



Review Article

Hypothyroidism and isolated hypothyroxinemia in pregnancy, from physiology to the clinic



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ABSTRACT

Many changes occur in the physiology of the maternal thyroid gland to maintain an adequate level of thyroid hormones (THs) at each stage of gestation during normal pregnancy, however, some factors can produce low levels of these hormones, which can alter the onset and progression of pregnancy. Deficiency of THs can be moderate or severe, and classified as overt or clinical hypothyroidism, subclinical hypothyroidism, and isolated hypothyroxinemia. Overt hypothyroidism has been reported in 0.3–1.9% and subclinical hypothyroidism in approximately 1.5–5% of pregnancies. With respect to isolated hypothyroxinemia, the frequency has been reported in approximately 1.3% of pregnant women, however it can be as high as 25.4%. Worldwide, iodine deficiency is the most common cause of hypothyroidism, however, in iodine-sufficient countries like the United States, the most common cause is autoimmune thyroiditis or Hashimoto's thyroiditis. The diagnosis and timely treatment of deficiency of THs (before or during the first weeks of gestation) can significantly reduce some of the related adverse effects, such as recurrent pregnancy loss, preterm delivery, gestational hypertension, and alterations in the offspring. However, so far there is no consensus on the reference levels of thyroid hormones during pregnancy to establish the diagnosis and there is no consensus on universal screening of women during first trimester of pregnancy to identify thyroid dysfunction, to give treatment and to reduce adverse perinatal events, so it is necessary to carry out specific studies for each population that provide information about it.

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Introduction

The most frequent thyroid alteration observed in pregnancy is hypothyroidism with subclinical hypothyroidism being more common than overt hypothyroidism [1,2]. However, the prevalence of hypothyroidism during pregnancy is variable, since it depends on the upper reference limit and method used to quantify thyroid stimulating hormone (TSH) [1]. Due to importance of making the diagnosis and monitoring of pregnant women with hypothyroidism, this review addresses molecular, epidemiological aspects, clinical presentation, diagnosis, treatment and prognosis of overt

and subclinical hypothyroidism, as well as isolated hypothyroxinemia.

Thyroid hormones during pregnancy

The pregnant woman

Many changes occur in the physiology of the maternal thyroid gland to maintain an adequate level of thyroid hormones (THs) at each stage of gestation during normal pregnancy [1,3,4]:

- (1) THs are transported in serum by the thyroxine binding globulin (TBG), transthyretin and albumin [4–6]. During pregnancy, the concentration of TBG is increased two to three times. This increase produces an elevation of total thyroxine (T4) and triiodothyronine (T3) levels, and reduction in TSH

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levels [6]. Transthyretin and albumin in conjunction with α -1-antitrypsin y β -1-acid glycoprotein are secreted into the maternal and fetal circulation. These proteins can locally regulate the maternal-fetal hormonal transport, alter the reuptake of THs and deiodination [4]. Transthyretin impedes active deiodination of maternal THs in the placenta, allowing it to reach high concentrations and passing THs to the fetal circulation [4]. Albumin has low affinity but high capacity for binding to THs and has been found in the trophoblast glycocalyx, where it can participate in the recapture and protection of THs or act as a transporter of the hormone in the fetal circulation [7].

- (2) The iodothyronine deiodinases are mediators of the action of THs and are found throughout the body [8]. The deiodinases can modify the signaling of THs in target cells to regulate the reservoir of cytoplasmic T3, the nuclear concentration of T3 and the saturation of THs receptors, all of this independently of circulating THs levels [6]. During pregnancy, changes in the expression of deiodinases occur in the uterus, type III deiodinase being the most expressed at the beginning of pregnancy and type II deiodinase the most expressed in the first trimester. Since THs can reach the fetus through the placenta, the amniotic fluid and the umbilical cord, the deiodinases are ubiquitously expressed in the fetus, as their activation or inactivation is crucial to protect the product from exposure to inappropriate THs [8].
- (3) The increase in renal clearance of iodine, secondary to increased glomerular filtration rate, causes a decreased concentration of circulating iodine during pregnancy, which constitutes a stimulus for the maternal thyroid with an increased risk of hypothyroidism and goiter due to iodine deficiency [4,6]. It is noteworthy that iodine is transported in the thyroid follicle and through the placental tissue by a similar mechanism involving the capture of iodine through the sodium-iodide symporter in the thyrocytes and their release into the thyroid follicle for THs synthesis through pendrin, an ion transporter. Both sodium-iodide symporter and pendrin are expressed in the placenta, which appears to allow the transport of iodine from the mother to the fetal circulation [9].
- (4) The human chorionic gonadotropin β -subunit has mild thyrotropic activity, and in pregnancy it levels is elevated, with increase in free THs and decreased levels of TSH [2,4,6].
- (5) Thyroglobulin often rises during pregnancy and has been associated with increased volume of the thyroid gland in goiter of pregnancy (5–15% of cases) [6].
- (6) The action of THs in target tissue requires their active transport across the plasma membrane. In the placenta, the expression of at least six different types of membrane THs transporters has been demonstrated: MCT8, MCT10, LAT1, LAT2, Oatpla2 and Oatp4a1 [10]. These proteins contribute to the maternal-fetal exchange of THs in the first weeks of pregnancy and apparently are involved in the regulation of trophoblast activity (equilibrium apoptosis/cellular proliferation) [10].

By the other hand, environmental factors can cause alterations in thyroid function during pregnancy, for example: environmental pollutants, such as dioxins (polychlorinated dibenzo-p-dioxins, dibenzofurans) and polychlorinated biophenyls (compounds that accumulate in the food chain) may affect thyroid function in pregnancy [11–13], and cigarette smoking has been associated with changes in maternal thyroid function throughout the pregnancy and in fetal thyroid function [14,15].

Offspring

Maternal THs can be identified in the embryo at approximately four weeks of gestation [16,17], however, nuclear receptors of THs are present in the fetal brain at eight to nine weeks of gestation reaching adult levels at 18 weeks of gestation (Fig. 1) [17].

In the first half of pregnancy, the THs involved in the development of the fetal central nervous system come only from the mother. At approximately six weeks of gestation, the participation of maternal free thyroxine (FT4) initiates neuronal proliferation and neuronal migration in the fetal cerebral cortex, the hippocampus, and the fetal medial ganglionic eminence. At the start of the second trimester, the fetal thyroid starts producing its own hormones, with a total development of the hypothalamic-pituitary-thyroid system at 18–20 weeks of gestation [16]. THs are also involved in neurogenesis, neuronal migration, axonal growth, dendritic branching and synaptogenesis, glial differentiation and migration, as well as the onset of myelination [17].

Finally, the maternal THs and those produced by the offspring are involved in neurodevelopment until birth, when the fetal thyroid reaches full maturity [17].

Hypothyroidism and hypothyroxinemia during pregnancy

Definition

Hypothyroidism is a condition characterized by insufficient production of THs by the thyroid gland (primary), by the decrease of the pituitary (secondary), or hypothalamic (tertiary) stimulus [18].

Deficiency of THs can be moderate or severe, called overt or clinical hypothyroidism when TSH is above the upper limit of normal and FT4 is lower than the range of reference [18], while subclinical hypothyroidism is when the level of TSH levels are above the upper limit of normal and FT4 is within the reference range. Isolated hypothyroxinemia is defined as a normal maternal TSH concentration and FT4 concentration is lower than the range of reference [19].

Epidemiology

Overt hypothyroidism, has been reported in 0.3–1.9% of pregnant women [1,2,20–22], whereas the subclinical hypothyroidism has been reported in approximately 1.5–5% of pregnancies [1,2,23–26]. Since the American Thyroid Association (ATA) recommended in 2011 to use the upper limit of TSH 2.5 mIU/ml in the first trimester, an increase in the prevalence of hypothyroidism during pregnancy was observed [27]. With respect to isolated hypothyroxinemia, the frequency has been reported in approximately 1.3% of pregnant women, however it can be as high as 25.4% [4]. Apparently these differences are related to maternal iodine intake, diagnostic criteria, trimester of pregnancy or the measurement method of FT4 [2,25].

Etiology

Worldwide, iodine deficiency is the most common cause of hypothyroidism, however, in iodine-sufficient countries like the United States, the most common cause is autoimmune thyroiditis or Hashimoto's thyroiditis [28]. Marginal dietary iodine deficiency is one of the most common causes of isolated hypothyroxinemia [2].

On the other hand, other risk factors for the development of hypothyroidism during pregnancy have now been defined (Table 1).

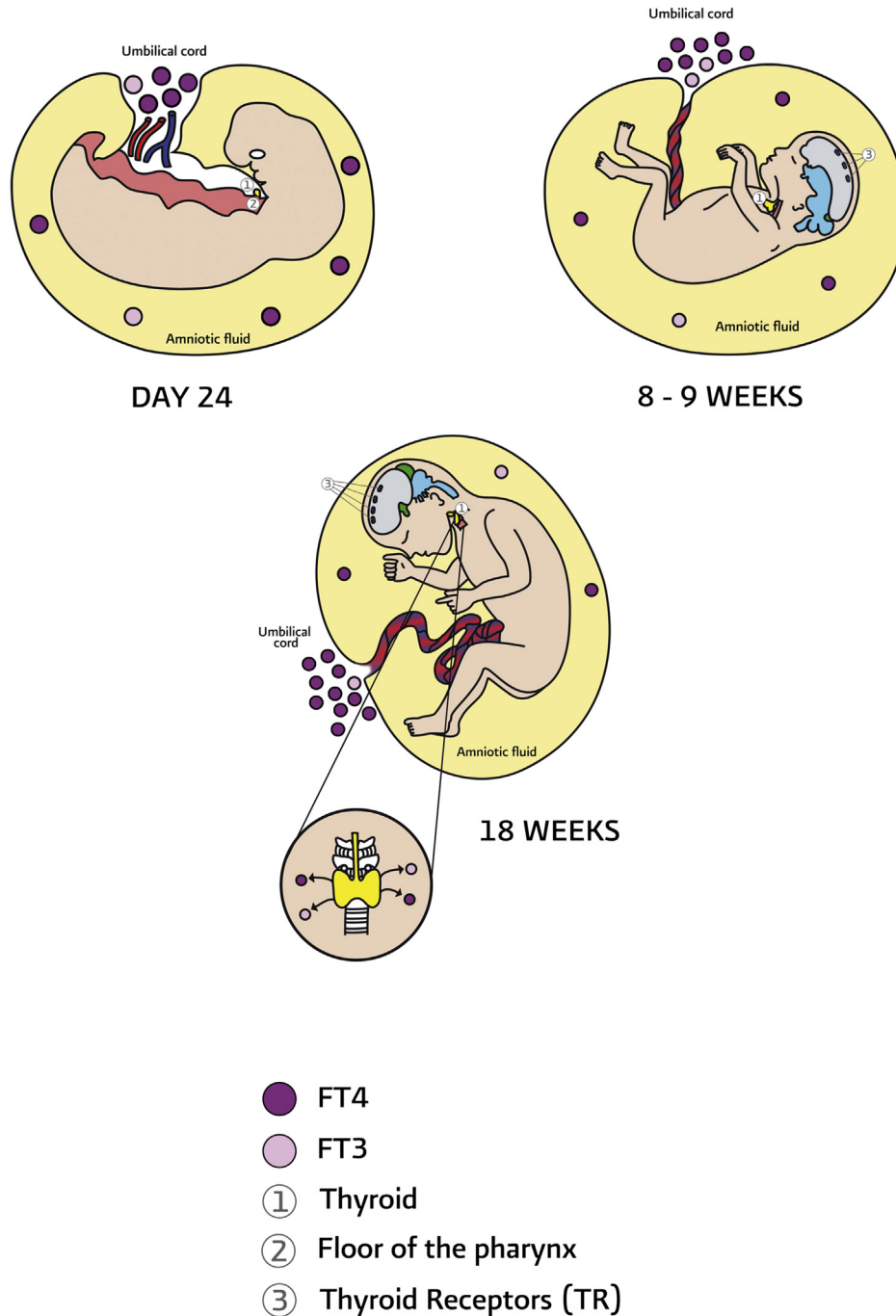


Fig. 1. Development of the thyroid gland on the 24th day of gestation: It is the first endocrine gland that appears in the developing embryo. It begins to form at approximately 24 days of gestation from the medial endodermal thickening in the floor of the primitive pharynx. The thyroid hormones (THs) are identified in the embryo from the 28th day of gestation. They come exclusively from the mother through the umbilical cord and the amniotic fluid. **Development of the thyroid gland at 8–9 weeks of gestation:** As the embryo grows, the thyroid gland descends through the neck, in front of the hyoid bone and laryngeal cartilages. For a short period, the thyroid gland is connected to the tongue by the thyroglossal duct. At seven weeks of gestation, the thyroid gland takes its final form and reaches its final location and the thyroglossal duct degenerates and disappears. Thyroid hormones (TH) come from the mother through the umbilical cord and amniotic fluid. The nuclear receptors of thyroid hormones are already present in the fetal brain. **Development of the thyroid gland at 18 weeks gestation:** The fetal thyroid gland is in its final position and initiates the production of thyroid hormones by the fetus, with the total development of the hypothalamic-pituitary-thyroid system. Thyroid hormones come from the mother and fetus [16].

Diagnosis

Clinical picture

Isolated hypothyroxinemia and subclinical hypothyroidism often be asymptomatic, whereas overt hypothyroidism may occur with highly nonspecific symptoms, such as weakness,

lethargy, slurred speech, memory impairment, intolerance to cold, coarse hair, eyelid edema, facial and peripheral edema, macroglossia, goiter, cardiomegaly, bradycardia, constipation, decreased osteotendonous reflexes, pale, cold, dry, thick skin, decreased sweating and inappropriate weight gain for gestational age [18].

Table 1
Risk factors for thyroid dysfunction during pregnancy [4,22–24].

• Age >30 years
• Personal history of thyroid dysfunction
- History of goiter
- History of positive antithyroid antibodies
• Personal history of thyroid surgery
• Family history of thyroid illness
• Clinical symptoms or signs suggestive of hypo-hyperthyroidism
• Diabetes mellitus type 1
• History of recurrent loss of pregnancy or preterm childbirth
• History of infertility
• Autoimmune disease (vitiligo, adrenal insufficiency, hypoparathyroidism, atrophic gastritis, pernicious anemia, systemic sclerosis, systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, among others)
• History of radiation in the head or neck
• Morbid obesity (body mass index ≥ 40 kg/m ²)
• Age greater than 30 years
• History of treatment with Amiodarone, Lithium, Interferon- α (IFN- α), Sorafenib or Sunitinib
• History of exposure to iodine contrast media in the last 6 weeks
• β -Thalassemia or pernicious anemia
• Hyperprolactinemia
• Dyslipidemia
• Depression
• Turner's Syndrome
• Down Syndrome
• History of cardiac failure
• Residing in an area moderate to severe iodine deficiency

Laboratory diagnosis

Due increased metabolic needs during pregnancy, thyroid function test results of healthy pregnant women differ from those of healthy nonpregnant women, the ATA in 2012 proposed pregnancy-specific and ideally trimester specific reference intervals for TSH and FT4 [19]. However, recent studies have shown that the TSH reference limit should be so strict, for example studies in Asia, India and Netherlands have been demonstrated only a modest reduction in the TSH upper reference limit [1]. Actually, primary overt hypothyroidism during pregnancy is defined by a TSH value greater than the upper limit expected during gestation (>4.0 mIU/L) and decreased serum FT4 concentration, or TSH levels of 10.0 mIU/L or above, irrespective of their FT4 levels [1]. Sub-clinical hypothyroidism in pregnancy is defined as a serum TSH value between 4.0 and 10 mIU/L with a normal FT4 levels [1]. Isolated hypothyroxinemia in pregnancy is defined as a normal TSH value in conjunction with FT4 concentrations in the lower 2.5th - 5th percentile of the reference range [1].

In view of the significant geographic and ethnic diversity in TSH concentrations of pregnancy, the new guideline of the ATA recommend calculating optimal reference range in each population, hospital, or laboratory, but if these are not available, in the first trimester a TSH upper reference limit of 4.0 mIU/L, with a gradual return towards the TSH range in thyroid disease-free non-pregnant individuals (0.45–4.5 mIU/L) [18,20] in the second and third trimester [1].

Interpretation of FT4 levels depends on the type of assay used for measurement, and the amount of iodine intake in each patient. The recommended method to assess FT4 is dialysate or ultrafiltrate of serum samples employing online solid phase extraction-liquid chromatography/tandem mass spectrometry [1,19,29].

Thyroid antibodies (TAB) can be detected in approximately 30–60% of pregnant women with an elevated TSH concentration, and thyroid peroxidase antibodies (TPOAb) positive women may be at increased risk for adverse events in comparison to TPOAb negative [30]. For this reason, ATA recommends assessment of TPOAb to make treatment decisions [4].

Treatment

Nonpregnant women or women who are planning pregnancy, should intake 150 μ g (μ g) daily of iodine (potassium iodide) (dietary and supplement) and pregnant and lactating women should intake 250 μ g [1].

Overt hypothyroidism should be treated before conception with levothyroxine as the first choice with a goal of TSH less than 2.5 mIU/L in women planning to become pregnant [2]. During pregnancy, there is a gradual increase in the requirements of T4 from four to six weeks to 16–20 weeks of gestation. As T4 requirements remain high until the end of pregnancy, monitoring of TSH and FT4 levels should be performed and appropriate adjustments in treatment made [31].

An increase of two doses per week (29% increase) immediately after a suspected pregnancy for women who before pregnancy remained euthyroid with a daily dose of levothyroxine (regardless of amount), is recommended, but it is important to take into account that both the etiology of maternal hypothyroidism as well as the preconception TSH levels may modify the requirements for levothyroxine [1,2,19]. Monitoring of TSH levels during pregnancy must be performed approximately every four weeks during the first half of pregnancy, and at least once between 26 and 32 weeks of gestation [32].

For women whose overt hypothyroidism is diagnosed in pregnancy, treatment with levothyroxine should be started immediately to normalize as soon as possible the thyroid function test. The re-evaluation of thyroid function should be performed within 30–40 days, and then every four to six weeks; based on this, adjust the dose of levothyroxine should be adjusted [2].

After the termination of pregnancy, the dose of levothyroxine should be further adjusted and reduced with monitoring of serum TSH levels six weeks later; however it must be taken into account that more than 50% of women with Hashimoto's thyroiditis required an increase in the pregestational THs dose in the post-partum period [1,19,33].

For women with subclinical hypothyroidism, only when TPOAb positive are present, treatment with levothyroxine is recommended to maintain the TSH level in the normal range for pregnancy [1,19,34], however, Italian Society of Endocrinology (ISE) and the Italian Thyroid Association (ITA) even suggest treating patients with TSH ranging from 2.5 to 4.0 mIU/L and positive TPOAb, particularly in the first trimester of pregnancy, because levothyroxine is not harmful and likely prevents further increases in serum TSH levels [35]. In the case of subclinical hypothyroidism with negative antibodies, levothyroxine therapy should be considered in accordance with recommendations of the ATA in 2017 [1], however, ISE and ITA suggested giving treatment with levothyroxine since negative test for TPOAb are found in a consistent proportion of patients with chronic autoimmune thyroiditis due to immune suppressive status in pregnancy and the disease also may occur in the absence of positive test for TPOAb (serum-negative autoimmune thyroiditis) [35]. If levothyroxine is prescribed for subclinical hypothyroidism, thyroid function should be reassessed after pregnancy to confirm whether continuation is necessary [36]. Levothyroxine therapy is not recommended for women with TPOAb negative with a normal TSH.

In the case of isolated hypothyroxinemia, in addition to iodine supplementation, there is insufficient evidence to recommend the use of levothyroxine [1,2,26].

Complications

Iodine deficiency and low concentrations of maternal THs are risk factors for some obstetric complications and are related to alterations in fetal growth and neurodevelopment.

(1) Women euthyroid with positive thyroid antibodies:

Some studies have reported increased risk of abortion [37], premature delivery [38], perinatal death [39], postpartum thyroid dysfunction [40], postpartum depression [41], neonatal respiratory distress syndrome [42] and delayed psychomotor and intellectual development in their offsprings [43].

(2) Women with overt hypothyroidism:

They have increased risk of abortion, anemia in pregnancy, arterial hypertension and preeclampsia, abruptio placentae, threatened preterm labor, preterm delivery, postpartum hemorrhage, cardiac insufficiency, low birthweight, increased neonatal respiratory distress, and stillbirth [26]. Restriction of intrauterine growth, which is usually linked with placental insufficiency, has been associated with mild deficits in neurodevelopment, and has been partially related with decreased circulating THs in the fetus and decreased cerebral expression of THs receptors [44]. The deficiency of iodine and maternal THs in early gestational ages has been associated with changes in behavior and decreased cognitive abilities in the offspring, particularly problems in attention and visual processing as well as changes in gross motor skills [38,45]. Untreated women with hypothyroidism in pregnancy, it has been associated with delayed psychomotor development, language and attention disorders and a decrease of approximately seven points in the intellectual development of the offsprings in comparison with those of euthyroid women [19,46,47].

(3) Women with subclinical hypothyroidism:

It has been reported that they have increased risk of loss of pregnancy, premature delivery, preeclampsia, breech delivery, and increase fetal mortality [23,24,48–50]. Also, subclinical hypothyroidism in pregnant women can adversely affect the performance on neuropsychological tests and vision development of their children [16,19,47,50,51]. However, other studies have not shown association of subclinical hypothyroidism with a consistent pattern of adverse outcomes [34].

(4) Women with isolated hypothyroxinemia:

Some studies have reported increased risk of premature delivery and premature rupture of membranes and higher mean birth weight [52]. Other study have shown that diagnosis in the first 20 weeks of gestation has been associated in some cases with increased risk of fetal distress (based on fetal heart rate variability analysis), musculoskeletal malformations and small for gestational age [50]. If the diagnosis is realized in the first 12 weeks, it has been associated with delayed psychomotor development at one to two years of age, a high risk of expressive language delay at 18–30 months of age [48,51]. However, other studies have reported no increased risk of alteration in the offsprings of women with isolated hypothyroxinemia [49,53].

Due high levels of TSH in women during pregnancy have been associated with adverse outcomes and impaired cognitive development in their offspring [54], randomized trial have evaluated the impact of levothyroxine treatment in women with subclinical hypothyroidism. It has been reported that levothyroxine treatment in women with TSH >2.5 mIU/L and TAb positive improves pregnancy outcome [25] and reduces the frequency of preterm delivery [34], but has not been reported significant effect of treatment on child intellectual development at 3.5 [55] and five years of age, however the results were limited by the late treatment initiated at an average of 17 weeks of gestation [56].

Screening

The decision whether or not to perform pregestational or in the first trimester of pregnancy universal screening should be based only on the possibility of identifying alterations in maternal thyroid hormone levels or the association that these alterations have with the higher frequency of adverse obstetric outcomes and offspring cognitive outcomes, but in the effect that the treatment of these alterations has on the frequency of adverse outcomes, so at present it is still controversial to universal screen for TSH and TAb. Therefore, studies that evaluate the effect of levothyroxine treatment from the first trimester of gestation on perinatal outcomes and on child intellectual development are necessary.

The American Association of Clinical Endocrinologists in 2002 recommended TSH routine screening for all women before pregnancy or in the first trimester [57]. By other hand, in 2017 the ATA recommended TSH testing in pregnant women only when they are considered high risk (Table 1) [4,18,19], however testing only high risk pregnant women, would miss about one third of women with hypothyroidism [49].

Newborns

In newborns TSH rises after birth, stimulating the thyroid gland to produce high concentrations of FT4 in the first postnatal week, where the synthesis of THs depends mainly on adequate prenatal and postnatal supplemental iodine [58].

Neonatal hypothyroidism has been reported with an incidence of one in 3000–4000 births and includes the temporary and permanent forms. Transient hypothyroidism can be caused by iodine deficiency or excess (paradoxical effect), use of anti-thyroid drugs and goitrogens during pregnancy, transplacental passage of maternal TAb that block the neonatal thyroid stimulating hormone receptors (TSHR), very low birthweight for gestational age and prematurity. However, even transient hypothyroidism can cause adverse outcomes, particularly alteration of neurological development in infants, so early diagnosis and treatment is widely recommended [58].

Pregnant women with autoimmune thyroid disease, including Hashimoto's thyroiditis, are at increased risk of fetal and neonatal complications. The clinical and hormonal picture in newborns depends on the type and amount of TAb that cross the placenta [58]. There is evidence of the relation between maternal autoimmune thyroid disease and transient congenital neonatal hypothyroidism. Close monitoring of newborns with TSH and FT4 at 48 h of life is recommended, with a repeat measurement between the 2nd and 4th week for those in whom an initial TSH >6 mUI/L has been reported, particularly in the case of mothers with autoimmune thyroid disease [58,59].

Conclusion

It is of paramount importance to understand the mechanisms of action of the THs, as well as the modifications during various stages of gestation that maintain adequate levels of these hormones, that participate not only in processes related to the implementation and progression of pregnancy, but also in key moments in the development of the embryonic, fetal and neonatal nervous system.

The ATA has suggested the use of specific benchmarks for each population, to establish the diagnosis of hypothyroidism. When using TSH reference points stricter than those used in nonpregnant women, there is the possibility of diagnosing an increased incidence of thyroid dysfunction during pregnancy. Some authors have even suggested universal screening to identify thyroid dysfunction for all women during the first trimester of pregnancy. Although this

measure would increase health care costs, it could permit the identification of hypothyroid women, and with timely provision of treatment and the reduction of perinatal and neonatal adverse events, this would result in health and economic benefits.

It is noteworthy that there is no consensus on the impact of universal screening in reducing adverse perinatal events. However, specific studies for each population could provide important information on the cost-benefit ratio of thyroid function evaluation, not only for women considered at risk. Also, it is crucial to evaluate the effect of early treatment with levothyroxine (before 16–20 weeks gestation) in the obstetrical and offspring risk, since the available evidence is limited to the late treatment initiation (after 17 weeks gestation, when the thyroid becomes functional).

Conflicts of interest statement

The authors have no conflicts of interest relevant to this article.

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