. In this, only pregnant women without thyroid disease, optimal iodine intake, and negative antithyroid peroxidase antibodies should be included. Or, another reasonable alternative is to use the ranges established by different consensuses [36,37].

Evaluation of the T4: As a result of the estrogenic stimulation, TBG concentrations, and consequently total T4 (T4T), increase up to 50% from week 7 of pregnancy and a plateau is reached at week 16.

The current uncertainty regarding the clinical usefulness of measuring Free Thyroxine (FT4) in pregnancy questions the use of any immunoassay for its determination. In this sense, the measurement of T4T and the index of free thyroxine (ITL), determined with a hormone uptake test of serum thyroxine, show an inverse relationship to serum TSH levels and are considered to be of greater clinical utility for the surveillance of T4 levels in the second half of pregnancy [38].

By establishing that TBG increases by about 50% during pregnancy, changes in the serum concentration of TT4 are predictable between week 7 to week 16 of gestation; this compared to the levels of pre-pregnancy stages [39]. This increase is maintained until the pregnancy ends.

However, it should be specified that this can only be calculated after the 16th week of pregnancy. If a T4 measure is required before that time (i.e. 7 weeks to 16 weeks of pregnancy), the upper reference range can be calculated by increasing the upper reference limit of non-pregnant women by 5% per week, with the week 7 as starting point.

Manifesto hypothyroidism, subclinical hypothyroidism and isolated hypothyroxinemia: Diagnosis and handling, maternal and perinatal prognosis

Maternal manifesto hypothyroidism: The overt hypothyroidism in pregnancy is specified as the elevated presence of Thyroid Stimulating Hormone (TSH) and a decrease in the serum concentration of FT4 during pregnancy; both concentrations with values outside the ranges determined by quarter.

ATA specifies this with high TSH levels ≥ 10 mU/L regardless of serum free T4 levels. When iodine intake is adequate, the most frequent cause is autoimmune thyroid disease, known as Hashimoto's thyroiditis.

It is important to exclude other less frequent causes of thyroid dysfunction, such as pituitary-secreting TSH tumors, patients with definitive treatment for Graves' disease, peripheral resistance to thyroid hormones, or central hypothyroidism with biological TSH dysfunction. It is estimated that 2% to 3% of healthy and non-pregnant women of childbearing age have a high serum TSH. The prevalence may be higher in areas of relative iodine insufficiency.

The population studies demonstrate substantial differences in the reference of the upper limit of serum TSH [40]. Such variations can be attributed to different factors, among which are: the differences in iodine sufficiency between populations, the technique used to measure TSH, body mass index and ethnicity. It has also been shown an important additive influence of the positivity of anti-Thyroid PerOxidase Antibodies (TPOAb) on the state of the maternal thyroid.

These data suggest an increased risk of obstetric complications in women who are TPOAb positive compared to those who are TPOAb negative, even in euthyroid patients; although the reasons for this are not clear. As a consequence of these factors, it is difficult to define with precision a universal TSH cut from which to initiate substitution therapy in pregnant women. Decisions about treatment with levothyroxine should be based on thyroid function tests and the TPOAb status.

Maternal overt hypothyroidism has been shown to be strongly associated with an increased risk of obstetric complications and with detrimental effects on fetal neurocognitive development. The most frequent obstetric complications are: the possibility of premature birth, low birth weight and the loss of pregnancy [41]. Hypothyroidism manifest in pregnancy can carry an estimated risk of up to 60% of fetal loss when it is not adequately controlled [42]. Likewise, an increase of 22% has been demonstrated for the development of gestational hypertension [43]. These data confirm the association between overt maternal hypothyroidism and the risk for maternal-fetal unit [44].

Maternal subclinical hypothyroidism: Subclinical hypothyroidism is determined from high TSH values (TSH 2.5 mU/L-10.0 mU/L) with normal FT4. This condition has been associated with greater complications in pregnancy, but the data are inconclusive. The difficulty in unifying the upper limit of TSH and the determination of TPOAb may explain, in part, the lack of uniformity of the studies. In addition, pregnancy loss occurs naturally in 20% to 30% of patients. A significant proportion of these losses occur even before the pregnancy is recognized clinically.

Subclinical hypothyroidism and complications in pregnancy: In 2010, Negro reported a significantly high rate of pregnancy loss in women with serum TSH levels between 2.5 mU/L and 5.0 mU/L and negative TPOAb compared to those with TSH levels below 2.5 mUI/L (6.1% *vs* 3.6%) [45]. In a cohort study with Australian women with early pregnancy, TSH levels above the 95th percentile were associated with an increased risk of pregnancy loss (OR, 3.66) although cases of subclinical and overt hypothyroidism were considered within the same category.

In another larger study, conducted by Casey, where subclinical maternal hypothyroidism and preterm labor were investigated, subclinical hypothyroidism was associated with an increased risk of preterm birth, before 34 weeks of gestation (4% *vs* 2.5%, p=0.01), but not with Preterm labor<32 weeks (2.5% *vs* 1%, p=0.07), or <36 weeks (7% *vs* 6%, p=0.39). The biological significance of this discontinuous effect has not been explained [46].

In contrast, Cleary-Goldman found no relationship between elevated TSH and prematurity before 37 weeks [47]. The difficulty in establishing associations between subclinical hypothyroidism and clinical outcomes is due in part to the fact that the methodological design of several studies groups manifest and subclinical hypothyroidism, different TSH cut-off values and an insufficient number of samples are used.

The link between preeclampsia and thyroid dysfunction has not been clearly delineated in subclinical hypothyroidism. In a follow up of 5082 women, in whom thyroid function was evaluated at 12 weeks of gestation, no relationship was found between thyroid function and perinatal mortality [48]. In a meta-analysis conducted by S. Chan in 2015, there was an increase in obstetric complications (loss of pregnancy, premature delivery and placental abruption) in relation to maternal subclinical hypothyroidism during early pregnancy. Despite the heterogeneity of the biochemical criteria of subclinical hypothyroidism and other methodological differences [49].

These outcomes are more evident in the presence of high titers of TPOAb, even in the presence of serum TSH only above 2.5

mU/L. In the 2010 essay by Negro, an increased risk of obstetric complications in pregnant women with subclinical hypothyroidism with positivity for TPOAb is suggested. Although this was not the primary outcome, it was reported that patients who were found to have TSH greater than 2.5 mIU/L during the screening, positive anti-TPO antibodies and levothyroxine treatment, showed a significant reduction in the composite primary outcome versus no treatment. The composite endpoint remains a limitation of the study because many variables were subjective in nature. In addition, it is essential to bear in mind that the main endpoint of the study was not superior, and showed no benefits in universal detection and treatment.

Subclinical hypotirodism and neurocognitive alterations: The detrimental effects of subclinical hypothyroidism on fetal neurocognitive development are less clear. On the one hand, in the context of overt hypothyroidism, a case-control study revealed a 7-point reduction in IQ among children born to women with untreated overt hypothyroidism, compared to euthyroid controls [50]. Subsequent studies have shown similar results for children born to women with isolated hypothyroxinemia [51]. On the other hand, the CATS study showed no improvement in the cognitive function of children of hypothyroid or hypothyroxemic mothers in their evaluation at 3 years of age. In this cohort, the initial detection of elevated levels of TSH or low FT4 was sufficient to initiate treatment with 150 mcg/d of LT4; the average start of treatment was 13 weeks of gestation [52].

These data were corroborated with a clinical trial published by Casey in 2017 where no benefit was discovered on the treatment of subclinical hypothyroidism in the neurocognitive development of the product [53].

Subclinical hypotiroidism and TPOAb: From another point of view, the causality of maternal hypothyroidism has changed in recent years, in such a way that autoimmune thyroid disease represents a frequent cause and generates mechanisms of damage different from that of goiter due to iodine deficiency; nevertheless, the individual role of TPOAb in clinical outcomes remains to be clarified.

There are several observational studies and clinical trials that suggest an increase in complications in pregnancy in the presence of positivity for TPO in euthyroid patients. An important group of these was analyzed by Thangaratinam in a meta-analysis published in 2011. In this systematic review of 31 studies with euthyroid women, a strong association was found between the presence of antibodies against thyroid peroxidase and spontaneous abortion (likelihood ratio, 3.90; 95% Confidence Interval (CI), 2.48 to 6.12, p<0.001) and preterm birth (likelihood ratio, 2.07, 95% CI, 1.17 to 3.68, p=0.01). Among the weaknesses of this publication is the inclusion of women with recurrent spontaneous abortion, infertile women and the lack of homogeneity in the selection criteria of the population [54].

Regarding clinical advances to assess the effect of the use of levothyroxine in this group of patients, three randomized trials have examined the use of levothyroxine in women with positivity for TPOAb and normal thyroid function. The pooled findings of the first two trials, one with an unselected population of 115 women and the other with 72 women who were in the assisted reproduction program showed a substantially lower incidence of spontaneous abortion, in the women who took levothyroxine, compared with those who received placebo or no treatment (relative risk, 0.48, 95% CI, 0.25 to 0.92, p=0.03) [55].

In 2017, another trial in women who underwent *in vitro* fertilization stated that the use of levothyroxine did not reduce the incidence of spontaneous abortions or premature births [56]. The trial included 600 women, including a total of 220 pregnancies and 23 spontaneous abortions.

In this context, Dhillon-Smith recently published a double-blind, placebo-controlled trial to show whether levothyroxine therapy improves live birth rates among euthyroid women positive for TPOAb and a history of spontaneous abortion or infertility. We randomly assigned 479 women who would receive 50 µg of daily levothyroxine and 476 who would receive placebo from the preconception period until the end of pregnancy. The primary outcome was live births after at least 34 weeks of gestation. At the end of the follow-up, it was concluded that there were no significant differences between the groups in the live birth rate, nor in other pregnancy outcomes, including pregnancy loss, preterm delivery or neonatal complications. In the levothyroxine group, serious adverse events occurred in 5.9% and in the placebo group in 3.8% (p=0.14) [57].

Thus, the evidence to support the use of levothyroxine in euthyroid patients with TPOAb positivity is not conclusive. The 2017 ATA guidelines state that "there is not enough evidence to conclusively determine whether LT4 therapy decreases the risk of pregnancy loss in euthyroid women with TPOAb-positive" and leave it to the treating physician's decision to use it in the context of recurrent pregnancy losses; this, in contrast to the low risk of complications associated with the substitution with levothyroxine. It should be noted that the lack of positive data does not rule out a possible harmful effect, nor does it suppress the theoretical effectiveness of any intervention.

Screening of thyroid disease in pregnancy: Whether a universal evaluation of thyroid disease should be performed before or during pregnancy remains a controversial issue. For universal screening to be recommended, any condition must have a high prevalence, be associated with adverse health outcomes and be treatable. In addition, therapy must exist, but it must also be practical and effective. Finally, the detection must be profitable.

The concern for the early detection of thyroid dysfunction in pregnancy arises from the publication in 1999 of two studies, in which maternal subclinical hypothyroidism was associated with an increased risk of neurodevelopmental deficiency in the product [58]. Likewise, the highest risk of obstetric complications such as fetal death, premature delivery or placental abruption was considered [59]. These data prompted societies, both medical, obstetric and endocrinological, to seek consensuses

to issue recommendations regarding the detection of thyroid disease during pregnancy, which are not totally consistent.

In 2015, the Committee of Obstetric Practice of the American College of Obstetricians and Gynecologists (ACOG) stated: "Universal detection of thyroid disease in pregnancy is not recommended because the identification and treatment of subclinical maternal hypothyroidism has not been shown to produce an improvement in the neurocognitive function of the offspring" when taking as a reference the results of the CATS study where it was demonstrated that the detection and treatment of women with subclinical hypothyroidism during pregnancy do not improve the cognitive function of the products at the age 3 years old [60,61].

It is reasonable to perform a serum TSH determination at the first obstetric visit in women with a higher risk of thyroid dysfunction. In the ATA Clinical Guidelines for Thyroid and Pregnancy, universal screening is not recommended, but health professionals are strongly encouraged to ask in person during preconception counseling or at the first obstetric visit about the risk factors for the disease the thyroid.

However, several studies have systematically shown the lack of recognition of women at risk of thyroid dysfunction, using a strategy of case detection based on the actual symptoms of thyroid dysfunction, personal or family history of thyroid disease and obstetric history. [62-64]

In counterpart Black and his colleagues reported on a large randomized study of 4562 women in southern Italy. These were randomly assigned to the universal detection group or to the case-finding group. Women in both groups were stratified as high or low risk, depending on the risk factors for thyroid disease. Their conclusion was that the universal evaluation did not affect the rate of adverse events compared to the detection of high-risk cases. However, a subgroup of low risk patients detected with hypothyroidism was treated with levothyroxine and compared with an untreated group. As a result, the rate of adverse events related to pregnancy was reduced by almost 40% after detection and treatment [65].

A number of conditions must be considered before being able to recommend the detection of universal thyroid function in pregnancy. These include the selection of thyroid function tests (TSH, FT4, TPOAb), the threshold applied to characterize an abnormality, weeks of gestation, appropriate intervention, and monitoring. Despite some concerns about existing data, the Level I evidence suggests that there is no benefit to the universal detection and treatment of hypothyroidism in pregnancy.

Most of the current recommendations require physicians to adopt an active strategy for the search of cases and selection of high-risk patients based on their background, physical examination and rational use of laboratory studies. The ATA, for its part, proposes that patients with a history of: Hypothyroidism, hyperthyroidism or current symptoms or signs of thyroid dysfunction, thyroid antibody positivity or presence of goiter, a history of radiation in the head or neck or previous thyroid surgery, older than 30 years, with presence of type 1 diabetes or other autoimmune disorders, history of pregnancy loss, premature birth or infertility, multiple previous pregnancies, family history of autoimmune thyroid disease or thyroid dysfunction, morbid obesity (BMI<40 kg/m^2), use of amiodarone or lithium, or recent administration of iodinated radiological contrast or residing in an area with moderate iodine insufficiency, should be subjected to biochemical scrutiny of dysthyroidism.

Isolated hypotiroxinemia: It has been reported that the prevalence of hypothyroxinemia during the first trimester of pregnancy is 2% to 8.7%, although there are large differences between recent studies. The biochemical diagnostic criteria used are probably the main cause of these discrepancies.

Hypothyroxinemia has been considered as the 10th, 5th or 2.5th percentile lower of free T4 with negative or positive thyroid autoimmunity, in addition to a normal maternal concentration of TSH. Another confounding variable is the iodine status of different populations that has been studied, together with the lack of recommended cut-off values for diagnosis due to important differences between the available assays for free T4.

Therefore, additional studies are required to standardize these variables, since the available data do not suggest that hypothyroxinemia could be a laboratory phenomenon despite the limited accuracy of free T4 trials in pregnancy [66]. Pop initially reported a decrease in psychomotor test scores in children born to women with FT4 indices in the lowest percentile 10, despite having normal serum TSH levels.

In recent years, nonrandomized prospective studies have reported adverse outcomes in children of children born to mothers with isolated hypothyroxinemia. These results include lower IQ, delayed speech and motor function, smaller head circumference, and increased risk of autism. The available data suggest an association with higher birth weight and higher risk of premature birth [67-69].

Hypotroxinemia may be associated with a higher maternal Body Mass Index (BMI), a susceptibility to develop gestational diabetes and macrosomia, although the latter may be related to higher BMI and gestational diabetes [70].

In general, the available evidence seems to show an association between hypothyroxinemia and the cognitive development of children, with uncertain effects on prematurity and low birth weight. In a recent study by Korevaar showed that both low and high concentrations of FT4 may be associated with a decrease in the children's IQ and the reduction of brain gray matter volume by magnetic resonance imaging.

Treatment of hypothyroidism in pregnancy

Manifesto hypothyroidism: The consequences of not managing overt hypothyroidism both in the evolution of pregnancy and in the neurocognitive development of the product are evident, even with a high risk of spontaneous abortion from levels higher than 4.5 mU/L. Therefore, therapy should not be delayed.

Levothyroxine is a drug classified within group A by the FDA and is considered the therapy of choice in the management of maternal hypothyroidism [71]. It is noteworthy that most of the fetal T3 present in the CNS during pregnancy is derived from the maternal T4, actively transported by the placenta. In contrast, T3 is rapidly converted to rT3 by placental deiodinase 3. Therefore, the use of T3 in the treatment of hypothyroidism in pregnancy is not recommended.

Hypothyroidism manifesto preconception: It is recommended that all treated hypothyroid women optimize the substitution in the preconception. A concentration of TSH in maternal serum between the lower reference limit and 2.5 mU/L seems an appropriate target for these women.

Hypothyroidism gestational manifesto: In women with known hypothyroidism, serum hCG and TSH cannot stimulate adequate production of T4 to adapt to increased requirements during pregnancy. Clinical studies have confirmed that the increase in the requirement of thyroxine (or exogenous LT4) occurs from week 4 to 6 of pregnancy [72]. These data provide the basis for recommending adjustments of the LT4 dose.

The adjustment of LT4 should be made as soon as possible after the pregnancy is confirmed. For women who are adequately substituted, if the pregnancy is suspected or documented before 12 weeks, two additional doses of levothyroxine should be increased weekly [73]. Another option is to increase the daily dose of LT4 by approximately 25%-30%. The dose increase should occur as soon as possible, from the loss of menstruation or when there is suspicion of pregnancy, which should be confirmed simultaneously. Generally, the requirements will remain constant after the 16th to 20th week of gestation until delivery [73].

In case the pregnant patient with known and treated hypothyroidism is evaluated after 12 weeks of gestation, the substitution dose should be adjusted with levothyroxine according to the TSH objectives per trimester.

For patients in whom a diagnosis of hypothyroidism is made during pregnancy and that have no substitution with levothyroxine, the dose of treatment with levothyroxine depends on the TSH levels at the time of evaluation. TSH values between 2.5 mU/L and 10 mU/L require 50 L-thyroxine mcg daily. For TSH values>10 mU/L, the recommended daily dose of L-thyroxine is 100 mcg [74].

Hypotiroidism in the postpartum: The increase in LT4 dose requirements during pregnancy is a function of pregnancy itself. Consequently, after delivery, the maternal dose of LT4 should be reduced to pre-pregnancy levels, and a serum TSH should be evaluated 6 weeks later. In women who started LT4 during pregnancy due to thyroid autoimmunity in the absence of elevated TSH, LT4 can be interrupted at delivery; especially if they received doses lower than 50 mcg/24 hrs of levothyroxine, with a serum TSH evaluation at 6 weeks after delivery to determine the behavior to be followed.

Subclinical hypothyroidism: There is controversial evidence about the most appropriate scenario to treat subclinical hypothyroidism, derived from the contradictory results of prospective and retrospective studies on the increased risk of pregnancy complications associated with slightly elevated maternal concentrations of TSH, especially in women with positive TPOAb. However, only a small number of studies have investigated the impact of LT4 treatment on pregnancy complications in these women.

Within the strongest evidence in favor of treatment is the result of an RCT that showed a decrease in premature delivery and pregnancy loss in euthyroid women (defined as TSH <4.2 mU/L) positive for TPOAb who were treated with LT4 from the first trimester of pregnancy. Despite this, the majority of pregnancy losses in the control group occurred before the average onset of LT4 therapy.

Many studies have stratified the risk associated with hypothyroidism according to the status of TPOAb and consistently show that this risk is higher in women with positive TPOAb [75]. Such data also suggest that the adverse impact associated with maternal TSH levels is evident at lower TSH elevations in women positive for TPOAb, compared to women who are negative for TPOAb.

In addition, two studies suggest a reduction in pregnancy loss when women with positive TPOAb are treated with LT4, even when they are biochemically euthyroid [76]. These statements are challenged by an essay published by Dhillon-Smith in 2019, in which it was not possible to demonstrate any benefit of treatment with levothyroxine to euthyroid patients with positive TPOAb.

Taking into account all the risk subgroups and the complex interaction, the ATA in 2007 suggests treatment with only 50 mcg/d for women with subclinical hypothyroidism in some groups of patients where the evidence points to a probable benefit.

On the other hand, the European Thyroid Association (ETA) and the American Endocrine Society recommend the replacement of levothyroxine in all women with subclinical hypothyroidism, regardless of the status of TPOAb, since they consider that the advantages of the therapy far outweigh the disadvantages potentials. However, a prospective Dutch study has questioned such practices, because it revealed an association between thyroid function tests in early pregnancy and the IQ of the product at six years, as well as brain morphology in MRI at the eight years. Both low and high levels of fT4 were associated with reduced IQ and reduced gray matter and cortical volume. Therefore, the authors recommended caution when prescribing levothyroxine for subclinical administration.

Isolated hypotiroxinemia: There are no studies in which it has been demonstrated that the administration of levothyroxine improves the neurocognitive prognosis of the products with isolated hypothyroxinemia. Although there is evidence that low levels of maternal LT4 have an impact on the neurocognitive development of the product, no data have been published demonstrating beneficial effects of LT4 therapy.

Currently, only two randomized, prospective intervention

trials in which women with low FT4 were treated with LT4 are documented at week 13 and week 17 of gestation, respectively. Both explorations showed no beneficial effect on cognitive development after LT4 administration; although an important limitation of the studies was the delay in the time of beginning of the intervention. Based on the existing intervention data, the treatment of isolated hypothyroxinemia cannot be recommended at this time.

The ATA guidelines do not suggest the treatment with T4 of gestational hypothyroxinemia, while the guidelines of the Endocrine Society leave it to the discretion of the doctor. For its part, the European Thyroid Association [37] considered T4 therapy in hypothyroxinemia alone detected in the first trimester.

Monitoring of therapy with levotiroxin: TSH should be considered as a treatment goal in the lower half of the specific reference range of the trimester. When this is not available, it is reasonable to aim for maternal concentrations of TSH below 2.5 mU/L.

The determination of serum TSH should be made approximately every 4 weeks until the middle of pregnancy and at least once around 30 weeks of gestation.

Fetal monitoring: In the care of women with adequately treated hypothyroidism, no other maternal or fetal tests (such as serial fetal ultrasound, prenatal testing and/or umbilical blood sampling) beyond the measurement of maternal thyroid function are suggested unless necessary due to other circumstances of pregnancy. An exception to this is women with GD who are effectively treated with 131I ablation or surgical resection, which requires monitoring of the TSH receptor antibody (TRAb).

Coma mixedematoso: Myxedema coma represents a decompensated form of hypothyroidism that is triggered by a variety of diseases or non-thyroid factors, which cause a widespread commitment of extreme severity, with fatal outcomes of not making an early diagnosis, an interdisciplinary management and intensive treatment.

The clinical picture is characterized by a patient with neurological alterations: lethargy that progresses to stupor and finally coma, hemodynamic deterioration and respiratory failure; as well as manifestations of severe hypothyroidism such as dry skin, alopecia, hoarse voice, peri orbital and generalized edema, macroglossia and hyporeflexia [77].

The incidence of coma in the non-obstetric patient is low, 0.22 cases per 1,000,000 are estimated. Myxedema coma should be considered a medical emergency, the mortality rate is still high, between 60%-80%; this percentage has decreased in recent years to 20%-25% given the advances in intensive care [78].

Cases of myxedema coma in women are reported; of the 36 documented 79, it is more frequent to occur in the winter months, so it is suggested that the cold is a predisposing factor, as for the myxedema coma in pregnancy there are only some case reports, since hypothyroidism severe presents anovulatory cycles in up to 70% of women. In addition, it tends to arise from a primary hypothyroidism, whose most frequent cause is autoimmune thyroiditis. Other causes of primary hypothyroidism are the history of treatment of hyperthyroidism with radiation, thyroid surgery, and the chronic use of amiodarone, or lithium. There are precipitating factors of myxedema coma.

Clinical manifestations: The cardinal signs of myxedema coma are: neurological deterioration, hypothermia, arterial hypotension, bradycardia, deterioration of respiratory mechanics, among the most frequently associated biochemical alterations are hypoglycemia, hypoxia, hypercapnia, hyponatremia and hypokalemia. For what is classified as a medical emergency.

Literature Review

Diagnosis

It should be considered in any patient with or without a history of hypothyroidism who presents neurological alterations, hypothermia, hyponatremia and/or hypercapnia.

The following entities should be examined in a targeted manner and search for clinical signs: history of thyroid dysfunction, goiter, thyroidectomy, iodine therapy, cervical radiotherapy, pituitary radiotherapy and surgery, head trauma, postpartum hemorrhage and treatment with levothyroxine. The diagnosis of severe hypothyroidism requires clinical suspicion and can be confirmed with the presence of elevated TSH and low levels of T4 (thyroxine) and T3 (triiodothyronine), however, biochemical confirmation should not delay the start of treatment.

Popoveniuc and collaborators 80 have designed a score for myxedema coma that evaluates and gives a score to each of the signs and symptoms present.

- Score less than 25 points: improbable diagnosis of myxedema coma
- Score between 29 points-59 points: suggestive of risk of myxedema coma
- Score greater than 60 points: highly suggestive of diagnosis of myxedema coma

Treatment for acute thyroid failure will depend on age, weight, and risk of complications. For the myxedema coma, admission to the Intensive Care Unit (ICU) is required.

Mixedematoso coma treatment

The management of these patients must be performed in the ICU, with interdisciplinary management and maternal-fetal surveillance [79,80]. They must also consider background, clinical picture, predisposing factors. Supportive treatment should be initiated immediately, an adequate hemodynamic status should be guaranteed, and cardiovascular status should be evaluated before hormonal supplementation. Currently, most consensus recommendations recommend sequential treatment:

Steroids: Severe hypothyroidism is associated with a decrease in the endogenous production of cortisol, therefore when initiating thyroid hormone replacement, the requirements and clearance of cortisol will increase, which can precipitate an adrenal crisis;

glucocorticoids should always be administered before thyroid replacement.

Hydrocortisone: 50 mg-100 mg IV every 6 hours-8 hours for 7 days-10 days or until hemodynamically stabilize the patient. Suspend if hypocortisolism is ruled out by laboratory

- Identify and treat the precipitating factor of myxedema coma
- Thyroid hormone replacement therapy
  1. High dose of LevoThyroxine (LT4) with the objective of replacing the deficit and saturating the circulating deposits of thyroid hormone
  2. Start with a dose of 200 mcg-400 mcg IV bolus in the first 48 hours, followed by a more physiological dose of 50 mcg-100 mcg IV per day until the oral route can be administered
  3. Combined therapy of T4/T3
  4. T3 therapy has a rapid onset of action and does not require plasma conversion. Its disadvantages are its shorter half-life, very fluctuating serum levels; it can precipitate cardiac alterations (conduction and heart failure) and the lack of controlled studies that demonstrate its superiority against part with the substitution with T4
  5. Simultaneous bolus administration of 10 mcg IV with the dose of LT4 and continue with 10 mcg every 8 hours-12 hours along with the LT4
- Supportive therapy is a broad spectrum antibiotic coverage given the suspicion of infectious processes
  1. In pregnant women with hypoxemia, hypercapnia and neurological alterations, invasive mechanical ventilation should be considered, in order to maintain adequate oxemia and normocapnia
  2. Hypothermia: Passive heating (warm blankets, hot bath)
  3. Hypotension: Volume replacement, early onset of vasopressor in case of fluid overload and not maintaining perfusion TAM
  4. Hyponatremia: Correction of hyponatremia

Hypertiroidism and pregnancy

Hyperthyroidism during pregnancy is a rare pathology, its prevalence ranges between 0.1% and 1% depending on whether it is considered overt hyperthyroidism or also subclinical forms [81,82]. Despite the low incidence, its identification in a pregnant woman is essential, since it can involve serious complications in both the mother and the fetus.

In general, hyperthyroidism is rarely associated with adverse gestational outcomes; however, the presence of severe thyrotoxicosis significantly increases the risk of maternal and fetal complications, such as pregnancy-induced hypertension, maternal congestive heart failure, pregnancy loss, prematurity, low birth weight, fetal death, intrauterine growth restriction [83,84].

The clinical effects on the fetus depend not only on the intensity of thyrotoxicosis, but on other factors that ultimately modulate the function of the fetal thyroid, the most important are: the transplacental passage of the maternal TSH Receptor Antibodies (TRAb), the transport of iodine, the activity of deiodinases, the permeability of thyrostatic agents (MethiMazole (MMI), CarbiMazole (CM), and Propyl Thiouracil (PTU) that are also related to birth defects and maternal liver injury.

Due to the above, the management of pregnant and lactating women with hyperthyroidism requires special care. It must be taken into account that both maternal thyroid excess and pharmacological management can negatively affect the health of the newborn.

Next, we discuss the diagnosis and management of hyperthyroidism in pregnancy, with a central interest in transient Gestational Thyro Toxicosis (GTT) and Graves' Disease (GD), together with the impact of thyrotoxicosis and drugs on fetal development.

Causes of hypertiroidism during pregnancy: The two most common causes of hyperthyroidism in pregnant women are Graves' Disease (GD), due to thyroid stimulation by TRAbs, and transient Gestational ThyroToxicosis (GTT) resulting from the cross-stimulation of human Chorionic Gonadotropin (hGC) during the first trimester pregnancy. Both forms of hyperthyroidism can present with classic thyrotoxic symptoms and signs; the preparation of an adequate clinical history and the physical evaluation, together with the appropriate laboratory tests, are essential for an adequate diagnosis.

Other less frequent causes of hyperthyroidism in pregnancy include toxic multinodular goiter and toxic thyroid adenoma. The prevalence of these forms of hyperthyroidism is low in women of childbearing age. Thyrotoxicosis without hyperthyroidism is less frequent, in this scenario subacute de Quervain thyroiditis, painless thyroiditis and acute thyroiditis are the main causes, within the extrathyroidal sources of thyroid hormone, and is overtreatment with LevoThyroxine (LT4), factitious ingestion of thyroid hormone, struma ovarii and metastases of functional thyroid cancer.

Due to the physiological adaptation of the thyroid during pregnancy, TSH levels are lower than those of non-pregnant euthyroid women, especially during early pregnancy, detection of TSH levels, below or near the lower limit of the reference range, may not be indicative of maternal hyperthyroidism, since this decrease is found in up to 15% of healthy women at this time of pregnancy [85]. However, if a suppressed serum TSH is identified, an accurate clinical evaluation should be performed and complementary laboratory studies ordered to exclude or confirm hyperthyroidism [86,87].

Gestational Transitory Thyrotoxicosis (GTT): GTT refers to hyperthyroidism presented in pregnant women without evidence of autoimmunity against thyroid. It resolves spontaneously at the end of the first trimester or at the beginning of the second trimester [88]. According to the geographical area, GTT is

estimated to occur in 1%-5% of pregnancies, although prevalences as low as 0.3% in Japan or as high as 11% in Hong Kong have been reported [89,90].

It is considered a manifestation secondary to stimulation of the thyroid by hCG [91]. The structural homology between the hCG and TSH molecules (as well as between their corresponding receptors) provides the physiological basis for thyrotropic action of hCG, whose concentrations physiologically peak in the first 8 weeks to 11 weeks of pregnancy, then decrease and remains on a plateau until the end of pregnancy. The symptoms of thyrotoxicosis are usually parallel to the changes of hCG, and occur for the first time at 4 weeks-9 weeks of gestation and remit at the end of the 1st or early 2nd trimester of pregnancy. In agreement with the physiopathological role of hCG in thyroid hyperfunction, women affected with GTT usually do not have a history of hyperthyroidism prior to conception.

In most cases, GTT is secondary to placental alterations that generate an excessive production of human gonadotropic hormone such as twin pregnancy, multiple pregnancies, hyperplacentosis or hydatidiform mole, but may also be due to hCG isoforms [92]. Circulating with greater thyrotropic activity and/or prolonged half-life [93]. Similarly, a heterozygous mutation of the TSH Receptor gene (TSHR), which results in the exchange of lysine by arginine at position 183 in the extracellular domain of TSHR, has been observed as a rare cause of GTT (with levels normal serum levels of hCG) due to thyroid hypersensitivity to hCG.

Due to its short and self-limited course, GTT usually does not require treatment and milder forms are not recognized. Exceptions include cases characterized by more severe hyperthyroidism, which is often associated with nausea, vomiting, or Hyperemesis Gravidarum (HG). The latter occurs in 0.3%-1.0% of pregnancies, and is defined as persistent vomiting, weight loss (at least 5% of weight), dehydration, ketonuria and acid-base abnormalities (hypochloraemic alkalosis, hypokalemia and hyponatremia) [94]. The pathogenesis of HG remains poorly understood, and hormonal, infectious and genetic factors are indicated as possible causes [95].

The clinical findings in the physical examination are generally not very noticeable, but they can include all the typical signs of thyrotoxicosis (tachycardia, hyperreflexia, hand tremors), while the goiter is usually absent and no manifestations of Graves' orbitopathy are detected.

The clinical diagnosis is confirmed by laboratory tests, which corroborates the absence of serum TRAb along with undetectable TSH and increased levels of FT4. The highest elevations in serum T4L are generally observed in women with GTT associated with HG, in whom the severity of vomiting correlates with the degree of concentration of FT4 and hCG.

In contrast, triiodoThyronine (T3) is usually normal, or only slightly elevated in less than 20% of affected women. This finding is consistent with the increased action of deiodinase 3 on T4 that generates reverse triiodothyronine (rT3) in response to starvations, whose concentrations has been documented, are increased in women with HG. Furthermore, since in patients with GTT free T4 levels are generally higher than serum free T3, a decrease in the FT3/FT4 ratio has been proposed as a useful biochemical parameter to differentiate between GTT and active Graves' disease [96].

Although the biochemical evidence of hyperthyroidism is usually associated with serum hCG at levels of 100,000 IU/L-500,000 IU/L, the diagnostic usefulness of measuring hCG in serum is limited, unless gestational trophoblastic diseases are suspected [97,98]. Similarly, thyroid ultrasound tends to be less informative, and is performed primarily to distinguish GTT from Graves' disease.

Probably, GTT is not associated with significant obstetric complications and adverse neonatal outcomes. However, children born to mothers who suffered GTT complicated by severe hyperemesis have a significantly lower birth weight compared to gestational matched infants born to unaffected mothers.

With regard to treatment, in most cases GTT does not require any treatment, due to its spontaneous recovery in a few weeks. Antithyroid drugs are not indicated, as thyroid levels recover between 14 weeks and 18 weeks of gestation.

The use of thionamides in early pregnancy increases the risk of birth defects. When GTT is associated with severe hyperemesis, in addition to treatment with fluids and electrolytes, propanolol can be administered transiently, due to its efficacy in reducing hyperemesis and thyrotoxicosis symptoms.

Severe disease (Hyperemesis gravidarum (EG)) in pregnancy: GD is the most common cause of hyperthyroidism in women of childbearing age; occurs before pregnancy in 0.4%-1.0% women and, approximately, in 0.2% of pregnant women. The pathogenesis of hyperthyroidism by EG in pregnant women is the same as in non-pregnant women.

As for other autoimmune diseases, EG generally improves during the second and third trimesters, and often relapses in the postpartum period. This evolution mainly reflects the pattern of changes in TRAb levels, as a result of the tolerogenic state that occurs during normal pregnancy [99].

The gestational immune tolerance, intended to prevent the fetus from being rejected as foreign tissue and to keep the mother and fetus protected against infection, implies a complex interaction between hormonal factors, trophoblastic tissue immunological molecules and subsets of specific T cells (T cells) (TREG) regulators, generated within the maternal decidua.

In addition to maintaining fetal alloantigen tolerance, TREG cells that migrate to the maternal circulation indirectly induce a generalized and transient state of immunosuppression, which explains an improvement in DG in pregnancy. However, although the clinical and biochemical characteristics of thyrotoxicosis improve with the progression of pregnancy, a transient worsening of hyperthyroidism may be observed during the first trimester due to the stimulating activity of the hCG's thyroid [100].

Finally, in the puerperium, the abrupt fall of the TREG cells provides an explanation for the rebound of thyroid autoimmunity, with worsening or re-exacerbation of the EG [101].

Clinical and biochemical diagnosis of serious disease in pregnancy: The diagnosis of EG during pregnancy can be difficult, because many clinical symptoms of hyperthyroidism, such as palpitations, insomnia, anxiety, fatigue, are nonspecific and can be overlooked or interpreted as symptoms of normal pregnancy.

However, signs such as lack of weight gain or loss, despite a higher intake of food, the presence of goiter or eye changes are highly suggestive of a diagnosis of hyperthyroidism due to EG in a pregnant patient [102].

The clinical diagnosis of hyperthyroidism can be confirmed only by the increase in thyroid hormone levels and suppressed serum TSH levels. If biochemical hyperthyroidism is detected, the measurement of TRAb is indicated, since the presence of these antibodies discriminates the EG from other causes of gestational hyperthyroidism. Beyond its diagnostic utility, the determination of these antibodies has a clear prognosis. TRAb can cross the placenta, with abnormal stimulation of the fetal thyroid glands, similar to what occurs in the mother [103].

In general, the risk in the fetus of neonatal thyrotoxicosis is higher in babies born to mothers with recent onset of GI, in whom TRAb titers are generally higher than in those with less recent diseases or in those who previously received ablative therapy (radioiodine or thyroidectomy) [104].

Fetal and neonatal hyperthyroidism in children of mothers with severe disease: As indicated, maternal TRAbs can cross the placenta and have the potential to induce fetal hyperthyroidism. The likelihood that this event will happen, ultimately, depends on maternal TRAbs, the higher the concentrations of maternal TRAb, the higher the risk in the fetus to develop hyperthyroidism [105]. However, DTAs also cross the placenta and are effective in the fetal thyroid therefore, when treating the mother, the net effect on the production of fetal thyroid hormone will eventually depend on the balance of TRAb stimulation and ATD inhibition.

It is estimated that the risk of fetal hyperthyroidism is very low, only in 1% of children of mothers with EG [106,107]. However, in fetuses of EG mothers with uncontrolled hyperthyroidism in the second half of pregnancy, and/or with high levels of TRAb, they require close monitoring. Fetal thyroid ultrasound has been shown to be extremely sensitive and specific for detecting intrauterine thyroid dysfunction.

Ultrasound findings suggesting fetal hyperthyroidism include goiter, sustained heart rate>160 bpm-170 bpm, accelerated bone maturation, growth restriction, oligo/polyhydramnios. Cordocentesis can be used to measure fetal thyroid hormone directly, but its use is limited to selected cases because of the risks associated with this procedure.

Due to the persistence of maternal TRAb in the infant circulation (half-life around 2 weeks), 1% to 5% of babies of mothers with high levels of TRAb are at risk of developing neonatal hyperthyroidism [108]. In newborns of mothers treated with ATD until delivery, hyperthyroidism may not manifest clinically until these medications are eliminated from the neonatal circulation. Although typically transient, overt neonatal hyperthyroidism must be appropriately treated to limit short and long-term morbidity and control neonatal thyroid function [109].

Following the disappearance of maternal TRAb from newborns, a phase of neonatal central hypothyroidism may also occur, probably due to prolonged suppression of pituitary TSH production during fetal and neonatal hyperthyroidism [110].

Treatment of serious disease in pregnant: Thyroidamide-type Anti Thyroid Drugs (ATD) are the mainstay of treatment for hyperthyroidism in pregnancy due to GD, since radioactive iodine therapy is obviously contraindicated and thyroidectomy, although feasible, should be reserved for highly selected cases and its completion it is only safe during the second trimesters of pregnancy [111].

The therapeutic objective is to control maternal hyperthyroidism to prevent complications. When GD is diagnosed for the first time in pregnancy, the decision to prescribe DTA must be based on a careful risk-benefit assessment on an individual basis; similarly, the severity of maternal hyperthyroidism or the possible detrimental effects of DTAs in the fetus should be considered.

In general, the initial doses of DTA during pregnancy are within the range of 200 mg to 400 mg daily for PTU (propylthiuracil) or 10 mg-20 mg daily for MMI (methimazole). If DTA therapy is started during the first trimester, PTU is preferred over MMI because the risk of serious birth defects is lower. After initiation, close monitoring of maternal thyroid function and dose of DTA should be performed to adjust it and maintain maternal thyroid hormone levels in the upper reference range.

The approach of women who have already been treated with ATD before pregnancy depends on the severity and activity of the DG when the pregnancy is established. In general, the suspension of antithyroid drugs can be considered for women without large goitre or without positive TRAB, who have received ATD for at least 6 months before becoming pregnant and are euthyroid with low doses of MMI or PTU (≤ 5 mg/day-10 mg/day and ≤ 100 mg/day-200 mg/day, respectively). Conversely, women at high risk of thyrotoxicosis should remain in medical therapy (PTU in the first trimester, MMI thereafter) at the lowest dose useful to maintain thyroid hormone levels in the upper reference range.

In both circumstances, that is, if the treatment is discontinued or continues, the maternal thyroid function should be monitored closely (every 1 weeks-2 weeks during the first trimester and every 2 weeks-4 weeks, during the 2nd trimesters and 3rd trimesters), this to guide additional management (conservative or interventional), bearing in mind that both hyperthyroidism and excessive treatment can have detrimental effects.

Effects on the fetus: All available DTAs (MMI (Methi Mazole), CM (Carbi Mazole), PTU (Propyl Thiuracil) can cross the placenta and, therefore, have the potential to cause fetal hypothyroidism [112].

Early studies suggested that the placenta was less permeable to PTU than to MMI and, consequently, PTU has been considered the preferred DTA to treat hyperthyroidism in pregnancy. However, subsequent studies with in vitro perfusion techniques did not demonstrate differences in the placental transfer kinetics of PTU and MMI to exert similar effects on fetal thyroid function [113].

It has been repeatedly reported that CMs are associated with several birth defects and malformations; it includes aplasia cutis congenita, choanal atresia, tracheoesophageal fistula, omphalocele and other less common normalities.

A retrospective case-control study of almost 6000 infants born to mothers affected with EG, treated with MMI/PTU or who never received DTA, showed a significantly higher rate of significant abnormalities among children of mothers treated with IMM than in exposed infants (4.1% *vs* 2.1%). On the contrary, no differences were found in the incidence rates of malformations among children born to mothers treated with OCT and controls.

Thyroid storm: Thyroid storm is an infrequent medical emergency characterized by a hypermetabolic state produced by the elevation of thyroid hormones. It occurs in 1% of women with hyperthyroidism not treated during pregnancy; it presupposes a high risk of heart failure, maternal heart failure, neurological alterations, stupor, coma, and maternal mortality in up to 25% of cases [114].

It is relevant to consider in women during pregnancy, childbirth and puerperium, the history of hyperthyroidism, as well as the presence of unexplained fever, alterations in mental state, cardiac arrhythmia, heart failure, confusion and seizures. Precipitating factors such as trauma, surgery, infection, stress, preeclampsia, and ketoacidosis have been associated with the presence of thyroid storm.

The treatment does not differ from non-pregnant women and an interdisciplinary management must be carried out, composed of medical specialists: obstetricians, maternal-fetal, endocrinologists, in the ICU with continuous fetal monitoring. Thus, multimodal management should include beta-adrenergic blockers (propanolol) doses of PTU, steroids. In addition to the administration of oxygen, antipyretics, resuscitation with volume, and adequate nutrition [115].

For the termination of pregnancy should include fetal considerations. Women with thyroid storm have increased blood pressure, headache, abdominal pain, heart failure, heart failure, acute pulmonary edema, data that may be compatible with the presence of severe preeclampsia, which can make the diagnosis of a thyroid storm difficult.

The clinical signs of hyperthyroidism, such as increased thyroid gland, goiter, thyroid murmur, or exophthalmos are more specific for women with thyroid abnormalities. Laboratory tests include thyroid functioning tests: Thyroid Stimulating Hormone (TSH), Free Triiodothyronine (FT3), and Free Thyroxine (FT4), complete blood count, complete metabolic panel, and serum electrolytes.

The diagnosis of thyroid storm has hyperthyroidism and compatible clinical data. Some other indicative data are the increase of leukocytes, hyperglycemia, hypercalcemia, elevation of liver enzymes, and hydroelectrolytic alterations.

Burch and Wartosfky have developed a commonly cited clinical scoring system for the probability of thyroid storm. They are considered: the elevation of the temperature, the heart rate, and some dysfunctions that indicate a high, medium or low probability of diagnosis.

In cases where fetal bradycardia or presence of cardiac rhythm alterations are present, or the lack of response to maternal resuscitation maneuvers, a cesarean section operation should be performed.

Treatment: It is advisable to keep the patient euthermic for which cooling measures can be used, place peripheral accesses to maintain adequate base acid balance, continuous monitoring, with close monitoring of saturation by pulse oximetry for the risk of heart failure, stroke electrocardiogram, echocardiogram, cardiac arrhythmia control the most frequent atrial fibrillation.

Occasionally, in patients without improvement in cardiac failure and with respiratory failure, intubation and support of invasive mechanical ventilation may be required. In addition to support and surveillance in the ICU, the management of the thyroid storm requires a series of medications:

- For the reduction of thyroid hormone levels: Propylthiouracil (PTU) and methimazole are thionamides and act in the thyroid gland to inhibit the follicular growth, development and production of iodothyronines in T4 and T3
- PTU decreases the production of thyroid hormones, as well as the conversion to the peripheral level. It has been associated with cases of fulminant hepatic failure and associated death, as well as cases in pregnancy
- Methimazole: Linked with some teratogenic effects (aplasia cutis and choanal atresia)
- Potassium iodide: Inhibits the release of active thyroid hormone; oral dose of 5 drops every 8 hours or IV sodium iodide 500-1000 mg every 8 hours

Steroids: A fundamental part in the management of the patient with thyroid storm, due to the decrease in systemic inflammation and the effects at the peripheral level of the conversion of T4 to T3.

Beta-blockers: Such as propranolol, which reduces the peripheral conversion of T4 to T3, and reduces the complications of tachycardia, cardiac arrhythmia, heart failure. Its long-term use is associated with the restriction of fetal growth, but it is considered safe in pregnancy in a risk/benefit balance.

Support medications: Antipyretics (paracetamol). Thyroid storm is a rare disease, but it represents a condition that threatens the life of the mother and complicate pregnancy. It requires early recognition, multidisciplinary care and aggressive therapy to improve maternal and fetal outcomes.

Conclusion

Early diagnosis and management of thyroid disorders during pregnancy is essential to decrease adverse maternal-fetal outcomes. Therefore, it is recommended to women of reproductive age and with thyroid alterations, to perform a pre-pregnancy risk assessment, where the state of thyroid dysfunction is considered. In women with a diagnosis of hypothyroidism and hyperthyroidism in gestational state, they will require appropriate treatment.

References

1 Krassas GE, Poppe K, Glinoer D (2010) Thyroid function and human reproductive health. Endocr Rev 31: 702-755.

2 Li Y, Shan Z, Teng W, Yu X, Li Y, et al. (2010) Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months. Clin Endocrinol 72: 825-829.

3 Korevaar TI, Muetzel R, Medici M, Chaker L, Jaddoe VW, et al. (2016) Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: A population-based prospective cohort study. Lancet Diabetes Endocrinol 4: 35-43.

4 Vanderpump MPJ (2011) The epidemiology of thyroid disease. Br Med Bull 99: 39-51.

5 Blatt AJ, Nakamoto JM, Kaufman HW (2012) National status of testing for hypothyroidism during pregnancy and postpartum. J Clin Endocrinol Metab 97: 777-784.

6 Haddowt JE, Faix JD, Browns RS, HermosT RJ, Puikkinent A, et al. (1991) Prevalence of thyroid deficiency in pregnant women. Clin Endocrinol 35:41-46.

7 Kyriacou A, McLaughlin J, Syed AA (2015) Thyroid disorders and gastrointestinal and liver dysfunction: A state of the art review. Eur J Intern Med 26: 563-571.

8 Bianco AC, Larsen PR (2005) Cellular and structural biology of the deiodinases. Thyroid 15: 777-786.

9 Calvo RM, Jauniaux E, Gulbis B, Asunción M, Gervy C, et al. (2002) Fetal tissues are exposed to biologically relevant free thyroxine concentrations during early phases of development. J Clin Endocrinol Metab 87: 1768-1777.

10 Burman KD, Read J, Dimond RC, Strum D, Wright FD, et al. (1976) Measurements of 3,3',5'-triiodothyronine (reverse t3), 3,3'-l-diiodothyronine, t3, and t4 in human amniotic fluid and in cord and maternal serum. J Clin Endocrinol Metab. 43: 405-607.

11 Zhang JS, Lazar MA (2000) The mechanism of action of thyroid hormones. Annu Rev Physiol 62: 439-466.

12 Klein I, Ojamaa K (2001) Thyroid hormone and the cardiovascular system. N Engl J Med 344: 501-509.

13 Delitala AP, Steri M, Pilia MG, Dei M, Lai S, et al. (2016) Menopause modulates the association between thyrotropin levels and lipid parameters: The SardiNIA study. Maturitas 92: 30-34.

14 Rodríguez CAC, Martínez LP (2012) Clinical implications of thyroid hormones effects on nervous system development. Pediatr Endocrinol Rev 9: 644-649.

15 Braverman LE (2013) Werner and Ingbar's the thyroid: A fundamental and clinical text. Lippincott 10: 304-506.

16 Korevaar TIM, Medici M, Visser TJ, Peeters RP (2017) Thyroid disease in pregnancy: New insights in diagnosis and clinical management. Nat Rev Endocrinol 13: 610-622.

17 Samuels MH (2002) Lab med pract guidel lab support diagnosis. Monit Thyroid Dis Thyroid 13: 32257-32592.

18 Glinoer D (1997) The regulation of thyroid function in pregnancy : Pathways of endocrine adaptation from physiology. Endocr Rev 18: 404-433.

19 Ahmed OM, Abd El-Tawab SM, Ahmed RG (2010) Effects of experimentally induced maternal hypothyroidism and hyperthyroidism on the development of rat offspring: The development of the thyroid hormones-neurotransmitters and adenosinergic system interactions. Int J Dev Neurosci 28: 437-454.

20 Glinoer D (2007) The importance of iodine nutrition during pregnancy. Public Health Nutr 10: 1542-1546.

21 Retardation IG (2000) Circulating Iodide Concentrations during and after. J Clin Endocrinol Metab 85:1999-2001.

22 Sterrett M (2019) Maternal and fetal thyroid physiology. Clin Obstet Gynecol 62: 302-307.

23 Glinoer D, Sterrett M (2000) Food and nutrition board IM dietary references intakes. J Clin Endocrinol Metab 85: 1999-2001.

24 Fanciulli G, Zoledziewska M (2001) Assessment of the iodine deficiency disorders and monitoring their elimination. WHO 23: 102-107.

25 Alexander EK, Elizabeth P, Brent G (2007) Guidelines of the American thyroid association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 27: 315-389.

26 Chin LC, Jones MK, Kingham JGC (2007) Celiac disease and autoimmune thyroid disease. Clin Med Res 5: 184-192.

27 Delitala AP, Fanciulli G, Zoledziewska M (2015) Allelic variant in CTLA4 is associated with thyroid failure and faster β-cell exhaustion in latent autoimmune diabetes in adults. J Diabetes 7:68-73.

28 Tomer Y, Davies TF (2003) Searching for the autoimmune thyroid disease susceptibility genes: From gene mapping to gene function. Endocr Rev 24: 694-717.

29 Weetman AP (1994) Autoimmune thyroid disease: Further developments in our understanding. Endocr Rev 15: 788-830.

30 Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Rasmussen U, et al. (2003) Laboratory medicine, practice guidelines, laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid 32: 257-259.

31 Glinoer D, Riahi M, Grün JP (1994) Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. J Clin Endocrinol Metab 79: 197-204.

32 Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, et al. (2006) Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: Effects on obstetrical complications. J Clin Endocrinol Metab 91: 2587-2591.

33 Seror J, Amand G, Guibourdenche J, Ceccaldi PF, Luton D (2014) Anti-TPO antibodies diffusion through the placental barrier during pregnancy. PLoS One 9: 2-6.

34 Patel J, Landers K, Li H, Mortimer RH, Richard K (2011) Delivery of maternal thyroid hormones to the fetus. Trends Endocrinol Metab 22: 164-170.

35 Li H, Patel J, Mortimer RH, Richard K (2012) Ontogenic changes in human placental sodium iodide symporter expression. Placenta 33: 946-948.

36 Panesar NS, Li CY, Rogers MS (2001) Reference intervals for thyroid hormones in pregnant Chinese women. Ann Clin Biochem 38: 329-332.

37 De Groot L, Abalovich M, Alexander EK (2012) Management of thyroid dysfunction during pregnancy and postpartum: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 97: 2543-2565.

38 Fadeyev VV (2015) Comments to the European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Clin Exp Thyroidol 10: 20.

39 Lee RH, Spencer CA, Mestman JH, Miller EA, Petrovic I, et al. (2009) Free T4 immunoassays are flawed during pregnancy. Am J Obstet Gynecol 200: 260-260.

40 Weeke J, Dybkj L, Kj E, Laurberg P, Magnusson B (1982) A longitudinal study of serum TSH , and total and free iodothyronines during normal pregnancy. Eur J Endocrinol 101: 531-537.

41 Bestwick JP, John R, Maina A, Guaraldo V, Joomun M, et al. (2014) Thyroid stimulating hormone and free thyroxine in pregnancy: Expressing concentrations as multiples of the median (moms). Clin Chim Acta 430: 33-37.

42 Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, et al. (2000) Maternal thyroid deficiency and pregnancy complications: Implications for population screening. J Med Screen 7: 127-130.

43 Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, et al. (2002) Overt and subclinical hypothyroidism complicating pregnancy. Thyroid 12: 63-68.

44 Leung AS, Millar LK, Koonings PP, Montoro M (1993) Perinatal outcome in hypothyroid pregnancies. Obs Gynecol 81: 349-353.

45 Taylor PN, Minassian C, Rehman A (2014) TSH levels and risk of miscarriage in women on long-term levothyroxine: A community-based study. J Clin Endocrinol Metab 99: 3895-3902.

46 Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, et al. (2010) Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. J Clin Endocrinol Metab 95: 44-48.

47 Casey BM, Dashe JS, Spong CY, McIntire DD, Leveno KJ, et al. (2007) Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. Obstet Gynecol 109: 1129-1135.

48 Cleary Goldman J, Malone FD, Lambert Messerlian G (2008) Maternal thyroid hypofunction and pregnancy outcome. Obstet Gynecol 112: 85-92.

49 Männistö T, Vääräsmäki M, Pouta A, Hartikainen AL, Ruokonen A, et al. (2010) Thyroid dysfunction and autoantibodies during pregnancy as predictive factors of pregnancy complications and maternal morbidity in later life. J Clin Endocrinol Metab 95: 1084-1094.

50 Chan S, Boelaert K (2015) Optimal management of hypothyroidism, hypothyroxinaemia and euthyroid TPO antibody positivity preconception and in pregnancy. Clin Endocrinol (Oxf) 82: 313-326.

51 Haddow JE, Palomaki GE, Allan WC (1999) Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 55: 3-9.

52 Korevaar TIM, Muetzel R, Medici M (2016) Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: A population-based prospective cohort study. Lancet Diabetes Endocrinol 4: 35-43.

53 Reading R (2012) Antenatal thyroid screening and childhood cognitive function. Child Care Health Dev 38:605-608.

54 Casey B (2016) Effect of treatment of maternal subclinical hypothyroidism or hypothyroxinemia on IQ in offspring. Am J Obstet Gynecol 214: 2-10.

55 Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, et al. (2011) Association between thyroid autoantibodies and miscarriage and preterm birth: Meta-analysis of evidence. BMJ 342: 1-8.

56 Negro R, Mangieri T, Coppola L (2005) Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: A prospective study. Hum Reprod 20: 1529-1533.

57 Wang H, Gao H, Chi H (2017) Effect of Levothyroxine on miscarriage among women with normal thyroid function and thyroid autoimmunity undergoing in vitro fertilization and embryo transfer a randomized clinical trial. J Am Med Assoc 318: 2190-2198.

58 Dhillon-Smith RK, Middleton LJ, Sunner KK (2019) Levothyroxine in women with thyroid peroxidase antibodies before conception. N Engl J Med NEJ 12: 9-25.

59 Pop VJ, Kuijpens JL, Van Baar AL, Verkerk G, Van Son MM, et al. (1999) Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf) 50: 147-155.

60 Casey BM (2006) Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol Surv 61: 415-420.

61 Bestwick JP (2015) Practice Bulletin No. 148: Thyroid disease in pregnancy. Obstet Gynecol 125: 996-1005.

62 Lazarus JH, Bestwick JP, Channon S, Paradice R, Maina A, et al. (2012) Antenatal thyroid screening and childhood cognitive function. New Eng J Med 366: 493-501.

63 Vaidya B, Anthony S, Bilous M, Shields B, Drury J, et al. (2007) Brief report: Detection of thyroid dysfunction in early pregnancy: Universal screening or targeted high-risk case finding? J Clin Endocrinol Metab 92: 203-207.

64 Ong GSY, Hadlow NC, Brown SJ, Lim EM, Walsh JP (2014) Does the thyroid-stimulating hormone measured concurrently with first trimester biochemical screening tests predict adverse pregnancy outcomes occurring after 20 weeks gestation? J Clin Endocrinol Metab 99: 2668-2672

65 Thung SF, Funai EF, Grobman WA (2009) The cost-effectiveness of universal screening in pregnancy for subclinical hypothyroidism. Am J Obstet Gynecol 200: 266-267.

66 Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, et al. (2010) Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. J Clin Endocrinol Metab 95: 1699-1707.

67 Roti E, Gardini E, Minelli R, Bianconi L, Flisi M (1991) Thyroid function evaluation by different commercially available free thyroid hormone measurement kits in term pregnant women and their newborns. J Endocrinol Investig 14: 1-9.

68 Medici M, Timmermans S, Visser W, Schrama SM, Jaddoe VW, et al. (2013) Maternal thyroid hormone parameters during early

pregnancy and birth weight: the Generation R Study. J Clin Endocrinol Metab 98: 59-66.

69 Korevaar TI, Schalekamp-Timmermans S, de Rijke YB, Visser WE, Visser W, et al. (2013) Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: The generation R study. J Clin Endocrinol Metab 98: 4382-4390.

70 Palareti G, Legnani C, Cosmi B, Antonucci E, Erba N, et al. (2016) Comparison between different D-D imer cutoff values to assess the individual risk of recurrent venous thromboembolism: Analysis of results obtained in the Dulcis. Int J Lab Hematol 38: 9-42.

71 Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, et al. (2004) Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med 351: 241-249.

72 Yassa L, Marqusee E, Fawcett R, Alexander EK (2010) Thyroid hormone early adjustment in pregnancy (the THERAPY) trial. J Clin Endocrinol Metab 95: 3234-3241.

73 Calina D, Docea AO, Golokhvast KS, Sifakis S, Tsatsakis A, et al. (2019) Management of endocrinopathies in pregnancy: a review of current evidence. Int J Environ Res Public Health 16: 781.

74 Liu H, Shan Z, Li C, Mao J, Xie X, et al. (2014) Maternal subclinical hypothyroidism, thyroid autoimmunity, and the risk of miscarriage: A Prospective Cohort Study. 24: 1642-1649.

75 Lepoutre T, Debiève F, Gruson D, Daumerie C (2012) Reduction of miscarriages through universal screening and treatment of thyroid autoimmune diseases. 74: 265-273.

76 Dubbs SB, Spangler R (2014) Hypothyroidism: Causes, killers, and life-saving treatments. 32: 303-317.

77 Rodriguez I, Fluiters E, Perez-Mendez LF, Luna R, Páramo C, et al. (2004) Factors associated with mortality of patients with myxoedema coma: prospective study in 11 cases treated in a single. Int J Environ Res. 180: 50.

78 Popoveniuc G, Chandra T, Sud A, Sharma M, Blackman MR, et al. (2014) A diagnostic scoring system for myxedema coma. Endocrine Practice. 20:808-817.

79 Popoveniuc G, Chandra T, Sud A, Sharma M, Blackman MR, et al. (2014) A diagnostic scoring system for myxedema coma. Endocr Pract 20: 808-817.

80 Cooper DS, Laurberg P (2013) Hyperthyroidism in pregnancy. Lancet Diabetes Endocrinol 1: 238-249.

81 Andersen SL, Olsen J, Carlé A, Laurberg P (2015) Hyperthyroidism incidence fluctuates widely in and around pregnancy and is at variance with some other autoimmune diseases: A Danish population-based study. J Clin Endocrinol Metab 100: 1164-1171.

82 Casey BM, Dashe JS, Wells CE, McIntire DD, Leveno KJ, et al. (2006) Subclinical hyperthyroidism and pregnancy outcomes. Obstet Gynecol 107: 337-341.

83 Krassas GE, Poppe K, Glinoer D (2010) Thyroid function and human reproductive health. Endocr Rev 31: 702-755.

84 Moleti M, Trimarchi F, Vermiglio F (2014) Thyroid physiology in pregnancy. Endocrine Practice 20: 589-596.

85 Glinoer D, Spencer CA (2010) Serum TSH determinations in pregnancy: How, when and why?. Nat Rev Endocrinol 6: 526-529.

86 Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, et al. (2017) Guidelines of the American thyroid association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid 27: 315-389.

87 Goldman AM, Mestman JH (2011) Transient non-autoimmune hyperthyroidism of early pregnancy. J Thyroid Res.14: 2413.

88 Goodwin TM, Montoro M, Mestman JH (1992) Transient hyperthyroidism and hyperemesis gravidarum: Clinical aspects. Am J Obstet Gynecol 167: 648-652.

89 Yeo CP, Khoo DH, Eng PH, Tan HK, Yo SL, et al. (2001) Prevalence of gestational thyrotoxicosis in Asian women evaluated in the 8th to 14th weeks of pregnancy: correlations with total and free beta human chorionic gonadotrophin. Clin Endocrinol 55: 391-398.

90 Grün JP, Meuris S, De Nayer P, Glinoer D (1997) The thyrotrophic role of human Chorionic Gonadotrophin (hCG) in the early stages of twin *(versus* single) pregnancies. Clin Endocrinol 46: 719-725.

91 Lockwood CM, Grenache DG, Gronowski AM (2009) Serum human chorionic gonadotropin concentrations greater than 400,000 IU/L are invariably associated with suppressed serum thyrotropin concentrations. Thyroid 19: 863-868.

92 Pekary AE, Jackson IM, Goodwin TM, Pang XP, Hein MD, et al. (1993) Increased *in vitro* thyrotropic activity of partially sialated human chorionic gonadotropin extracted from hydatidiform moles of patients with hyperthyroidism. J Clin Endocrinol Metab 76: 70-74.

93 Quinlan JD, Hill DA (2003) Nausea and vomiting in pregnancy. Am Fam 68: 121-128.

94 Shaheen M, Sulaman H, Tariq M, Shahid A, Nayyer U (2021) Comparison of efficacy and tolerability of ondansetron *vs* metoclopramide in the treatment of hyperemesis gravidarum. Pakistan J Medical Health Sci 15: 1205-1207.

95 Yoshihara A, Noh JY, Mukasa K, Suzuki M, Ohye H, et al. (2015) Serum human chorionic gonadotropin levels and thyroid hormone levels in gestational transient thyrotoxicosis: Is the serum hCG level useful for differentiating between active Graves' disease and GTT. Endocr J 62: 557-560.

96 Glinoer D, De Nayer PH, Robyn C, Lejeune B, Kinthaert J, et al. (1993) Serum levels of intact Human Chorionic Gonadotropin (HCG) and its free a and β subunits, in relation to maternal thyroid stimulation during normal pregnancy. J Endocrinol Invest 16: 881-888.

97 Walkington L, Webster J, Hancock BW, Everard J, Coleman RE (2011) Hyperthyroidism and human chorionic gonadotrophin production in gestational trophoblastic disease. Br J Cancer 104: 1665-1669.

98 Weetman AP (2010) Immunity, thyroid function and pregnancy: molecular mechanisms. Nat Rev Endocrinol. 6: 311-318.

99 Aluvihare VR, Kallikourdis M, Betz AG (2004) Regulatory T cells mediate maternal tolerance to the fetus. Nat Immunol 5: 266-271.

100 Pearce EN (2015) Thyroid disorders during pregnancy and postpartum. Best Pract Res Clin Obstet Gynaecol 29: 700-706.

101 Marx H, Amin P, Lazarus JH (2008) Hyperthyroidism and pregnancy. Brit Med J 336: 663-667.

102 Luton D, Le Gac I, Vuillard E, Castanet M, Guibourdenche J, et al. (2005) Management of Graves' disease during pregnancy: the key role of fetal thyroid gland monitoring. J Clin Endocrinol Metab 90: 6093-6098.

103 Rotondi M, Cappelli C, Pirali B, Pirola I, Magri F, et al. (2008) The effect of pregnancy on subsequent relapse from Graves' disease after a successful course of antithyroid drug therapy. J Clin

Endocrinol Metab 93: 3985-3988.

104 Van Dijk MM, Smits IH, Bisschop PH (2018) Maternal thyrotropin receptor antibody concentration and the risk of fetal and neonatal thyrotoxicosis: A Systematic Review. Thyroid 28: 257-264.

105 Polak M (1998) Hyperthyroidism in early infancy: Pathogenesis, clinical features and diagnosis with a focus on neonatal hyperthyroidism. Thyroid 8: 1171-1177.

106 Polak M, Le Gac I, Vuillard E, Guibourdenche J, Leger J, et al. (2004) Fetal and neonatal thyroid function in relation to maternal Graves' disease. Best Pract Res Clin Endocrinol Metab 18: 289-302.

107 Zimmerman D (1999) Fetal and neonatal hyperthyroidism. Thyroid 9: 727-733.

108 Okosieme OE, Lazarus JH (2015) Important considerations in the management of Graves' disease in pregnant women. Expert Rev Clin Immunol 11: 947-957.

109 Matsuura N, Harada S, Ohyama Y, Shibayama K, Fukushi M, et al. (1997) The mechanisms of transient hypothyroxinemia in infants born to mothers with Graves' disease. Pediatr Res 42: 214-218.

110 Mandel SJ, Cooper DS (2001) The use of antithyroid drugs in pregnancy and lactation. J Clin Endocrinol Metab 86: 2354-2359.

111 Bliddal S, Rasmussen AK, Sundberg K, Brocks V, Feldt-Rasmussen U (2011) Antithyroid drug-induced fetal goitrous hypothyroidism. Nat Rev Endocrinol 7: 396-406.

112 Marchant B, Brownlie BE, Hart DM, Horton PW, Alexander WD (1977) The placental transfer of propylthiouracil, methimazole and carbimazole. J Clin Endocrinol Metab 45: 1187-1193.

113 Khoo CM, Lee KO (2013) Endocrine emergencies in pregnancy. Best Pract Res Clin Obstet Gynaecol 27: 885-891.

114 Tingi E, Syed A A, Kyriacou A, Mastorakos G, Kyriacou A (2016) Benign thyroid disease in pregnancy: A state of the art review. J Clin Transl Endocrinol 6: 37-49.

115 Sugiyama Y, Tanaka R, Yoshiyama Y (2017) A case of sudden onset thyroid storm just before cesarean section manifesting congestive heart failure and pulmonary edema. JA Clin Reports. 3: 20.