SUBCLINICAL HYPOTHYROIDISM

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ABSTRACT: Subclinical hypothyroidism (SKH) is a thyroid disorder in which the level of thyroid hormones, thyroskin and triiodothyronine in the blood is normal, but the level of thyrotropin - TSH, pituitary hormone, which regulates the work of the thyroid gland with negative feedback, is elevated. This is a biochemical diagnosis, because patients are typically asymptomatic and without signs of disease and the detection of SCC is usually accidental. Gender, age, race, geographical area, iodine status. Depending on the degree of increase in baseline TSH levels, 5-8% of patients with SCH annually have progression to clinical hypothyroidism. Iodine is chronic autoimmune thyroiditis. Existing guidelines for the treatment of SKH differ from each other, as there is conflicting evidence on the benefits of long-term levothyroxine substitution in this condition. Although there are data from several comprehensive reviews of the clinical outcomes of SKH treatment, no definitive conclusion has yet been reached on the benefits of this approach. Factors that support application of levothyroxine therapy are: clinical trial due to symptoms of hypothyroidism, patient's desire, depression, infertility / ovulatory dysfunction, progressive increase in TSH, pregnancy, or pregnancy planning, children, adolescents. Research data show that pregnant women with SCC have an increased risk of gestational diabetes, miscarriage, gestational hypertension, preeclampsia, premature birth, and the therapeutic procedure in pregnancy differs from the rest of the adult population. The approach in children with SKH, amiodarone-induced SKH and micronutrients will be briefly mentioned.

Key words: subclinical hypothyroidism, levothyroxine, pregnancy, amiodarone

INTRODUCTION

Subclinical hypothyroidism (SKH) is a common clinical condition about which there is much controversy. To date, there has been no definite consensus among thyroidologists on several aspects. First of all, the question arises whether it is necessary to do screening at SKH, ie. actively search for disorder in a wider asymptomatic population at routine periodic / preventive examinations, or find cases according to clinical indications. Another aspect of the problem is how to assess the significance of this clinical condition, as well as possible adverse effects on the cardiovascular system, metabolic parameters and mental health of the individual patient. From the first two questions the third one arises, and that is what kind of therapeutic approach to have in SKH - to treat it or not.

WHAT IS SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism is a thyroid disorder in which the level of thyroid hormones (TH), thyroskin (T4) and triiodothyronine (T3) in the blood is normal, but the level of thyrotropin (TSH), a pituitary hormone that regulates thyroid function, is elevated. This is a biochemical diagnosis, because patients are typically asymptomatic and without signs of disease and the detection of SCH is usually accidental. Over time, SKH may progress to clinical hypothyroidism (KH). [1,2] SKH, depending on the duration and degree of TSH elevation, may be associated with an increased risk of cardiovascular (CV) disease and CV mortality, adverse effects on metabolic parameters, cognitive dysfunction, anxiety and depression [2,3]. Several alternative names describing the condition of SKH have been suggested such as: compensated hypothyroidism, preclinical hypothyroidism, mild hypothyroidism, decreased thyroid reserve, mild thyroid weakness [4].

WHAT IS THE PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM

The estimated total prevalence of SKH in the general population is 4-10% depending on the characteristics of the examined population,

ie. gender, age, race, geographical area, iodine status [4]. SKH is more common in women and the elderly. In women, the prevalence is 8-10%, and in women older than 60, the published prevalence is up to 20% [5,6]. The prevalence is about three times higher in whites than in blacks [7]. Also, during an increase in iodine intake in a previously iodine-deficient population, there may be a slight increase in the prevalence of SKH and thyroid autoimmunity [8]. There are studies in which the prevalence of SKH in people with metabolic syndrome (MetS) is almost two and a half times higher [9]. In addition, SKH is more common in patients with Type 2 Diabetes Mellitus (DM T2) than in the healthy population and is about 10% according to some reports [10]. SKH is a relatively common condition in patients with chronic renal failure (HBI) and can be found in about 18% of patients with HBI who are not on dialysis [11]. The reported incidence of SCH in pregnant women is 2-2.5%, in some countries such as China, Belgium and northern Spain even 4-13.7%, and in children the prevalence is less than 2% [12].

Of course, in order to assess the prevalence of this condition in the population / populations, accurate registration and adequate health statistics are necessary. Estimated prevalences are often based on meta-analyzes of published articles in available databases of professional and scientific papers, in which data from limited samples of respondents are analyzed. However, differences in the estimated prevalence may also be influenced by different diagnostic criteria for this condition, e.g. use, or not, of specific serum TSH reference ranges, in this case upper limits of the reference range for individual population groups. Research shows that it is necessary to determine the distribution of concentration and range of normal TSH values, probably due to genetic factors, according to age and race, or other specific characteristics of the population, which would be used to assess the presence of thyroid dysfunction (TD) [13]. In this regard, some authors believe that the prevalence of SKH in the elderly is overestimated, because the upper limit of the reference range for TSH increases with age [14].

CAUSES OF SUBCLINICAL HYPOTHYROIDISM

The most common cause of subclinical hypothyroidism, as well as clinical, in areas with sufficient iodine intake, is chronic autoimmune thyroiditis - Hashimoto's thyroiditis (HT), atrophic thyroiditis (AT), postpartum thyroiditis (PPT) [3]. Autoimmune thyroid diseases (AITB), which include HT, AT and PPT, are 5 to 10 times more common in women than in men, the prevalence increases with age, they are more common in people with other autoimmune diseases, as well as in their blood relatives [3, 15-17].

AITB is characterized by pathological infiltration of the thyroid gland by sensitized T lymphocytes and the presence of thyroid autoantibodies in the blood - antimicrosomal antibodies / antibodies to thyroid peroxidase (TPOAb), antithyroglobulin antibodies (TgAb), prescription (TgAb) and 3 antibodies, [18], TSA [19], TSA antibodies. Determination of these antibodies in serum is one of the key diagnostic methods for the diagnosis of AITB.

On the other hand, a very common cause of SCC is iodine deficiency in the diet, because the problem of iodine deficiency areas is still pronounced worldwide [20]. Iodine is a microelement necessary for the production of thyroid hormones (TH), thyroxine (T4) and triiodothyronine (T3), which must be taken into the body through food, at least 150 μg per day.

Causes of SKH can also be iatrogenic, for example the condition after radioiodine, or surgical therapy of benign and malignant diseases of the thyroid gland, ie. diffuse toxic goiter, toxic adenoma, polynodose toxic goiter, benign and malignant atoxic nodular goiter. Also, radiation therapy to the thyroid gland can lead to radiation therapy of the neck due to non-thyroid diseases of the head and neck, including lymphoma.

Iatrogenic SKH can also be pharmacological, caused by the use of drugs for non-thyroid diseases, or diagnostics, such as iodine-rich antiarrhythmics, amiodarone, then lithium, used in psychiatry, iodine contrast agents, interferon alpha and other cytokines, tyrosine kinase inhibitors (TKI), antituberculotic Paraaminosalicylic acid (pAS), less often aminoglutethimide, which lead to SKH by various mechanisms e.g. thyroid cytotoxicity, blockade of TH production and release of excess iodine, reducing blood supply to thyroid tissue, action on type 2 and 3 deiodinases, which participate in the production of TH and their metabolites, and others [21-26]. Of course, there are also antithyroid drugs that are given in the

treatment of hyperthyroidism, ie. methimazole and propyl thyrouracil, may lead to SKH.
Infiltrative diseases, such as amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riddle's thyroiditis, can also affect the thyroid gland and be the cause of reduced functional reserves, ie. SKH [27,28].

As already mentioned, SKH as a consequence of AITB can often be associated with other autoimmune diseases, e.g. DM type 1, Addison's disease, rheumatoid arthritis [29-31], but also chromosomal disorders such as Down's or Turner's syndrome [32,33], which requires mandatory examination of thyroid function in patients with these diseases and syndromes.
Consumptive, or "expendable" SKH is a rare condition that occurs in patients with hemangiomas and other tumors in which type 3 deiodinase is expressed, causing accelerated degradation of T4 and T3 [34].

Finally, transient SCH can be found in patients in the recovery phase from non-autoimmune thyroiditis, subacute and painless thyroiditis, as well as during recovery from severe non-thyroid disease (NTB) [35].

THE COURSE OF SUBCLINICAL HYPOTHYROIDISM

In most patients, SKH remains stable over time. Depending on the degree of increase in the initial level of TSH, annually 5-8% of patients with SKH have a progression to clinical hypothyroidism (KH) [36]. On the other hand, thyroid function may return to normal over time in 6-35% of patients, also depending on baseline TSH levels as well as thyroid autoantibody levels [37]. In patients with elevated TPOAb, the progression of SKH to KH is 4.3% per year, and in those with normal TPOAb levels, almost twice as low, 2.6% per year [38]. Therefore, after the diagnosis of SCH, thyroid function tests (TFT) are repeated in 8-12 weeks and additional measurement of thyroid autoantibody levels is performed. If SKH persists, TFTs are repeated for 6 months during the first two years of follow-up, and then once a year if the findings are stable. In contrast, if TFTs are normal after repeated determinations and the patient has no symptoms, goiter, and elevated thyroid autoantibodies, further monitoring is not necessary [3].

DIAGNOSIS OF SUBCLINICAL HYPOTHYROIDISM

The diagnosis of SKH is made when elevated TSH values are detected in the patient (the reference range of most tests is 0.4 - 4.0 to 5 m IU/L) with normal FT4 values in the blood [39] . Bearing in mind that the diagnosis of SKH is based on the results of laboratory analyses, the specificity, sensitivity and reference values of the applied test should be taken into account, and the finding should be interpreted accordingly [40]. Although elevated serum TSH is most often a sign of primary hypothyroidism, it is important to know that measured concentrations may be elevated (usually <8 mU/L) in individuals over 65 years of age without clinical and laboratory evidence of thyroid disease [41]. Other conditions, such as post-radiotherapy of the neck, adrenal insufficiency, pregnancy, use of certain drugs (lithium, AMD), or the presence of specific antibodies in the blood (HAMA, or macro TSH) may mimic SKH [42-44]. In addition, pathological obesity due to the effect of leptin on thyrotropin releasing hormone (TRH) leads to a reversible increase in blood TSH [45]. Fluctuations in TSH concentration are expected in acute, especially severe netiroid diseases, as well as after surgical procedures - hemithyroidectomy, which should be taken into account when interpreting laboratory findings [42,46]. Laboratory diagnosis should be postponed for 2-3 months after recovery from acute diseases, due to the effects of cytokines on TSH concentration, and supplementation with biotin, which is a part of many multivitamins (especially those recommended for hair and nail health) should be stopped at least 2 days before laboratory tests, Analysis, due to interference with immunoassays [42,47,48].

There are two categories of SKH according to the degree of TSH increase. Slightly elevated TSH, of 4–10 m IU/L, found in 80–90% of patients, and significantly elevated TSH,> 10 m IU/L [3]. After the diagnosis of TSH, the cause should be determined, ie. an etiological diagnosis should be made. Additional laboratory analyses in order to establish the etiological diagnosis are measurement of thyroid autoantibodies (TAT), TPOAb mainly due to higher sensitivity and less often TgAb, as well as ultrasound examination of the thyroid gland which can detect characteristic parenchymal changes in autoimmune thyroiditis, which is the most common cause of SKH [50].

The level of TSH in a healthy person has small variations over time, about 1/3 of the reference range, which is called its own "TSH

setpoint", which tends to increase with age [51,52]. Thus, as mentioned, in the elderly we use a wider reference range (4.0-7.0 m IU/L), i.e., a slightly elevated TSH level in the elderly is considered a physiological adaptation to aging [41].

In both healthy and SKH, TSH levels have circadian fluctuations in serum concentrations - the lowest concentration is in the early afternoon, with about 30% higher concentrations in the evening and overnight.

Delayed night peak TSH can be found in: night shift workers; those with sleep disorders; after strenuous physical activity; in mood disorders - depression [3].

Biologically inactive forms of TSH may be the reason for measured higher TSH values in some individuals [53].

Let us repeat that the level of TSH correlates with BMI and markers of insulin resistance, so the finding of TSH> 3.5 is common in obese [54].

CLINICAL CHARACTERISTICS OF SUBCLINICAL HYPOTHYROIDISM

Symptoms

By definition, SKH is an asymptomatic condition, with no clinical signs of hypothyroidism (Table 1). However, is SKH really asymptomatic? Some studies show that a small but statistically significant number of patients with SKH have more frequent symptoms of hypothyroidism than healthy ones: drier skin, poorer memory, slower thinking, weaker muscles, faster fatigue, more frequent muscle cramps, greater winter fever, deeper and hoarse voice, swollen eyes and more frequent constipation [5]. On the other hand, since the symptoms and signs of hypothyroidism are general and can occur in other conditions, some studies show that there is no improvement in symptoms in patients with SCI when levothyroxine substitution is introduced [55]. However, most patients with SCH do not have hypothyroid symptoms.

Mood and mental health disorders

Based on many studies, it seems that there may be mild disorders of declarative memory (knowledge of facts), procedural memory (skills that are performed automatically) and mood in younger people with SCC, which are improved by levothyroxine substitution [56]. However, such evidence is generally not found in the population over 65 years of age [57].

Table 1. Symptoms and signs of hypothyroidism

SYMPTOMS	SIGNS
Fatigue, weakness, suffocation	Bradycardia
Dry goat	Dry, rough skin
Feeling cold / cold	Cold extremities
Hair loss	Diffuse alopecia
Weight gain with normal, or poor appetite	Swelling of the face, hands, feet, myxedema
Constipation	Prolonged tendon relaxation time
Hoarseness	A deeper, hoarse voice
Impaired concentration, impaired memory	Efusions into serous cavities
Impaired hearing, paresthesias	Carpal tunnel syndrome
Menorrhagia, oligomenorrhea, amenorrhea	

Obesity, glycoregulation, insulin resistance, diabetes mellitus, dyslipidemia

Serum TSH levels are positively correlated with body weight [58] and it has been shown that for each unit of increase in log TSH, body weight is 2.3 kg higher in women and 1.1 kg in men [59]. In contrast, a significant decrease in body weight is associated with a decrease in TSH levels [60]. However, a sample relationship between SKH and obesity has not been shown.

SKH could reduce insulin sensitivity by reducing the number of glucose transporters in plasma membranes (cell organelle membranes) and by directly affecting insulin secretion and clearance, as is known to occur to a significant extent in hypothyroidism [61]. In patients with established diabetes mellitus (DM) type 2, a change in glycemic control may indicate SKH and long-term thyroid disorders, while the prevalence of SKH with elevated TAT in a patient with type 1 DM is up to 30% [62].

Large epidemiological studies have shown a positive correlation between TSH levels and dyslipidemia, indicating a potential impact of SKH on the lipid profile [5]. Similarly, another large study showed e.g. that an increase in TSH

levels of 1.0 m IU / L was associated with an average increase in total cholesterol levels in women of 0.09 mmol, indicating gender differences in the relationship between SCH and lipid profile. Also, the relationship between TSH levels and lipid profile is more pronounced with advancing age [63].

Cardiovascular system, heart failure and ischemic heart disease

SKH is associated with functional cardiac disorders, such as left ventricular diastolic dysfunction and decreased systolic function at rest and physical exertion [64]. Vascular abnormalities in this condition have also been shown, such as increased vascular resistance, arterial stiffness, endothelial dysfunction, and atherosclerosis [65]. Many studies point to SKH as an independent risk factor for the development of heart failure, as well as for the worsening of existing ones [64].

Some of the results of research on the impact on ischemic heart disease did not show an association between AITB and ischemic heart disease, but by re-analyzing a population-based Whickham study (66), it was found that in patients with SKH a significantly higher frequency of cardiac ischemic events and mortality due to ischemic heart disease was found. A meta-analysis of several relevant prospective studies has shown similar results [67].

Degree of TSH increase

It is not insignificant, as the results of the study show, how much TSH is elevated in SKH. We said that there are two categories of SKH according to the degree of TSH increase: slightly elevated TSH, from 4-10 m IU/L and significantly elevated. TSH> 10 m IU/L. Symptoms, manifestations, and potential complications, including endothelial, lipid, and cardiovascular disorders, are related to the degree of TSH elevation but depend, as has been said, on gender and age [68]. The results of numerous completed, as well as ongoing studies will be useful to determine both the TSH threshold and the age threshold for considering therapeutic intervention, levothyroxine substitution.

THERAPEUTIC APPROACH IN SUBCLINICAL HYPOTHYROIDISM

SKH, like KH, is treated with levothyroxine substitution. The goal of the treatment, as with KH, should be to eliminate the symptoms of hypothyroidism by achieving normalization of TSH [69].

However, since it is by definition an asymptomatic disorder in most patients, a disorder only at the blood level, two questions should be kept in mind when deciding on the treatment: what is the effect of levothyroxine treatment on long-term clinical outcomes in patients with SLE and what is the outcome of follow-up without levothyroxine treatment, on long-term outcomes in patients with SCV [70]. Existing guidelines for the treatment of SKH differ from each other, as there is conflicting evidence on the benefits of long-term levothyroxine substitution in this condition. Although there are data from several comprehensive reviews of the clinical outcomes of SKH treatment, no definitive conclusion has yet been reached on the benefits of this approach. (1). Certainly, as it was emphasized in the previous text, before starting the substitution, the TSH test should be repeated within 3 months from the diagnosis of SKH. This is important because in about 60% of patients TSH normalizes within 3 months, and in about 62% over 5 years [71,44]. On the other hand, in patients with SCC and hypothyroid symptoms, other possible causes for existing symptoms should be considered first.

According to most guides, levothyroxine substitution in SKH should be started when TSH is> 10 mIU/L, regardless of the absence of symptoms. Levothyroxine substitution should be considered in cases where TSH is between 5-10 mIU/L in repeated measurements and there are symptoms similar to hypothyroidism. However, if symptoms do not resolve after 3-4 months of levothyroxine substitution and TSH normalization, the treatment should be discontinued [70,1]. In other cases, the decision to treat SCH, when the TSH is between 5-10 mIU/L in repeated measurements, should be adjusted individually depending on age, comorbidity, degree of TSH elevation, persistence and progression of TSH elevation, TAT presence and goiter. The meaning of substitution would be based on reducing the risk of adverse CV events and possibly preventing progression to CH. It should be borne in mind that levothyroxine substitution can lead to iatrogenic subclinical / clinical thyrotoxicosis, especially in elderly patients, which in itself may be a risk of worsening CV condition and there is no evidence that substitution is useful in people

65 years of age and older [42]. Factors that support the application of left thyroxine therapy are: clinical trial due to symptoms of hypothyroidism, patient's desire, bipolar disorder, depression, infertility / ovulatory dysfunction, presence of TAT, progressive increase in TSH, pregnancy, or pregnancy planning, children, adolescents.

RECOMMENDATIONS [3]

There are two categories of SKH according to TSH level: Slightly elevated TSH - 4-10 m IU / L found in 90% of people with SKH; and TSH> 10 m IU / L

The finding of elevated TSH with normal FT4 in the first measurement should be repeated in 2-3 months, by re-measuring TSH, T4 and TPOAb

TSH and FT4 should be measured in individuals with elevated TPOAb / TgAb and / or ultrasound indicating AIT

Age-specific reference ranges should be used to diagnose SKH in the elderly population.

In patients younger than 65 years and with TSH> 10 m IU/L, even in the absence of symptoms of hypothyroidism, the introduction of L-thyroxine substitution is recommended.

In patients younger than 65 years with symptoms of hypothyroidism and TSH <10 m IU/L, a clinical trial by introducing L-thyroxine substitution should be considered.

After hemithyroidectomy, persistent SKH should be treated with L-thyroxine in order to normalize TSH.

Patients with diffuse or nodular goiter and persistent SKH should be treated with L-thyroxine in order to normalize TSH.

In patients with type 1 DM, TSH levels should be monitored once a year.

In patients with DM type 2 and unexplained deterioration of glycemic control, TSH and FT4 should be performed.

There is limited evidence that L-thyroxine substitution in younger people with SKH leads to improved mental function.

There is no evidence of beneficial effects of L-thyroxine therapy in obese individuals with TSH <10 m IU/L and normal FT4 on weight loss.

L-thyroxine therapy in SKH can lower both total and LDL cholesterol, but lipid normalization is rarely achieved.

The effect of L-thyroxine substitution on serum lipid concentrations is most pronounced in patients with TSH levels> 10 mIU/L before treatment.

The oldest elderly people, over 80 years of age, with a TSH level ≤ 10 m IU / L, should be carefully monitored, avoiding the introduction of L-thyroxine substitution.

If the hormones in the control test are normal, with a normal TAT level and the absence of goiter - no further testing is needed.

If SCH persists and L-thyroxine therapy is not started, hormones should be tested for 6 months for at least first 2 years, and then once a year.

PREGNANCY AND SUBCLINICAL HYPOTHYROIDISM

SKH in pregnancy is defined as a condition in which serum TSH is higher than the upper limit of the reference range specific to the trimester of pregnancy, while serum T4 and T3 are in the reference ranges [72,73,14,74]. It occurs in approximately 2-2.5% of pregnant women, with the number being significantly higher in some countries and as high as 13.7% in northern Spain [75].

Isolated hypothyroxinemia is defined as a serum FT4 concentration below the 2.5 percentile of the reference range (0.80 ng/dL; 10.30pmol/L), with a normal TSH concentration [72,12].

The diagnosis of SCH in pregnancy is made only on the basis of laboratory analyses, as the symptoms and signs are non-specific and very similar to problems that may be associated with lifestyle variations, or problems that result from many other conditions and pregnancy itself [72,12,74]. The reference range of TFT in pregnant women differs from the reference range of the general population, and also differs by trimesters of pregnancy. Based on published studies, mainly in Western countries, the following reference range for TSH in pregnancy is proposed: first trimester 0.1 - 2.5 mU/L; second trimester 0.2 - 3.0 mU/L, third trimester 0.3–3.5 mU/L [76-78]. However, it is advisable to determine these values for each country or region individually. It should be noted that during pregnancy there is an increase in the concentration of T4, which is highest during the first trimester of pregnancy, while this increase is significantly less during the second and third trimesters. Despite the increased binding of hormones to transport proteins, which are also increased in pregnancy, many authors believe that the reliability of the determination of free thyroxine (FT4) by standard immunoassay for FT4 is satisfactory [72,12].

As the definition of SKH is based on elevated TSH levels in combination with normal FT4 values, it would be crucial to determine the trimester-specific TH reference range. Available data from the literature indicate that in the first trimester of pregnancy the lower limit of FT4 2.5th percentile of the reference range detected by immunoassays is about (0.80 ng/dL; 10.30pmol/L) [72,12]. In order to obtain a reference value specific for the first trimester of pregnancy, some authors suggest that the normal values of total, for transport protein bound T4 (TT4), which are 5–12 mg / dL, or 50–150 nmol/L for non-pregnant women, be multiplied by 1.5 and the values thus obtained used as reference values specific to the first trimester [72,12].

Antibodies to thyroid peroxidase (TPOAb) are present in about 50% of pregnant women with SCC, and up to 80% in pregnant women with clinical hypothyroidism. In pregnant women with SCI, the determination of TPOAb is recommended in order to determine the AITB. Antibodies to thyroglobulin (TgAb) should not be neglected either. Elevated TgAbs were found in 5% of women with SKH and normal TPOAb. Women with elevated TgAb, and normal TPOAb, had significantly higher serum TSH levels compared with women without AITB. Thus, TgAb should be determined in pregnant women with negative TPOAb. After the first trimester, TAT may be negative due to immunosuppression during pregnancy, and in the presence of elevated TSH values and negative antibodies, thyroid ultrasound should be performed [72,12].

Side effects of SKH during pregnancy

Manifested clinical hypothyroidism during pregnancy is clearly associated with adverse events such as preeclampsia, eclampsia, gestational hypertension, cretinism, fetal death, and miscarriage. However, there is less evidence of complications during pregnancy and SCI. Studies dealing with this problem show conflicting results. Most studies indicate an increased risk of gestational diabetes (GD), with a positive correlation between TSH levels and the risk of GD.

Several studies have confirmed the association of SKH with miscarriages, very early embryo loss, gestational hypertension and preeclampsia. The risk of preterm birth is also present in pregnant women with SCI. Other complications that are mentioned as possible, but also quite rare, are: placental abruption, increased perinatal mortality, low Apgar score and low birth weight. However, the association between SKH in pregnancy and offspring developmental disorders has not been fully demonstrated [72,12].

Effects of SKH treatment during pregnancy

Treatment of SKH with levothyroxine is thought to outweigh the potential benefits. SKH that occurs before conception, or during gestation, should be treated with levothyroxine. In contrast, there are no studies that show the benefit of treating isolated hypothyroxinemia during pregnancy in terms of maternal obstetric complications. However, levothyroxine therapy may be considered in isolated hypothyroxinemia detected in the first trimester of pregnancy, due to its association with more favorable neuropsychological development in children. Levothyroxine therapy is not recommended in isolated cases of hypothyroxinemia detected in the second and third trimesters.

Levothyroxine therapy should be initiated in patients with TSH> 10 mU/l in the first trimester, regardless of the presence of TPOAb. Also, therapy should be initiated in pregnant women with TSH> 4 mU/L and TPOAb positive. Therapy should be considered in pregnant women with TSH of 2.5-4mU/L with positive TPOAb and in pregnant women with TSH of 2.5-10mU/L with negative TPOAb. In patients preparing for pregnancy with assisted reproductive techniques, the TSH should be <2.5 mU/L. In these patients, TSH should be determined two weeks before and two weeks after insemination and in vitro fertilization (VTO) [79].

If a decision is made to introduce substitution in pregnant women with CKD, the suggested doses of levothyroxine are: 1.20 μg / kg / day for TSH ≤ 4.2 mU / L; 1.42 μg / kg / day for TSH> 4.2–10 m IU / L and 2.33 μg / kg / day for TSH> 10 mU / L. TSH values should be checked every 4-6 weeks during the first trimester and once during the second and third trimesters.

In patients with morning sickness, late levothyroxine administration may be a legitimate option. The goal of levothyroxine treatment during pregnancy is to normalize maternal serum TSH values within trimester-specific reference values.

Most cases of SKH in pregnancy are transient and recover after pregnancy. However,

pregnant women with positive TPOAb and TSH> 5 mU/L are more likely to have persistently elevated TSH, i.e. that hypothyroidism will persist after pregnancy. After delivery, the dose of levothyroxine should be reduced to the pre-conception dose. In women diagnosed with SKH during pregnancy, whose TSH is <5 mU/L and who have negative TPOAb, as well as in women whose replacement dose was less than 50 μg of levothyroxine, discontinuation of postpartum substitution may be attempted. Thyroid status checked 6 weeks postpartum, then at 6 and 12 months. In other women diagnosed with SCC after pregnancy, thyroid status should be checked 6 months and one year after delivery and the need for substitution should be determined. Levothyroxine therapy is not recommended for euthyroid women with positive antibodies [72,12]. Evidence for screening for SKH in pregnancy is ambiguous. Although there are still no well- controlled studies to justify general screening, a large number of authors recommend screening. Also, a large number of authors advocate screening only for pregnant women who are at special risk, ie. women with a history of thyroid disease, women with a family history of thyroid disease, women with goiter, women with DM type 1, women with other autoimmune diseases, women with infertility of unknown cause, women with a history of head and neck radiotherapy, women with a history of abortion and premature birth [72,12,74,80].

SUBCLINICAL HYPOTHYROIDISM IN CHILDREN

The subject of our consideration is primarily SKH in adult population, but we will make a few remarks about this condition in children. When it comes to possible prenatal impact, the results of numerous studies on the relationship between the mother's SKH and impaired neurophysiological development of the child are not consistent, as is very clear in KH [12], and further research is needed to determine the exact impact. In newborns and early childhood, especially in the first 3 years of life, THs play an irreplaceable role in the process of maturation and brain development, and the impact on linear growth persists until the closure of the pineal gland in adolescence [81]. After birth, large changes in thyroid function occur in the newborn, and the level of TSH> 5 mU / L, can be considered elevated after 1 month of age. Therefore, it is necessary, as in the elderly population, to use age-specific reference values to interpret diagnostic biochemical findings [82]. In the general pediatric and adolescent population with SCH, hormones are normalized in over 70% of them, or persist unchanged in most of the rest, for the next 5 years after the diagnosis [12]. SKH is 10 times more common in children with Down syndrome than in the general population [83]. In obese children, a TSH level of 5-7 m IU/L is likely a consequence rather than a cause of obesity [84]. In areas with sufficient iodine intake, SKH in young children is most often idiopathic (so-called persistent "Hyperthyrotropinemia" and "Non-autoimmune" idiopathic SKH), or caused by various perinatal and genetic causes. In older children and adolescents, the most common cause is AITB [12]. To date, there is insufficient evidence to recommend levothyroxine substitution in most children with SKH and TSH <10 mU/L [85].

AMIODARON-INDUCED SUBCLINICAL HYPOTHYROIDISM

Chronic therapy with amiodarone (AMD), an iodine-rich antiarrhythmic, is associated with the appearance of predictable changes in TFT, as well as the appearance of thyroid dysfunction, which is responsible for both iodine load and cytotoxicity of the antiarrhythmic [86]. According to research by the authors of this paper, amiodarone-induced subclinical hypothyroidism (AISKH) is found in the area with sufficient iodine intake in 10% of cardiac patients treated with this antiarrhythmic, more often in women, patients with enlarged thyroid gland and patients with elevated TPOAb [87]. In most patients with AISK, the condition does not progress to KH, and in a large number there is a spontaneous normalization of thyroid status, even with continued amiodarone therapy [88]. A case of amiodarone-induced thyrotoxicosis (AIT) after AISC in a patient during continued amiodarone therapy has also been described [89]. Also, during recovery from AIT, SKH may develop, transient but also permanent [87,89]. It is recommended that thyroid status be determined before initiating amiodarone therapy and monitored regularly, usually every 6 months, during therapy with this antiarrhythmic. In patients at increased risk for thyroid dysfunction, i.e. women, patients with goiter and elevated TAT, the use of another antiarrhythmic should be considered, or thyroid

status should be monitored more frequently. We believe that it is not necessary to discontinue amiodarone therapy in AISCH, but to continue regular monitoring of thyroid status [90,91].

MICRONUTRIENTS AND SUBCLINICAL HYPOTHYROIDISM

Life habits including sleep, smoking, diet, and physical activity are significant factors influencing normal thyroid function in SKH [92]. Iodine, selenium and iron are necessary for the synthesis of thyroid hormones. Hem-bound iron is part of thyroid peroxidase (TPO), which enables the incorporation of iodine atoms into tyrosine molecules in the process of synthesis of thyroid hormones [93]. Myo-inositol, as a secondary messenger of phospholipase C, also stimulates the organization of iodine and its incorporation into thyroid hormones through the inositol phosphate / Ca 2+ / diacylglycerol signaling pathway [94]. Selenium (daily requirements are 55 μg, and in pregnancy and lactation 60-70 μg) as an integral part of the enzyme deiodinase, enables the synthesis of triiodothyronine, or inactivation of thyroxine by conversion to reverse T3. In addition, selenoproteins, glutathione peroxidase, and thioredoxin reductase affect iodine organization through their effects on the concentration of reactive oxygen species, particularly H 2 O 2., [93] .

Adequate iodine intake (about 150 μg per day), as well as adequate TSH synthesis, are the basic prerequisites for the synthesis of thyroid hormones. Iodine deficiency in the diet leads to reduced synthesis of thyroid hormones, but its excessive intake has the same effect, due to the Wolff-Chaikoff effect [94]. Due to the effect on iodine organization, iron deficiency (daily requirements are about 9 mg for men and about 15 mg for menstruating women) affects thyroid status as well as myo-inositol deficiency, which, unlike iron, selenium and iodine, can still synthesize in the body from glucose, so deficits are rare [94,95] . In the case of a combined deficiency of iodine and selenium, in order to normalize the function of the thyroid gland, it is necessary to first compensate for the deficiency of iodine, and only after that the deficiency of selenium [94,96] .

CONCLUSION

SKH is a common condition and most do not require treatment, but only follow-up. There is a consensus that levothyroxine substitution should be indicated in adult patients with SCC whose TSH is ≥ 10 m IU/L. In all other cases, the assessment is individual. Recommendations regarding SCH screening vary widely among professional associations and expert groups. Overall, screening is not recommended in the general population and should be limited to people at high risk for the condition, such as patients with autoimmune diseases, positive personal or family history of thyroid disease, and those with symptoms similar to hypothyroidism. Even in asymptomatic pregnant women, opinions about the need for universal screening are divided. Most professional associations suggest targeted screening of only certain groups of patients.

LITERATURE:

1. Bauer SB, Azcoaga-Lorenzo A, Agrawal U, McCowan C. Management strategies forpatients with subclinical hypothyroidism: a protocol for an umbrella review. Syst Rev 2021;10:290. https://doi.org/10.1186/s13643-021-01842-y BMC
2. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinicalthyroid disease: scientific review and guidelines for diagnosis and management. Jama. 2004;291:228–38.
3. Simon H.S. Pearce HSS, Brabant G, Duntas HL, Monzani F, Peeters PR, Salman Razvi S, Wemeau JL. 2013 ETA Guideline: Management of Subclinical Hypothyroidism. Eur Thyroid J 2013;2:215–228. DOI: 10.1159/000356507
4. Gharib H, Tuttle MR, H. Baskin J, Fish HL, Singer AP, McDermott TM. Consensusstatement: Subclinical Thyroid Dysfunction: A Joint Statement on Management from the American Association of Clinical Endocrinologists,the American Thyroid Association, and The Endocrine Society. J Clin Endocrinol Metab 2005; 90(1):581–585.
5. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC: The Colorado thyroid disease prevalence study. Arch Intern Med 2000; 160: 526–534.
6. Vanderpump MP, Tunbridge WM, French JM, et al: The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol 1995; 43: 55–68.
7. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III) J Clin Endocrinol Metab. 2002;87:489–499.
8. Zimmermann BM, Boelaert K. Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol 2015;3:286–95. http://dx.doi.org/10.1016/ S2213-8587(14)70225-6
9. Uzunlulu M, Yorulmaz E, Oguz A. Prevalence of Subclinical Hypothyroidism in Patients with Metabolic Syndrome. Endocrine Journal 2007;54(1):71–76.

10. Han C, He X, Xia X, Li Y, Shi X, Shan Z, Teng W.Subclinical Hypothyroidism and Type 2 Diabetes: A Systematic Review and Meta-Analysis.PLoS One. 2015;10(8):e0135233.
11. Chonchol M, LippiG, Salvagno G, Zoppini G, Muggeo M, Targher GConclusions: These findings suggest that subclinical primary hypothyroidism is a relatively common condition (~18%) among persons with CKD not requiring chronic dialysis, and it is independently associated with progressively lower estimated GFR in a large cohort of unselected outpatient adults.. Prevalence of Subclinical Hypothyroidism in Patients with Chronic Kidney Disease. Clin J Am Soc Nephrol. 2008; 3(5):1296–1300. doi: 10.2215/CJN.00800208
12. Lazarus J, Brown SR, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. Guidelines for the Management of Subclinical Hypothyroidism in Pregnancy and in Children. Eur Thyroid J 2014;3:76–94. DOI: 10.1159/000362597
13. Surks IM, Boucai L. Age- and Race-Based Serum Thyrotropin Reference Limits. J Clin Endocrinol Metab 2010;95(2):496–502. https://doi.org/10.1210/jc.2009-1845
14. Hennessey VJ, Espaillat R. Subclinical hypothyroidism: a historical view and shifting prevalence. Int J Clin Pract. 2015; 69(7):771–782. doi: 10.1111/ijcp.12619
15. Dittmar M, Kahaly GJ. Polyglandular autoimmune syndromes: immunogenetics and long-term follow-up. J Clin Endocrinol Metab. 2003;88:2983-2992.
16. Broadley SA, Deans J, Sawcer SJ, Clayton D, Compston DA. Autoimmune disease in first-degree relatives of patients with multiple sclerosis. A UK survey. Brain. 2000;123:1102-1111.
17. Heward J, Gough SC. Genetic susceptibility to the development of autoimmune disease. Clin Sci (Lond). 1997;93: 479-491.
18. Menconi F, Monti MC, Greenberg DA, et al. Molecular amino acid signatures in the MHC class II peptide-binding pocket predispose to autoimmune thyroiditis in humans and in mice. Proc Natl Acad Sci USA. 2008;105:14034-14039.
19. Ban Y, Greenberg DA, Davies TF, Jacobson E, Concepcion E, Tomer Y. Linkage analysis of thyroid antibody production: evidence for shared susceptibility to clinical autoimmune thyroid disease. J Clin Endocrinol Metab. 2008;93:3589-3596.
20. Andersson M, de Benoist B, Delange F, Zupan J. Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. Public Health Nutr. 2007;10:1606-1611.
21. Emerson CH, Dysno WL, Utiger RD. Serum thyrotropin and thyroxine concentrations in patients receiving lithium carbonate. J Clin Endocrinol Metab. 1973;36:338-346.
22. Preziati D, La Rosa L, Covini G, et al. Autoimmunity and thyroid function in patients with chronic active hepatitis treated with recombinant interferon alpha-2a. Eur J Endocrinol. 1995;132:587-593.
23. Martino E, Bartalena L, Bogazzi F, Braverman LE. The effects of amiodarone on the thyroid. Endocr Rev. 2001;22:240-254.
24. Kappers MH, van Esch JH, Smedts FM, de Krijger RR, et al. Sunitinib-induced hypothyroidism is due to induction of type 3 deiodinase activity and thyroidal capillary regression. J Clin Endocrinol Metab. 2011;96:3087-3094.
25. Santen RJ, Misbin RI. Aminoglutethimide: review of pharmacology and clinical use. Pharmacotherapy1981;1(2):95-120.
26. Matveyeva SL, Shevchenko OS, Pogorelova OO. The function of the thyroid gland in patients with multi-drug resistant tuberculosis. Antimicrobial Resistance and Infection Control 2017;6:82-84. DOI 10.1186/s13756-017-0238-4
27. Moreno DM, Miguélez González M, González Fernández L, Percovich Hualpa HC. A review of systemic infiltrative diseases and associated endocrine diseases Endocrinología,DiabetesyNutrición (English ed.) 2021;68:312-320.
28. Ozen Oz Gul, Soner Cander, Canan Ersoy. . An uncommon infiltrative disease of thyroid: Riedel's thyroiditis. Endocrine Abstracts 2014; 35:P282. DOI: 10.1530/endoabs.35.P282
29. Payami H, Joe S, Thomson G. 1989 Autoimmune thyroid disease in type I diabetic families. Genet Epidemiol. 1989;6:137-141.
30. Nerup J. Addison's disease—clinical studies. A report of 108 cases. Acta Endocrinol (Copenh). 1974;76:127-141.
31. Torfs CP, King MC, Huey B, Malmgren J, Grumet FC. Genetic interrelationship between insulin-dependent diabetes mellitus, the autoimmune thyroid diseases, and rheumatoid arthritis. Am J Hum Genet. 1986;38:170-187.
32. Murdoch JC, Ratcliffe WA, McLarty DG, Rodger JC, Ratcliffe JG. Thyroid function in adults with Down's syndrome. J Clin Endocrinol Metab. 1977;44:453-458.
33. Radetti G, Mazzanti L, Paganini C, et al. Frequency, clinical and laboratory features of thyroiditis in girls with Turner's syndrome. The Italian Study Group for Turner's Syndrome. Acta Paediatr. 1995;84:909-912.
34. Mouat F, Evans HM, Cutfield WS, Hofman PL, Jefferies C. Massive hepatic hemangioendothelioma and consumptive hypothyroidism. J Pediatr Endocrinol Metab. 2008;21:701-703.
35. Robin P. Peeter. Subclinical Hypothyroidism. N Engl J Med 2017;376:2556-2565. DOI: 10.1056/NEJMcp1611144
36. Huber G, Staub JJ, Meier C, et al: Prospective study of the spontaneous course of subclinicalhypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. J Clin Endocrinol Metab 2002;87:3221–3226.
37. Diez JJ, Iglesias P: Spontaneous subclinical hypothyroidism in patients older than 55 years: an analysis of natural course and risk factors for the development of overt thyroid failure. J Clin Endocrinol Metab 2004; 89:4890–4897.
38. Meyerovitch J, Rotman-Pikielny P, Sherf M, et al: Serum thyrotropin measurements in the community: five-year follow-up in a large network of primary care physicians. Arch Intern Med 2007;167:1533–1538.
39. Walsh JP, Bremner AP, Feddema P, et al. Thyrotropin and thyroid antibodies as predictors of hypothyroidism: a 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. J. Clin. Endocrinol. Metab. 2010;95:1095–1104.
40. Kalaria T, Sanders A, Fenn J, et al. The diagnosis and management of subclinical hypothyroidism is assay-

dependent– Implications for clinical practice. Clin. Endocrinol. (Oxf). 2021;94:1012–1016.
41. Surks MI & Hollowell JGAge-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J. Clin. Endocrinol. Metab. 2007;92:4575–4582.
42. Biondi B, Cappola AR & Cooper DS. Subclinical Hypothyroidism: A Review. JAMA 2019;322:153–160.
43. Hattori N, Ishihara T, Yamagami K, et al. Macro TSH in patients with subclinical hypothyroidism. Clin. Endocrinol. (Oxf). 2015;83:923–930.
44. Koulouri O, Moran C, Halsall D, et al. Pitfalls in the measurement and interpretation of thyroid function tests. Best Pract. Res. Clin. Endocrinol. Metab. 2013;27:745.
45. Santini F, Marzullo P, Rotondi M, et al. Mechanisms in endocrinology: the crosstalk between thyroid gland and adipose tissue: signal integration in health and disease. Eur. J. Endocrinol. 2014;171:R137–R152.
46. Kim WG, Park S, Jeon MJ, et al. Clinical Features of Early and Late Postoperative Hypothyroidism After Lobectomy. J. Clin. Endocrinol. Metab. 2017;102:1317–1324.
47. Ardabilygazir A, Afshariyamchlou S, Mir D, et al. Effect of High-dose Biotin on Thyroid Function Tests: Case Report and Literature Review. Cureus 2018;10.
48. Katzman BM, Lueke AJ, Donato LJ, et al. Prevalence of biotin supplement usage in outpatients and plasma biotin concentrations in patients presenting to the emergency department. Clin. Biochem. 2018;60:11–16.
49. Garber JR, Cobin RH, Gharib H, et al: Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid 2012;22:1200–1235.
50. Pedersen OM, Aardal NP, Larssen TB, et al: The value of ultrasonography in predicting autoimmune thyroid disease. Thyroid 2000;10:251–259.
51. Andersen S, Pedersen KM, Bruun NH, Laurberg P: Narrow individual variations in serum T 4 and T 3 in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab 2002;87:1068–1072.
52. Bremner AP, Feddema P, Leedman PJ, et al: Age-related changes in thyroid function: a longitudinal study of a community-based cohort. J Clin Endocrinol Metab 2012;97: 1554–1562.
53. Persani L, Borgato S, Romoli R, et al: Changes in the degree of sialylation of carbohydrate chains modify the biological properties of circulating thyrotropin isoforms in various physiological and pathological states. J Clin Endocrinol Metab 1998;83:2486–2492.
54. Asvold BO, Bjoto T, Vatten LJ: Association of serum TSH with high body mass differs between smokers and never-smokers. J Clin Endocrinol Metab 2009;94:5023–5027.
55. Villar HC, Saconato H, Valente O, Atallah AN: Thyroid hormone replacement for subclinical hypothyroidism. Cochrane Database Syst Rev 2007;3:CD003419.
56. Samuels MH, Schuff KG, Carlson NE, et al: Health status, mood, and cognition in experimentally induced subclinical hypothyroidism. J Clin Endocrinol Metab 2007;25:2545– 2551.
57. Parle J, Roberts L, Wilson S, et al: A randomized controlled trial of the effect of thyroxine replacement on cognitive function in community- living elderly subjects with subclinical hypothyroidism: the Birmingham Elderly Thyroid Study. J Clin Endocrinol Metab 2010;95:3623–3632.
58. Kitahara CM, Platz EA, Ladenson PW, et al: Body fatness and markers of thyroid function among US men and women. PLoS One 2012;7:e34979.
59. Fox CS, Pencina MJ, D'Agostino RB, et al: Relations of thyroid function to body weight: cross-sectional and longitudinal observations in a community-based sample. Arch Intern Med 2008;168:587–592.
60. Wolters B, Lass N, Reinehr T: TSH and freetriiodothyronine concentrations are associated with weight loss in a lifestyle interventionand weight regain afterwards in obese children. Eur J Endocrinol 2013;168:323–329.
61. Maratou E, Hadjidakis DJ, Kollias A, et al: Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. Eur J Endocrinol 2009;160:785–790.
62. Triolo TM, Armstrong TK, McFann K, et al: Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. Diabetes Care 2011;34:1211–1213.
63. Tognini S, Polini A, Pasqualetti G, et al: Age and gender substantially influence the relationship between thyroid status and the lipoprotein profile: results from a large cross-sectional study. Thyroid 2012;22:1096–1103.
64. Biondi B: Mechanisms in endocrinology: heart failure and thyroid dysfunction. Eur J Endocrinol 2012;167:609–618.
65. Shakoor SK, Aldibbiat A, Ingoe LE, et al: Endothelial progenitor cells in subclinical hypothyroidism: the effect of thyroid hormone replacement therapy. J Clin Endocrinol Metab 2010;95:319–322.
66. Vanderpump MP, Tunbridge WM, French JM, et al: The development of ischemic heart disease in relation to autoimmune thyroid disease in a 20-year follow-up study of an English community. Thyroid 1996;6:155–160.
67. Ochs N, Auer R, Bauer DC, et al: Meta-anal ysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortal ity. Ann Intern Med 2008;148:832–845.
68. Rodondi N, den Elzen WP, Bauer DC, et al. Thyroid Studies Collaboration: Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA 2010;304:1365–1374.
69. Jonklaas, J.; Bianco, A.C.; Bauer, A.J.; Burman, K.D.; Cappola, A.R.; et al. Guidelines for the treatment of hypothyroidism: Prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid 2014;24;1670–1751.
70. Calissendor J, Falhammar H. To Treat or Not to Treat Subclinical Hypothyroidism, What Is the Evidence? Medicina 2020;56:40. doi:10.3390/medicina56010040
71. Stott D.J., Rodondi N., Kearney P.M., Ford I.,Westendorp R.G.J. et al. Thyroid hormone therapy for older adults with subclinical hypothyroidism. N. Engl. J. Med. 2017;376:2534–2544.
72. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H,Dosiou C, et al. 2017 Guidelines of the American Thyroid Associationfor the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum.Thyroid. 2017;27(3):315-389.
73. Brenda S. Bauer, Amaya Azcoaga-Lorenzo, Utkarsh Agrawal and Colin McCowan. Management strategies

for patients with subclinical hypothyroidism: a protocol for an umbrella review. Syst Rev 2021;10:290.
74. Galina Khachikovna Safarian, Alexander Mkrtichevich Gzgzyan, Kharryasovna Dzhemlikhanova Lyailya and Dariko Alexandrovna Niauri. Does subclinical hypothyroidism and/or thyroid autoimmunity influence the IVF/ICSI outcome? Review of the literature. Gynecological Endocrinology. 2019;35(Sup1):56-59.
75. Aguayo A, Grau G, Vela A, Aniel-Quiroga A, Espada M, Martul P, Castano L, Rica IJ: Urinary iodine and thyroid function in a population of healthy pregnant women in the North of Spain. Trace Elem Med Biol 2013;27:302–306.
76. Haddow JE, Palomaki GE, McClain MR: Thyroid-stimulating hormone in singleton and twin pregnancy: importance of gestational age-specific reference ranges. Obstet Gynecol 2006;107:205–206.
77. Soldin OP, Soldin D, Sastoque M: Gestationspecific thyroxine and thyroid stimulating hormone levels in the United States and worldwide. Ther Drug Monit 2007;29:553–559.
78. Haddow JE, McClain MR, Lambert-Messerlian G, Palomaki GE, Canick JA, et al. First and Second Trimester Evaluation of Risk for Fetal Aneuploidy Research Consortium: Variability in thyroid-stimulating hormone suppression by human chorionic gonadotropin during early pregnancy. J Clin Endocrinol Metab 2008;93:3341-3347.
79. Kris Poppea, Peter Bisschopb Laura Fugazzolac, Gesthimani Minziorid, David Unuanee Andrea Weghofer. 2021 European Thyroid Association Guideline on Thyroid Disorders prior to and during Assisted Reproduction. Eur Thyroid J. 2020;9:281–295.
80. Vaidya B, Anthony S, Bilous M, Shields B, Drury J, Hutchison S, et al. Detection of thyroid dysfunction in early pregnancy: Universal screening or targeted high-risk case finding? J Clin Endocrinol Metab. 2007;92(1):203–7.
81. Brown RS: The thyroid; in Brook CGD, Clayton PE, Brown RS (eds): Brook's Clinical Pediatric Endocrinology, ed 6. Chichester, Wiley-Blackwell, 2009; pp 250–282.
82. Chaler EA, Fiorenzano R, Chilelli C, Llinares V, Areny G, Herzovich Vet al.: Age-specific thyroid hormone and thyrotropin reference intervals for a pediatric and adolescent population. Clin Chem Lab Med 2012; 50: 885–890.
83. King K, O'Gorman C, Gallagher S: Thyroid dysfunction in children with Down syndrome: a literature review. Ir J Med Sci 2014;107:118–119.
84. Ittermann T, Thamm M, Wallaschofski H, Rettig R, Volzke H: Serum thyroid-stimulating hormone levels are associated with blood pressure in children and adolescents. J Clin Endocrinol Metab 2012; 97: 828–834.
85. Aijaz NJ, Flaherty EM, Preston T, Bracken SS, Lane AH, Wilson TA: Neurocognitive function in children with compensated hypothyroidism: lack of short term effects on or off thyroxin. BMC Endocr Disord 2006;6:2.
86. Aleksić Ž, Aleksić A, Mitov V, Jolić A, Vešović D. Vrednosti in vitro pokazatelja funkcijskog tiroidnog statusa kod pacijenata na terapiji Amiodaronom. Medicinski glasnik Zlatibor. 2012;17(44 Suppl):90.
87. Aleksić Ž, Aleksić A.. Incidenca amiodaronom indukovanih tiroidnih disfunkcija i prediktivni faktori za njihov nastanak. Timočki medicinski glasnik 2011;36(Suppl 1):28.
88. Aleksić Ž, Aleksić A. Amiodaronom indukovan supklinički hipotiroidizam. Timočki medicinski glasnik 2015;40(Suppl 1):31.
89. Aleksić Ž, Aleksić A, Mitov V, Jolić A, Vešović D. Amiodaronom indukovana tirotoksikoza kod prethodno subklinički hipotiroidnog pacijenta na terapiji amiodaronom – prikaz slučaja. Timočki medicinski glasnik 2012;37(Suppl 1):92.
90. Aleksić Ž. Subklinički hipotiroidizam – dijagnostičke i terapijske dileme. Timočki medicinski glasnik 2018;43(Suppl 1):38.
91. Aleksić ŽP, Aleksić AZ, Mitov VM, Jolić AD, Vešović DM. Amiodarone induced subclinical thyroid dysfunction – what to expect during follow up? Is there reason for amiodarone withdrawal? Eur Thyroid J 2012;1(suppl 1):188.
92. Wu K, Zhou Y, Ke S, et al.Lifestyle is associated with thyroid function in subclinical hypothyroidism: a cross-sectional study. BMC Endocr. Disord. 2021;21:1–11.
93. Zimmermann MB & Köhrle J. The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health. Thyroid 2002;12:867–878.
94. Benvenga S, Nordio M, Laganà AS, et al.The Role of Inositol in Thyroid Physiology and in Subclinical Hypothyroidism Management. Front. Endocrinol. (Lausanne) 2021;12:458.
95. Soliman AT, De Sanctis V, Yassin M, et al.Chronic anemia and thyroid function. Acta Bio Medica Atenei Parm. 2017;88:119.
96. Ventura M, Melo M & Carrilho F. Selenium and Thyroid Disease: From Pathophysiology to Treatment. Int. J. Endocrinol. 2017:1297658. https://doi.org/10.1155/2017/1297658