Chapter 1

Hypothyroidism, Fertility and Pregnancy

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http://dx.doi.org/10.5772/54328

1. Introduction

Pregnancy has a profound effect on the thyroid gland and its function. In iodine-replete countries, the gland size has been found to increase by 10% during pregnancy, and in areas of iodine deficiency, the gland size increases by 20%–40%. The prevalence of hypothyroidism during pregnancy is estimated to be 0.3–0.5% for overt hypothyroidism and 2–3% for subclinical hypothyroidism. Worldwide, iodine deficiency remains one of the leading causes of both overt and subclinical hypothyroidism. However, there are many other causes of hypothyroidism during pregnancy, including autoimmune thyroiditis, the most common organic pathology [1]. Other causes include the following: thyroid radioiodine ablation (to treat hyperthyroidism or thyroid cancer), hypoplasia and/or agenesis of the thyroid gland, surgery (for thyroid tumors and, rarely, central hypothyroidism, including lymphocytic hypophysitis or ectopic thyroid) and some drugs, such as rifampin and phenytoin, which can alter thyroid metabolism [2].

It has long been recognized that iodine represents an essential element for fetal growth and development [3]. In fact, congenital hypothyroidism leads to cretinism, which is characterized by irreversible growth restriction and mental retardation. In mountain areas, such as the Himalayas, Alps and Andes, iodine depletion can be caused by glaciers and erosion [4], leading to the presence of cretinism in small sections of the population. Nonetheless, a significant proportion of the population is exposed to mild iodine deficiency, which is responsible for the clinical features of defined goiters, impaired cognition and hypothyroidism [5]. One way to escape the dangerous and hidden deficiency is to incorporate iodine into the daily diets of people all over the world [6]. Today, as a result of this strategy, there are no countries with endemic iodine deficiencies, and only approximately 32 countries in the world with a public problem of mild to moderate iodine deficiency [7]. Some meta-analyses have studied the intelligence quotient (IQ) reduction in children who suffered from iodine deficiency, but, due to confounding

factors, it has not been well elucidated whether the IQ reduction depends on an "intra-" or "extra-" uterine iodine deficiency [8]. However, some studies have stressed that cognitive disorders that are linked to a mild-moderate iodine deficiency are a reversible clinical phenomenon [9-16]. These considerations are interesting because recent data have indicated the recurrence of iodine deficiency in developed countries, such as the United States, Australia, New Zealand, United Kingdom and, especially, in Europe [17,18].

Given that maternal iodine supplementation has a positive impact on the developmental quotient of children living in areas of iodine deficiency, the current WHO guidelines suggest that iodized salt provides sufficient iodine intake for pregnant women [19]. In particular, iodine supplementation is recommended beginning in early pregnancy to ensure adequate fetal brain development. A useful test to verify sufficient iodine intake is the assessment of urinary iodine concentration. Thresholds for median urinary iodine sufficiency have been identified for populations but not for individuals, given the significant day-to-day variation of iodine intake [20]. The cut-off for iodine sufficiency is a median urinary iodine concentration of 100–199 μg/L in adults and of 150–249 μg/L in pregnant women [21]. However, in some areas, iodine intake is sufficient in schoolchildren but not in pregnant women. This situation necessitates an additional strategy if iodized salt is already in use [22]. Some studies analyzing mildly iodine-deficient pregnant European women revealed that iodine supplementation is stopped before or at the moment of delivery [23]. In these patients, iodine supplementation was observed to increase maternal urinary iodine excretion and reduce thyroid volume. Additionally, no alterations in newborn thyroid volumes and no increased thyroglobulin maternal serum levels were present. However, these studies only demonstrate that iodine supplementation affects infant growth and development. Several studies [24-26] have attempted to analyze the relationship between iodine supplementation and fetal effects, but no significant effects on mental or motor development in the offspring were observed [8].

It is important to emphasize that following delivery, maternal iodine remains the only iodine source for breastfed infants; a breastfeeding woman excretes approximately 75–200 μg iodine daily in her breast milk [27,28]. Dietary iodine intake during lactation ranges from 250 to 290 μg/day, higher than the 150 μg/day recommended for non-pregnant women and adults. Adequate breast milk iodine levels are important for normal neurodevelopment in infants, and iodine supplements are essential for mothers living in iodine deficient areas, who are unable to meet the increased demands for iodine intake.

In cases of iodine deficiency, the safe upper limit of iodine intake during pregnancy remains controversial. If an individual is exposed to high iodine levels, the synthesis of T4 and T3 will be acutely inhibited by a process known as the acute Wolff–Chaikoff effect [29].

In summary, there are contrasting recommendations for the upper limit of iodine intake. The U.S. Institute of Medicine recommends an upper limit of 1100 μg dietary iodine daily in pregnancy, while the World Health Organization (WHO) recommends an upper limit of 500 μg per day [21,30].

2. Hypothyroidism and fertility

Thyroid function may be altered by serum thyroid antibodies, including serum anti-thyroglobulin antibodies (TgAb) and anti-thyroid peroxidase antibodies (TPOAb), particularly in older women [31].

Several studies [32-39] indicate that elevated levels of anti-thyroid antibodies are present in women three times more often than in men. This discordant predominance in thyroid autoimmunity could be associated with the X chromosome, which preserves some sex and immune-related genes responsible for immune tolerance [40]. Genetic defects of the X chromosome (monosomy or structural abnormalities) could be responsible for increased and altered immune-reactivity. In fact, patients with Turner's syndrome [41] and those with a higher rate of X chromosome monosomy in peripheral white blood cells [42] exhibit a higher incidence of thyroid autoimmunity than karyotypically normal individuals. Similarly, skewed X-chromosome inactivation leads to the escape of X-linked self-antigens from presentation in thymus and a subsequent loss of T-cell tolerance. The result is an associated higher risk of developing autoimmune thyroid diseases.

Self-tolerance is maintained by two mechanisms: central tolerance, which is performed by thymus deletion of auto-reactive T cells during fetal life, and peripheral tolerance, whereby those cells that escape central tolerance are inhibited to prevent them from triggering autoimmunity. It is well known that hormonal changes and trophoblastic immune-modulatory molecules enable the tolerance of the fetal semi-allograft during pregnancy. Both cell-mediated and humoral immune responses are attenuated, shifting the immune response toward the humoral with subsequent immune tolerance of the fetal tissues. It is for this reason that during pregnancy, both TPOAb and TgAb concentrations decrease, reaching the lowest values in the third trimester [43-48]. In puerperium, the immune response rapidly returns to the pre-pregnancy state, potentially promoting or aggravating autoimmune thyroid disease [43]. TPOAb concentrations rapidly increase and reach the maximum level at about 20 weeks after delivery [46-48]. Postpartum thyroiditis is a frequent complication, and 50% of females with positive TPOAbs (TPOAb+) in early pregnancy develop this condition. The clinical features of postpartum thyroiditis may arise within the first year after delivery as a transient thyrotoxicosis and/or a transient hypothyroidism, but permanent hypothyroidism develops in approximately one third of females [49].

Some analyses demonstrate that weakened immunosuppression in late pregnancy could contribute to postpartum thyroid dysfunction. In fact, females with postpartum thyroiditis exhibit increased secretion of IFN and IL-4 but lower median plasma cortisol concentrations in the 36th week of gestation than do euthyroid females [50].

In nature, there is a particular phenomenon, fetal microchimerism, that is responsible for the transfer of fetal cells to the maternal circulation during pregnancy. Several years after the delivery, the chimeric cells can be detected in different maternal districts, including the peripheral blood [51,52] and maternal tissues such as the thyroid, lung, skin, or lymph nodes [53]. In puerperium, immunotolerance decreases, and consequently, the activation of the fe-

tal immune cells localized in the maternal thyroid gland can act as a trigger for autoimmune thyroid disease. In support of this, the presence of fetal microchimeric cells is significantly higher in autoimmune hypothyroidism than in the absence of autoimmune thyroid disease [54-57]. However, the data are contradictory. Some studies demonstrate that heterozygotic twins exhibit a significantly higher prevalence of Thyroid Antibodies (TAbs) compared to monozygotic twins [58] and that euthyroid females with a previous pregnancy more frequently exhibit positive TPOAb compared to nulliparous females [59]. However, large population-based studies have not confirmed the relationship between parity and autoimmune thyroid disease. Consequently, the contribution of fetal microchimerism to the pathogenesis of autoimmune thyroid disease remains to be elucidated [60-63].

Spontaneous pregnancy loss is an obstetrical complication occurring at less than 20 weeks of gestation and has a prevalence ranging between 17% and 31% of all gestations [64,65]. Recurrent pregnancy loss is defined as either two consecutive losses or three total spontaneous losses and may occur in up to 1% of all pregnant women [66]. The individual risk depends on several factors including maternal age, family history, environmental exposures [67], parental chromosomal anomalies, immunologic derangements, uterine pathology, endocrine dysfunction and medical co-morbidities [68]. Pregnancy loss may result in bleeding, infections, pain and surgical procedures. Obviously, patients are strongly emotionally involved in a negative pregnancy outcome. Endocrine disorders are important risk factors for spontaneous pregnancy loss; patients with poorly controlled diabetes mellitus may have up to a 50% risk of loss [69], and thyroid dysfunction has also been associated with elevated rates of pregnancy loss [70,71]. Stagnaro-Green and colleagues [72] published a prospective observational study indicating that patients positive for thyroid antibodies (TPO and Tg) had a twofold increase in the risk of a pregnancy loss. Similarly, Iijima and colleagues [73] also reported an association between spontaneous pregnancy loss and the presence of anti-microsomal antibodies. In support of these studies, a meta-analysis [74] demonstrated a clear association between thyroid antibodies and spontaneous abortion. The study also reported that TAb+ women were slightly older and had slightly higher TSH levels than did antibody-negative women. Negro and colleagues [75-76] performed a prospective, randomized interventional trial of Levothyroxine (LT4) in euthyroid patients who were TPOAb+. The authors reported a significantly decreased rate of pregnancy loss in the treated group, but their analyses were limited because the mean estimated gestational age of the patients commencing LT4 therapy was 10 weeks, and all but one of the losses occurred at less than 11 weeks. In a case–control study of Iravani and colleagues [77] and in the study of Kutteh et al. [78], patients with primary recurrent pregnancy losses (three or more) had a higher prevalence of anti-thyroid antibody. In the prospective observational study of Esplin and colleagues [79], no difference in thyroid antibody positivity between patients with recurrent pregnancy loss and healthy controls was observed. Other authors reported a higher rate of subsequent pregnancy loss in patients with recurrent losses and thyroid antibody positivity [80]. In the clinical trial by Rushworth and colleagues [81], there was no significant difference in live birth rates between women with recurrent losses who were positive for anti-thyroid antibodies and those who were not.

Additionally, the coexistence of more elements may create a synergic effect. The study by De Carolis et al. demonstrated an apparent interaction between anti-phospholipid antibodies and thyroid antibodies in the risk of recurrent pregnancy loss [82].

The data for an association between thyroid antibodies and recurrent pregnancy loss are less robust than for sporadic loss. The results are also somewhat contradictory, and many trials did not consider other potential causes of recurrent losses.

Recently, Lazzarin et al. [83] performed TRH stimulation (200 μg) to evaluate thyroid function in patients with recurrent miscarriages and anti-thyroid antibodies. The authors determined that thyroid autoimmunity could be considered an indirect sign of mild thyroid dysfunction and that TRH stimulation could be a useful tool to detect subtle thyroid dysfunction.

Some authors have also established an 'iTSHa index' (TSH increase after TRH adjusted for the levels of basal TSH), determining TSH serum levels at time 0 and 20 min after TRH stimulation in women with two or more miscarriages within the first 10 weeks of pregnancy. This index is useful to identify women with recurrent miscarriages due to transient thyroid dysfunction of early pregnancy. If validated, the index could be used for those patients with no evidence of thyroid dysfunction and TSH levels within the low-normal reference range who may nonetheless be at risk for recurrent abortions [84].

Some authors tried to analyze the possible use of intravenous immunoglobulin (IVIG) to prevent recurrent pregnancy loss in women with anti-thyroid antibodies. Three small non-randomized case series have been published [85-87], and the live birth rates ranged from 80% to 95%. One study involved a comparison of a group of women who refused IVIG therapy (control group) with an IVG-treated group. A highly significant improvement in live births was reported in the IVIG-treated cohort [86]. In one study, a higher rate of term delivery was achieved by the LT4-treated group [87] compared to that of the IVIG group. In summary, all three studies had serious methodological problems (small sample size, heterogeneous patient populations, lack of or limited randomization, and differences in the timing of the treatment). These are the limitations of the intervention trials with IVIG or LT4 in TAb+ women with recurrent abortions.

In consideration of these findings, the Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum [76] stress that there is insufficient evidence to recommend for or against screening all women for anti-thyroid antibodies in the first trimester of pregnancy (Level I). Additionally, it is stressed that, in euthyroid women with sporadic or recurrent abortions or in women undergoing in vitro fertilization (IVF), there is insufficient evidence to recommend for or against screening for anti-thyroid antibodies or treating in the first trimester of pregnancy with LT4 or IVIG (Level I). Similarly, in TAb+ euthyroid women during pregnancy, there is insufficient evidence to recommend for or against LT4 therapy (Level I).

Some authors [88] investigated the role of steroid pretreatment on the pregnancy rate and pregnancy outcomes in patients positive for anti-thyroid antibodies who were undergoing induction of ovulation and intrauterine insemination (IUI). The patients were

divided into 3 groups: a control group of infertile women without anti-thyroid autoimmunity and two groups of infertile women with anti-thyroid autoimmunity, one treated with prednisone (administered orally for 4 weeks before IUI) and the other receiving placebo. Prophylactic therapy with steroids was associated with a significantly increased rate of pregnancy compared with placebo in infertile women with anti-thyroid antibodies undergoing induction of ovulation and IUI, although the miscarriage rate did not significantly differ among the groups.

Several studies reported an increased risk of pregnancy loss after assisted reproductive procedures in women who were positive for anti-thyroid antibodies [89-91], whereas other authors have detected no association [92,93]. Additionally, patients undergoing IVF in the presence of anti-thyroid antibodies exhibited an increased risk of pregnancy loss (meta-analysis of four trials) [94]. Negro et al. [95] performed a prospective placebo–controlled intervention trial. No difference in pregnancy loss was observed when LT4 was used to treat TPOAb+ women undergoing assisted reproduction technologies. The variable results highlight that there are a number of reasons for infertility or subfertility that may characterize patients undergoing assisted reproductive procedures for infertility.

The guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum [76] stress that in euthyroid TAb+ women undergoing assisted reproductive technologies, there is insufficient evidence to recommend for or against LT4 therapy (Level I).

Some studies have analyzed the role of selenium in diminishing the TPOAb titers [96-101], but at present, the risk to benefit comparison does not support routine selenium supplementation for TPOAb+ women during pregnancy [76] (Level C).

3. Hypothyroidism and pregnancy

Several physiological changes take place in a pregnant woman that could cause an increased incidence of hypothyroidism in the later stages of pregnancy in iodine-deficient women who were euthyroid in the first trimester.

In pregnancy, the production of thyroxin (T4) and triiodothyronin (T3) rapidly increases by 50% together with a subsequent 50% increase in the daily iodine requirement. The fetal thyroid begins to concentrate iodine to create triiodothyronin (T3) and thyroxin (T4) beginning at 10-12 weeks of gestation, while TSH (fetal pituitary thyroid stimulating hormone) begins to control thyroid function at approximately 20 weeks of gestation [102].

Maternal thyroxin crosses the placenta and maintains normal fetal thyroid function primarily in the early stages of gestation [103]. T3 is the active thyroid hormone produced after the deiodination of T4 in different tissues, and both are largely bound to thyroid hormone binding globulin (TBG). Rising maternal estradiol levels in early pregnancy causes increased liver sialyation and glycosylation of TBG [104,105] with a consequent decrease in the peripheral metabolism of TBG [106,107]. This change creates an increased need for T3-T4

production. During pregnancy, T4 and T3 are degraded at an increased rate to inactive iodothyronin (reverse T3) [108]. In addition, higher placental T4 transfer and hCG act as weak stimulators of T3-T4 secretion and suppressors of TSH levels [109].

Additionally, the increase in the maternal glomerular filtration rate enhances the iodine requirements in pregnancy. In fact, iodine is passively excreted by the kidney, and increased renal glomerular filtration results in increased losses of dietary iodine [110].

Under the influence of placental human chorionic gonadotropin (hCG), which also binds to and stimulates the thyroidal TSH receptor [111], the levels of thyrotrophin (TSH) are decreased throughout pregnancy, with the lower normal TSH level in the first trimester not well defined and an upper limit of 2.5 mIU/L.

High estrogen levels in pregnant women are responsible for a 1.5-fold increase in serum thyroxin binding globulin (TBG) concentrations. Therefore, there are higher levels of bound circulating total triiodothyronin (T3) and thyroxin (T4). In order to maintain free (or unbound) thyroid hormone levels, thyroid hormone gland production is enhanced [112].

Some studies have demonstrated that total body T4 concentrations must increase 20%–50% throughout gestation to maintain an euthyroid state [113,114], confirming that the increased requirement for T4 (or exogenous LT4) occurs as early as 4–6 weeks of pregnancy [114] and that such requirements gradually increase through 16–20 weeks of pregnancy with a subsequent plateau until the time of delivery.

Primary maternal hypothyroidism is defined as the presence of elevated TSH concentrations during gestation. There are rare exceptions to this definition, including a TSH-secreting pituitary tumor, thyroid hormone resistance, and a few cases of central hypothyroidism with biologically inactive TSH.

Pregnancy-specific reference ranges are necessary to define elevations in serum TSH during pregnancy. When maternal TSH is elevated, measurements of serum FT4 concentrations are necessary. The aim of such measurements is to classify the patient's diagnosis as either overt hypothyroidism (OH) or subclinical (SCH) hypothyroidism.

Patients exhibiting elevated TSH levels (>2.5 mIU/L) together with decreased FT4 concentrations and those with TSH levels of 10.0 mIU/L or above, irrespective of their FT4 levels, are considered to have overt hypothyroidism.

Patients with a serum TSH value between 2.5 and 10 mIU/L and with a normal FT4 concentration are affected by subclinical hypothyroidism. The clinical definition is dependent upon whether FT4 is within or below the trimester-specific FT4 reference range.

Data from a US population of iodine-sufficient women demonstrated that elevated serum TSH levels are present in at least 2%–3% of apparently healthy, non-pregnant women of childbearing age [115,116]. When thyroid function tests were performed, 0.3%–0.5% of those women were diagnosed with OH and 2%–2.5% were diagnosed with SCH.

When iodine intake is normal, Hashimoto's thyroiditis is the most frequent cause of hypothyroidism; more than 80% of patients with OH and 50% of pregnant women with SCH exhibit thyroid autoantibodies [116].

Maternal and fetal effects of hypothyroidism have been well studied, and the results allow for clinical recommendations for OH but not for SCH. There is a strict association between overt maternal hypothyroidism and adverse pregnancy outcomes, particularly if this condition arises early in pregnancy [116]. Some of these complications include preeclampsia, eclampsia, pregnancy-induced hypertension, low birth weight [117], preterm birth [118,119], breech delivery [120], placental abruption, infant respiratory distress syndrome, spontaneous abortion [115,121], perinatal death [122] and fetal neurocognitive development [123,124].

In reproductive aged women, the prevalence of subclinical hypothyroidism is about 0.5-5% [125]. It is well established that thyroid hormone is essential for fetal brain development and maturation, explaining why the maternal transfer of thyroid hormone is essential, especially during the first trimester of pregnancy. Children born to women who were inadequately treated for subclinical hypothyroidism exhibit impaired mental development compared to those born to women well-treated [123], but it is not well established whether the impaired mental development is due to the thyroid hormone deficiency itself or to the subsequent obstetric complications [126].

Although data regarding SCH are less complete than those regarding OH, Negro and colleagues [127] found that SCH increases the risk of pregnancy complications in anti-thyroid peroxidase antibody positive (TPOAb+) pregnant women. Their trial screened a low-risk pregnant population with SCH for TPOAb+ and TSH >2.5 mIU/ L. Half of the patients with this combination underwent LT4 treatment to normalize serum TSH, and the other half served as the control group. The results confirmed a significant reduction in the combined endpoint of pregnancy complications. Further, Negro et al. [128] noticed that TPOAb- (negative) women with TSH levels between 2.5 and 5.0 mIU/L exhibited a higher miscarriage rate compared with pregnant women with TSH levels below 2.5 mIU/L.

These prospective data are supported by previous retrospective data published by Casey and colleagues [115], who identified a two- to three-fold increased risk of pregnancy-related complications in untreated women with SCH. However, some published data reached conflicting conclusions; Cleary-Goldman et al. [129] reported no adverse effects in SCH pregnant women (detected in the first and second trimester). The limitation of this study is that the analysis was performed with only a selected subgroup of the entire study cohort, with a mean gestational age of screening between 10.5 and 14 weeks of gestation.

Recently, Ashoor et al. [130] evaluated TSH and FT4 levels in 202 singleton pregnancies at 11–13 weeks that subsequently resulted in miscarriage or fetal death. The results demonstrated that these patients had increased TSH levels above the 97.5th percentile and FT4 levels below the 2.5th percentile compared to the 4318 normal pregnancies of the control group. This trial suggests that SCH is associated with an increased risk of adverse pregnancy outcomes, although the detrimental effect of SCH on fetal neurocognitive development is less clear. The case-control study by Haddow et al. [123] demonstrated a reduction in the intelli-

gence quotient (IQ) among children born to untreated hypothyroid women when compared to the children of pregnant euthyroid controls. In summary, adverse fetal neurocognitive development is biologically plausible [131], though not clearly demonstrated, in SCH. For this reason, clinicians should consider these potential increased risks associated with SCH and could consider LT4 treatment for these patients.

The guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum [76] note that SCH has been associated with adverse maternal and fetal outcomes. However, due to the lack of randomized controlled trials, there is insufficient evidence to recommend for or against universal LT4 treatment in TAb- pregnant women with SCH (Level I). The aim of LT4 treatment is to normalize maternal serum TSH values within a trimester-specific pregnancy reference range (Level A).

Numerous retrospective and case-controlled studies confirm the detrimental effects of OH on pregnancy and fetal health, and the available data confirm the benefits of treating OH during pregnancy. This recommendation is useful for women with TSH concentrations above the trimester-specific reference interval and with decreased FT4 levels as well as for all women with TSH concentrations above 10.0 mIU/L, irrespective of FT4 levels (Level A). In addition, women positive for TPOAb and affected by SCH should be treated with LT4 (Level B).

The recommended treatment for maternal hypothyroidism is oral LT4. It is strongly recommended that other thyroid preparations, such as T3 or desiccated thyroid, not be used (Level A).

In the literature, the reference range for TSH is well established to be lower in pregnancy; both the lower and the upper limit of serum TSH are decreased by approximately 0.1–0.2 mIU/L and 1.0 mIU/L, respectively, compared to the usual TSH reference interval of 0.4–4.0 mIU/L in non-pregnant women. Serum TSH and its reference range gradually rise throughout the pregnancy, but this interval remains lower than in non-pregnant women [122,132]. Several confounding factors (e.g., diet), can influence TSH values in women with no thyroid pathologies.

In multiple pregnancies, the higher hCG level is responsible for lower TSH serum concentrations [133]. Therefore, some authors have suggested specific TSH ranges in pregnancy of 0.1-2.5 mUI/L for the first trimester, 0.2-0.3 mUI/L for the second trimester, and 0.3-3.0 for the third trimester [76,134].

As previously defined, overt hypothyroidism is characterized by elevated serum TSH levels with low serum FT4 levels, whereas subclinical hypothyroidism is characterized by elevated serum TSH levels with normal serum FT4 levels.

Isolated hypothyroxinemia is characterized by normal maternal TSH concentrations and FT4 concentrations in the lower 5th or 10th percentile of the reference range. It is controversial whether isolated hypothyroxinemia causes any adverse effects on the developing fetus. In the study of Pop and colleagues [135], psychomotor test scores among offspring born to women with normal serum TSH values and FT4 indices in the lowest 10th percentile were

decreased compared to controls. In the analyses of Li et al. [124], mothers who experienced either hypothyroidism or isolated hypothyroxinemia during the first trimester gave birth to children with lower IQ scores. However, these studies have methodological limits.

In their prospective, Henrichs and colleagues conducted a prospective nonrandomized investigation on isolated maternal hypothyroxinemia [136] and reported that a 1.5- to 2-fold increased risk for adverse events (children at 3 years of age) in communication development was associated with maternal FT4 levels in the lower 5th and 10th percentiles. To date, there are no recommendations for isolated hypothyroxinemia, and consequently, isolated hypothyroxinemia should not be treated during pregnancy (Level C).

In the first trimester of pregnancy, approximately 10% to 20% of all pregnant women are TPO- or Tg-antibody positive and euthyroid. In addition, approximately 16% of the women who are euthyroid and positive for TPO or Tg antibodies in the first trimester will develop a TSH that exceeds 4.0 mIU/L by the third trimester, and approximately 33%–50% of women positive for TPO or Tg antibodies in the first trimester will develop postpartum thyroiditis. These data could be the result of a direct effect of the antibodies or an indirect marker of an autoimmune syndrome or the thyroid functional reserve [106].

Another important aspect to consider is the significant ethnic difference in serum TSH concentrations. In fact, pregnant women of Moroccan, Turkish, or Surinamese descent residing in The Netherlands exhibit TSH values 0.2–0.3 mIU/L lower than Dutch women throughout pregnancy [137]. Black and Asian women exhibit TSH values that are on average 0.4 mIU/L lower than those in white women; these differences persist during pregnancy [138,139].

There are different methods for the analysis of TSH levels, and TSH ranges vary slightly depending on the method used [140]. However, trimester-specific reference ranges for TSH should be applied (Level B). If they are not available in the laboratory, the following reference ranges are recommended: first trimester, 0.1–2.5 mIU/L; second trimester, 0.2–3.0 mIU/L; third trimester, 0.3–3.0 mIU/L (Level I).

Total T4-T3 values or the ratio of Total T4 to TBG are useful to calculate the normal ranges for the FT4 index, but there are not trimester-specific reference intervals for the FT4 index of a reference population. To assess serum FT4 during pregnancy, the optimal method is measurement of T4 in the dialysate or ultrafiltrate of serum samples employing on-line extraction/liquid chromatography/tandem mass spectrometry (LC/MS/ MS) (Level A). If not available, clinicians should use whichever measure or estimate of FT4 is available in their laboratory and should be aware of the limitations of each method. However, serum TSH remains the most accurate method to study thyroid status during pregnancy (Level A).

In the presence of high concentrations of bound T4, it is difficult to measure the levels of FT4 due to the abnormal binding-protein states such as pregnancy. Therefore, method-specific and trimester-specific reference ranges of serum FT4 are required (Level B).

The guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum [76] stress that, although not prospectively studied, the approach of not initially treating women with SCH in pregnancy should

involve monitoring the women for possible progression to OH by measuring serum TSH and FT4 levels approximately every four weeks until 16– 20 weeks gestation and at least once between 26 and 32 weeks gestation (Level I).

These considerations are important to make the therapy adjustments in affected women once pregnant and to plan the follow-up intervals for TSH in treated patients. If necessary, LT4 adjustments should be made as soon as possible after pregnancy is confirmed; it is important to stress that between 50% and 85% [113,114,141] of hypothyroid women treated with exogenous LT4 require increased doses during pregnancy. This need for adjustment is related to the etiology of hypothyroidism itself.

The clinical recommendation is that treated hypothyroid patients (receiving LT4) and newly pregnant women should independently increase their dose of LT4 by 25%–30% upon a missed menstrual cycle or positive home pregnancy test. Pregnant women could accomplish this adjustment by increasing LT4 from once daily dosing to a total of nine doses per week (29% increase). (Level B)

Obviously, the aim of treatment is to optimize a woman's preconception thyroid status. Different studies have analyzed the possible TSH cutoff values for women planning a pregnancy, but other factors, like maternal estrogen levels, can influence the LT4 augmentation necessary to maintain a euthyroid state during pregnancy.

The guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum [76] indicate that preconception serum TSH values <2.5 mIU/L are an indirect marker of a good thyroid state in treated hypothyroid patients (receiving LT4) who are planning a pregnancy. Similarly, TSH values <1.5 mIU/L will likely further reduce the risk of mild hypothyroidism in early pregnancy by reducing the risk of TSH elevation during the first trimester. However, no differences in pregnancy outcomes have been demonstrated by this approach (Level B).

In these patients, maternal serum TSH levels should be monitored approximately every 4 weeks during the first half of pregnancy. Indeed, further LT4 dose adjustments are often required (Level B), and maternal TSH should be checked at least once between 26 and 32 weeks gestation (Level I).

Following delivery, LT4 should be reduced to the patient's preconception dose. Additional TSH testing should be performed at approximately 6 weeks postpartum (Level B).

However, women with Hashimoto's thyroiditis could need an increased LT4 dose in the postpartum period [142] compared to their prepartum dose.

Pregnant women treated and monitored appropriately should not require any additional tests; there are no other maternal and fetal recommended tests in the absence of other pregnancy complications (Level A).

Some studies [75,119] confirmed an increased requirement for thyroid hormone during gestation in women who are TAb+. Both OH and SCH may occur during the stress of pregnancy as a result of compromised thyroid function. This situation usually occurs later in

gestation because in the first part of pregnancy, the residual thyroid function can act as a buffer.

Because the risk of hypothyroidism in women who are TAb+ is increased, a higher level of surveillance, by evaluating TSH levels approximately every 4–6 weeks during pregnancy, is required [114].

Fetal status in pregnant women under chronic therapy with levothyroxine has been studied by performing computerized FHR (fetal heart rate) analyses (cCTG). This is a sensible and reproducible method to identify pregnancies with a pathological neonatal outcome. Published data [143] suggest that maternal hypothyroidism and levothyroxine treatment have an important influence on FHR, and cCTG analyses are a sensible means of revealing and studying these conditions. In their analyses, the authors stressed that fetal reactivity, expressed by reduced baseline FHR and reduced fetal movements, remained suppressed in well-treated hypothyroid pregnant women who became euthyroid, suggesting that this suppression could be due to the influence of a chronic hypothyroid state.

4. Hypothyroidism and contraception

In the literature, there is little evidence about the influence of contraceptives on thyroid function. The study of Ågren et al. [144] analyzes the effects of two monophasic combined oral contraceptives (nomegestrol acetate/17 beta estradiol or levonorgestrel/ethinylestradiol) on androgen levels, endocrine function and sex hormone-binding globulin (SHBG) levels in 121 healthy women. The authors found that the levels of thyroxin-binding globulin (TBG), together with total cortisol and corticosteroid-binding globulin (CBG) levels, increased in both groups, with a significantly greater increase observed in the group with levonorgestrel/ethinylestradiol. Thyroid-stimulating hormone (TSH) and free thyroxin (T4) remained unaltered from their baseline values, and no difference was observed between the groups. If TBG rises, clearance of tri-iodothyronin (T3) and T4 is reduced, thereby increasing total T3 and T4 levels. However, as described, estroprogestin oral contraceptives have little or no effect on physiologically active free fractions of thyroid hormones. In fact, in the same study, no significant changes in free T4 or in TSH levels were observed in either group after six months of treatment, in agreement with other studies [145-147].

In summary, oral contraceptives can be responsible for increasing TBG without a significant influence on thyroid-stimulating hormone (TSH) and free thyroxin (T4) levels.

5. Conclusions

A euthyroid state is the goal for women affected by hypothyroidism; the normalization of thyroid markers is necessary for metabolic, endocrine and sexual improvement. Obviously, the presence of anti-thyroid antibodies signifies an underlying state of imbalanced patient-specific autoimmunity that can be addressed with effective treatments.

In pregnant women, treatment of hypothyroidism is not associated with adverse perinatal outcomes [148], and although it is not well known how levothyroxine treatment during pregnancy improves the neurological development of the offspring, clinical practice guidelines recommend this therapy [148, 149].

The choice of cut-off values for TSH in the three trimesters of pregnancy has important implications both for the interpretation of the literature and for the critical impact of the clinical diagnosis of hypothyroidism.

Overt hypothyroidism and overt hyperthyroidism have a deleterious impact on pregnancy. However, questions about hypothyroidism and pregnancy remain, including those regarding the impact of subclinical hypothyroidism on pregnancy; the impact of TAbs on miscarriage, preterm delivery and puerperal thyroiditis in euthyroid women; and if, when and who should be screened for anti-thyroid hormones during pregnancy. For this latter question, very recent papers addressed the problem with conflicting results: Lazarus et al. [150] conducted a randomized trial in which antenatal screening and maternal treatment for hypothyroidism did not result in improved cognitive function in three-year-old children (possible limitations of this study are that levothyroxine therapy was performed too late in gestation and that about 24% of the women were lost to follow-up) while Dosiou et al. [151] stressed that universal screening of pregnant women in the first trimester for autoimmune thyroid disease is cost-effective without the calculation of a possible decrease of the offspring cognitive function. The question remains open.

Acknowledgements

The strength of each recommendation was graded according to the United States Preventive Services Task Force (USPSTF) Guidelines [76]:

- Level A. The USPSTF strongly recommends that clinicians provide (the service) to eligible patients. The USPSTF found good evidence that (the service) improves important health outcomes and concludes that benefits substantially outweigh harms.
- Level B. The USPSTF recommends that clinicians provide (this service) to eligible patients. The USPSTF found at least fair evidence that (the service) improves important health outcomes and concludes that benefits outweigh harms.
- Level C. The USPSTF makes no recommendation for or against routine provision of (the service). The USPSTF found at least fair evidence that (the service) can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.
- Level D. The USPSTF recommends against routinely providing (the service) to asymptomatic patients. The USPSTF found at least fair evidence that (the service) is ineffective or that harms outweigh benefits.

- Level I. The USPSTF concludes that evidence is insufficient to recommend for or against routinely providing (the service). Evidence that (the service) is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

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