Among the different thyroid carcinomas, papillary carcinoma (PTC) is the most common malignant tumor of the thyroid gland, as well as the most common malignancy among all cancers of the endocrine glands. It is a cancer which - among other cancers - is characterized by clearly defined rules of diagnosis, treatment and monitoring (follow-up). One of the most important features of PTC is its slow growth and spread (PTC metastasizes very late, very slowly). The result is that in the majority of cases, cancer foci diagnosed exclusively in the thyroid gland (PTaNM0) are subjected to surgical treatment. Treatment is based on the performance of total thyroidectomy and - next - radioiodine 131I use, the latter to destroy the thyroid remnants - the source of thyroglobulin - for "clearing the foreground". After completion of therapy, thyroglobulin in these patients is becoming a tumor marker which is used to assess the effectiveness of therapy. The evaluation of thyroglobulin concentration after prior stimulation with TSH is the most sensitive method speaking for or against the presence of thyroid tissue in the possible metastases. Patients with differentiated thyroid carcinoma (especially with papillary cancer) are usually informed at the time of diagnosis that such a diagnosis is "a blessing in disguise". That means that the risk of dying from their disease is lower than in the case of communication accidents, and that they should not be afraid of this disease, just as usually they are not afraid of normal everyday activities like "leaving home". In other words, means that in their case, just this type of cancer and not another, is a real blessing. Unfortunately, a very good prognosis, resulting from the aforementioned slow cancer growth, even then carries the risk of recurrence of malignancy, and the recurrence time can be as long as the patient’s life is. These patients live all the time with the stigma of the cancer, the symptoms of which we will be looking for in their bodies - as doctors, despite the passing years. It can be treated, in a sense, as "the curse of cancer". Each patient’s next meeting with his/her doctor, whether in an out-patient clinic or in a hospital ward, for the patient is the reason for subsequent stress. It brings to mind all the worst, associated with the words "you suffer from cancer", words spoken once for the first time a long time ago. One should not forget about all of this and need to keep empathy, seeking to make such diagnostic methods, which are the least onerous for the body of the patient, methods which at the same time will allow for a quick and reliable assessment of disease activity (time to wait for the result drags on exceptionally), empowering the patient to the conclusion that "I am healthy! ... until the next test ...". Currently the preferred diagnostic method in monitoring differentiated thyroid cancer is to assess thyroglobulin concentration after TSH stimulation. One way to achieve a high TSH level is to withdraw L-T4, i.e. induction of endogenous thyrotropinemia (putting the patient in a state of primary hypothyroidism). However, the symptoms of hypothyroidism, which are highly unpleasant for the patient and fuel a depressive attitude, appearing during almost complete L-T4 deficiency, are often interpreted by patients as a manifestation of cancer relapse. The period of preparation for tests, often lasting for more than a month is an endless band of memories and reflections on the incurable disease. In this connection, doctor should seek to determine thyroglobulin concentration in the condition of exogenous stimulation with recombinant human TSH (rhTSH). This way of preparing for the test is safe and reliable for the patient, devoid of any adverse circumstances related to the stimulation with endogenous TSH. By that means, patients can reduce the burden related to disease consciousness and they more frequently mention the "blessing" than the "curse" associated with the established earlier diagnosis of differentiated thyroid cancer. In addition, you need to be aware that the use of rhTSH is generally considered to be more effective in achieving optimum of iodine uptake by thyroid tissue, than the introduction of endogenous thyrotropinemia [1]. A separate issue is the problem, whether being forms of papillary tumors, not provided for in the existing classification of thyroid tumors [2], actually exist. Some authors are inclined to such a concept but the view prevails that these are various papillary variants of follicular adenomas [3], and not benign papillary neoplasms.

**References**

Graves' disease (GD) is an autoimmune disorder characterized by the presence of circulating autoantibodies that stimulate the thyroid hormone receptor (TSHR), resulting in hyperthyroidism and goiter. GD may affect also other organs, leading to Graves' orbitopathy, Graves' dermopathy and acropathy. It is likely that the extrathyroidal manifestations of GD are due to autoimmunity against antigens common to the thyroid and other affected organs (for example TSHR). Although its exact etiology remains to be established, GD is believed to result from a complex interaction between genetic, environmental and endogenous factors. The clinical picture of GD is highly variable. Measurements serum levels of anti-TSHR autoantibodies (TRAb) and thyroid ultrasonography represent the most important diagnostic tests for GD. Existing treatment modalities for Graves' hyperthyroidism includes antithyroid drugs (ATDs), radioactive iodine, and surgery. The use of ATDs as the initial treatment option in GD is well accepted. However, the optimal treatment duration and the predictive marker of remission after ATDs therapy are still controversial. A high relapse rate after a course of ATDs (60-70%), implies the use of ablative treatments (radioactive iodine or surgery) that remove or decrease thyroid tissue leading to lifelong hyperthyroidism. There is a lack of general agreement as to which therapy for Graves' hyperthyroidism is the best as none is ideal and all may have severe side effects. Moreover, none of these treatments targets the autoimmune disease process. Therefore the treatment plan should be established individually and carefully discussed with the patient. Hopefully novel agents that might act on the autoimmune disease process will be approved for Graves' hyperthyroidism.

Conclusions: 1. In children, every thyroid nodule or incidentaloma should be evaluated according to an appropriate algorithm. 2. In each case, it is indispensable to follow thyroid function tests, as well as to assess the titer of anti-thyroid autoantibodies. 3. Ultrasound-guided FNA remains the GOLD STANDARD – the most important diagnostic method implied - in thyroid nodules both in children and adults. 4. Significant enlargement of thyroid nodule during observation or L-T4 pharmacotherapy is an urgent indication for surgery because it may indicate neoplastic growth. In such a case, FNA result implying benign lesion cannot justify abandoning surgery. 5. Thyroid goiter in children requires greater caution and more frequent control visits (at least once every 6 months) than in adults. In case of any doubt, radical treatment should be conducted.

A4
Intraoperative localization and protection of important structures of the neck in thyroid surgery
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Nodular thyroid disease affects thousands of people in Poland. Tumors of the thyroid account for about 1% overall human cancers. Thyroidectomy is...
the most common surgical operation in endocrine tumors. Operative therapy for benign thyroid nodules is recommended for: progressive increase in nodule size, substernal extension, compressive symptoms of the neck, the development of thyrotoxicosis and patient therapeutic prevalence. In Poland thyroidectomy is the fifth surgical procedure and comprises about 25 000 operations yearly. Reduction of surgical injury with simultaneous retention of current safety and radical nature of surgical intervention forces the work into a relatively small operating field. Electric devices enabling the achievement of full and lasting haemostasis during thyroidectomy supplant traditional surgical method (ligature, haemostatic sutures) with no impact on the incidence of perioperative complications, while at the same time allowing to shorten the duration of the procedure. The haemostatic effect is associated with generation of heat, which apart from the intended result may bring about thermal tissue injury. During the surgical procedure it is important to determine the thermal spread around the active tip of electric devices in the operating field during thyroidectomy, and the safe temperature range during the operation to protect important structures of the neck. The mean safe distance of the active tip of an electric device from important anatomic structures is 5 mm minimally and depends on the device type, time of operation and its power settings. All the modern techniques of vessel sealing are associated with generation of heat and its spherical spread, which causes thermal injury to the surrounding tissues. Their mode of operation through, among others, structural changes in collagen and elastin, leads to durable connection of sealed vessel walls and tissue structures. These systems enable a safe sealing of vessels of up to 7 mm in diameter. In conclusions: In the cases analyzed by the author concerning the thyroidectomy techniques, it is recommended to replace electric devices with ligatures or clips or human fibrinogen in place near the laryngeal nerves, parathyroid glands and the trachea. The decision of the change of the method of haemostasis maintenance in the vicinity of crucial structures has been left to the surgeon.

A5 The syndromes of reduced sensitivity to thyroid hormone – the current state of art
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The clinical, laboratory, genetic and molecular characteristics of syndromes of reduced sensitivity to thyroid hormone are the subject of this abstract. The syndrome of reduced sensitivity to thyroid hormone in the majority of cases is caused by point mutations in the thyroid hormone receptor β (TRb) gene. Before TRβ gene mutations were recognized, resistance to thyroid hormone (RTH) was subdivided on clinical basis into generalized, isolated pituitary and peripheral tissue. Nowadays this classification has a clinical usefulness, but it seems to have no logical etiologic grounds. The mutations in TRβ gene have been found in over 3000 individuals belonging to approximately 1000 families. While the clinical presentation is variable, the main features are: high serum T4 and usually also T3 concentrations, non-suppressed – sometimes slightly elevated serum thyrotropin (TSH), commonly a goiter. The majority of subjects have a near normal metabolic state, sometimes coexistence of clinical symptoms of thyroid hormones deficiency and excess takes place in one patient. Thus, delayed growth and bone maturation, and learning disabilities can be present along with hyperactive behavior and sinus tachycardia. Mental retardation was found in 3% of cases. Attention deficit hyperactivity disorder (ADHD) is also present in about half of patients with RTH syndrome. In 15% of families with RTH symptoms no mutations in the TRb gene were found. The term non-TR-RTH refers to this subgroup of individuals, clinically and biochemically identical with RTH caused by TRβ mutations. Recently, mutations in Trα1 gene have been described in two families. First nonsense mutation produces a truncated Trα1 (E403X) that lacks the C-terminal α-helix. It has been identified in a 6 year-old girl with chronic constipation, and growth and developmental delay. Another family with Trα1 gene mutation was described in 2012. In both cases, thyroid function tests were distinct from those in classical RTH with TRβ gene mutations. These patients had low serum T4, high T3 and very low TSH.

Two relatively novel syndromes presenting reduced sensitivity to thyroid hormone: membrane transport defect and thyroid hormone metabolism defect were described. This led to the broadening of the definition of reduced sensitivity to thyroid hormone to encompass all the defects that can interfere with the biological activity of a chemically intact hormone, secreted in normal amounts. Thyroid hormone cell membrane transporter defect (THCMTD) is caused by mutations in the MCT8 gene. It is an X-linked defect. Mutations have 100% penetrance in males who manifest both neuropsychomotor impairment and characteristic thyroid test abnormalities (high serum T4, low T3, normal or low TSH with slightly elevated TSH level). The effect of the intracellular metabolism of thyroid hormones (THMD) is caused by mutations in the SECISBP2 gene who is required for the synthesis of selenoproteins, including thyroid hormone deiodinases. It was described in 10 patients from 8 families.

References

A6 New evidence concerning the pathomechanism and treatment of thyroid associated orbitopathy
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Thyroid associated orbitopathy (TAO) is an immune-mediated inflammatory disorder that causes expansion of the orbital adipose tissue and muscles and deposition of glycosaminoglycans and collagen. No specific therapy has been established, and treatment still relies on high-dose IV. glucocorticoids in the acute inflammatory phase of the disease and surgical procedures in a burnt-out state. However, the results of the medical treatment are unsatisfactory, since up to 20% of patients are unresponsive and another 20% experience disease relapses after therapy withdrawal. Therefore, as in other autoimmune diseases, new therapeutic options based on biological treatment are under experimental and clinical investigation. The efficacy of rituximab (RTX), has been reported since 2006. This humanized chimeric anti-CD-20 antibody blocks the activation and differentiation of B cells, since CD-20 protein is expressed on the surface of pre-B and mature B lymphocytes, but not on stem cells, pro-B lymphocytes and plasma cells. Therefore, treatment with RTX leads to specific elimination of B cells without affecting their regeneration or production of immunoglobulins by plasma cells. Preliminary studies in patients with TAO indicate that blocking of CD-20 significantly and positively affected the clinical course of disease by rapid reduction of inflammation and degree of proptosis. The number of CD-20+ cells was lower in orbital tissues than in periphery.
RTX given locally as retrobulbar injections in patients resistant to glucocorticoid therapy resulted in a significant amelioration of the clinical symptoms. No side effects of that procedure were observed.

The outcome of the first randomized controlled study of rituximab or steroid treatment in TAO showed a superiority of RTX, used in single 500 mg dose, in the reduction of disease activity, improvement of QoL, and prevention of relapse over the traditional methylprednisolone protocol. These effects do not seem to be related to TRab concentrations and may be due to the influence on antigen presentation (M. Salvi, ESE 2014).

RTX is the best tested therapeutic antibody in the treatment of TAO and may become an attractive treatment option.

A7

Intraoperative neuromonitoring and other techniques limiting the number of complications in thyroid surgery

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Evolution of surgical techniques, together with progress in other fields of medicine (e.g., in anesthesiology), limits - practically to zero - the mortality in thyroid surgery. Further development in thyroid surgery is directed towards limitations of postoperative complication rates. The specific complications after thyroid surgery are hypoparathyroidism and recurrent laryngeal nerve (RLN) palsy (uni- or bilateral). The former, although mostly transient in character, has a frequency reaching up to 60% in cases of total thyroidectomy with central neck dissection because of thyroid cancer. At present, only meticulous preparation by experienced surgeons, together with PTH and calcium concentration monitoring, may be helpful in prevention and early diagnosis of hypoparathyroidism. Subsequent substitutive therapy with calcium and vitamin D metabolites should prevent hypocalcaemia.

Recent two decades was the time of intensive development of intraoperative neuromonitoring (IONM) of laryngeal nerves. Nowadays this technique, although still developing, has a stable place in thyroid surgery. Intraoperative neuromonitoring - at its present form - cannot prevent laryngeal nerve palsy, nevertheless together with stage thyroidectomy and careful preparation allows to avoid the most serious complication in thyroid surgery - bilateral RLN palsy. Recently developed continuous intraoperative neuromonitoring of vagal nerve is a promising tool and probably the next step in modern prevention of RLN palsy. Efforts in further development and standardization of the technique will hopefully result in the technique of IONM, allowing not only to intraoperatively diagnose but also to prevent RLN palsy. Further efforts are needed in limiting the invasiveness of the procedure.

A8

The thyroid gland and the process of aging

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The endocrine organs, including the thyroid gland, undergo important functional changes during aging. It is known that the prevalence of thyroid disorders increases with age. Importantly, subclinical disturbances of thyroid function are more frequent than overt diseases in the elderly. Moreover, the clinical course of thyroid diseases in elderly people differs from that observed in younger subjects; namely, symptoms are more subtle and are often attributed to normal aging, and therefore, require special attention in elderly individuals.

One of the subclinical thyroid function disturbances is subclinical hypothyroidism, which is characterized by normal free thyroid (FT4) and increased thyrotropin (TSH) levels. The prevalence of subclinical hypothyroidism increases with aging and ranges from 3 to 16% in individuals aged 60 years and older [1]. In contrast to overt hypothyroidism, the subclinical hypothyroidism in elderly subjects is not associated with impairment of physical and cognitive function, depression, metabolic disturbances or poor quality of life [2,3]. Subclinical hypothyroidism is also not associated with the increased overall mortality risk [2]. Moreover, there is no association between subclinical hypothyroidism and incident coronary heart disease (CHD), heart failure (HF) or cardiovascular (CV) mortality [4]. Similarly, total mortality was not increased in subjects with subclinical hypothyroidism, although the risk of CHD events and of CHD mortality increased with TSH levels 10 mU/L or higher [5]. Importantly, a quite high rate of reversion of subclinical hypothyroidism to euthyroidism in individuals aged at least 65 years with lower baseline TSH levels (4.5-6.9 mU/L) and antithyroid peroxidase antibody (TPOAb) negativity (≤ 37 IU/L) was observed [6]. In turn, higher TSH levels and TPOAb positivity were independently associated with lower chance of reversion to euthyroid status; TSH levels ≥ 10 mU/L were independently associated with progression to overt hypothyroidism [6].

There are obvious indications for overt hypothyroidism treatment. In turn, indications for treatment of subclinical hypothyroidism are still quite controversial. Nevertheless, the replacement therapy with L-thyroxine is not uniformly recommended in elderly people with subclinical hypothyroidism. For example, L-thyroxine replacement therapy did not improve cognitive function in elderly individuals with subclinical hypothyroidism [7]. Moreover, despite improvement of lipid profile due to treatment of L-thyroxine in subclinical hypothyroidism, there is no clear evidence that this beneficial effect can be associated with decreased cardiovascular or all-cause mortality in elderly patients [8]. Intriguingly, thyroid hypofunction, as well as elevated thyrotropin (TSH) levels, may contribute to the extended lifespan. A potential contribution of TSH and thyroid hormones to lifespan regulation was observed in the studies performed on thyroid disease-free population of Ashkenazi Jews, characterized by exceptional longevity (centenarians). For example, the higher serum TSH level in these individuals in comparison with the control groups was observed [9]. Thus, increased serum TSH level seems to be associated with extreme longevity [9]. Moreover, two single nucleotide polymorphisms (SNPs) in TSH receptor (TSHR) gene (namely rs10149689 and rs12050077) were associated with increased TSH level in Ashkenazi Jewish centenarians and their offspring [10]. Also, an inverse correlation between FT4 and TSH levels in centenarians was reported [9] which may suggest a potential role of decreased thyroid function in lifespan regulation, leading to extended longevity. The findings obtained in the Leiden Longevity Study actually show the associations between low thyroid activity and exceptional familial longevity [11]. Also in animals, a reduced thyroid function with low levels of T4 seems to be associated with extended longevity [12-14]. A very severe thyroid hypofunction was observed in Ames dwarf (ddf/ddf) mice. These animals are characterized by mutations at the Prop-1 (Prophet of pituitary factor 1) gene and demonstrate a lack of growth hormone (GH), prolactin and TSH. These features may unexpectedly contribute to remarkable longevity in Ames dwarf mice [12]. Furthermore, severe hypothyroidism in Ames dwarfs and mice with targeted disruption of the growth hormone (GH) receptor/GH binding protein gene (GH receptor knockout; GHHRKO) with mild thyroid hypofunction, have decreased thyroid follicle size which may explain decreased thyroid hormone levels in these long-lived mutants [15].

In conclusion, the altered thyroid function may play, via different mechanisms [16], a relevant role in lifespan regulation. Namely, decreased thyroid function may lead to extended longevity.

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Graves’ disease complicates about 0.1-1.0% of all pregnancies [1,2]. Despite its rare occurrence in pregnant women, Graves’ disease constitutes a great therapeutic challenge. Maternal thyroid stimulating antibodies (TSAbs) cross the placenta and can overstimulate the fetal thyroid after the 20th week of gestation (WG), when fetal TSH receptors become responsive to TSH and TSAb. On the other hand, transplacental passage of antithyroid drugs (ATD), which influence fetal thyroid much more than the maternal gland, can cause fetal hypothyroidism.

The progress in prenatal ultrasonography (US) enables early diagnosis of fetal thyroid dysfunction without performing invasive procedures such as fetal blood sampling. According to all the current guidelines [1-4], fetal US monitoring should be performed after the 18th–22nd WG in case of either ATD therapy or maternal Graves’ disease with elevated TSH receptor antibodies (TRAb), irrespective of maternal thyroid function.

The US symptoms of fetal hyperthyroidism include goiter, tachycardia (over 160 beats per minute registered for over 10 minutes), cardiomegaly, hydrops, accelerated bone maturation (presence of femoral epiphyses ossification centre before the 31st WG) and intrauterine growth restriction (IUGR). Fetal hypothyroidism can manifest with goiter, bradycardia (below 120 beats per minute), delayed bone maturation (absence of femoral epiphysis ossification centre after the 33rd WG) and IUGR. Fetal goiter presents on US as an anterior neck mass which is solid, homogenous and maintains a characteristic lobular shape. A large goiter can cause head hyperextension and precludes vaginal delivery. Compression of the esophagus and trachea can lead to polyhydramnios and airway compromise at birth. So that early diagnosis of fetal goiter is essential and relies upon comparing thyroid size with reference values [5-8]. As the presence of goiter accompanies both fetal hyper- and hypothyroidism the evaluation of blood flow by the Doppler technique may be helpful in discriminating these two abnormalities. An increased central blood flow throughout thyroid gland is indicative of fetal hyperthyroidism. In fetal hypothyroidism various patterns of thyroid vascularization are observed but an increased peripheral blood flow is the most characteristic feature.

According to some observations fetal goiter is demonstrative of fetal thyroid dysfunction with sensitivity 92%, specificity 100%, PPV 100% and NPV 98% [9]. On the other hand, abnormalities in fetal bone maturation which can be registered on US at the late stage of pregnancy, between 31 and 33 weeks of gestation, occurred in only 36% of cases when fetal thyroid dysfunction. Abnormal fetal heart rate appeared to be even more uncommon (14%) and is a late sign of fetal hypo- or hyperthyroidism [9,10]. Despite the great value of US, it must be emphasized that in the final assessment of the fetal thyroid status, serum concentrations of maternal thyroid hormones and anti-TSH receptor antibodies and the doses of maternal ATDs must be taken into account.

The author’s own experience [11,12] based on the observation of 42 cases of pregnant women with Graves’ disease and US evaluation of the fetus indicates that:

- Fetal thyroid dysfunction occurs much more often than has been commonly reported. 21% vs. 1-5% [3,13].
- Fetal goiter is the most sensitive US sign of fetal thyroid dysfunction.
- Fetal thyroid gland affected by translacental passage of maternal TSAb can demonstrate the same characteristic US features of Graves’ disease as in adults: enlargement, hypochoegenicity and hypervascularisation.
even after a long period of hypothyroidism, L-T4 replacement improved the growth rate, leading to a partial recovery of the GH-IGF-I axis [5]. In GH-deficient children from the beginning of rhGH therapy - in euthyroid status - has not been recommended the obligatory L-T4 supplementation due a little evidence for the development of clinically significant hypothyroidism in most of previously euthyroid patients and spontaneous recovery to pre-treatment thyroid function in most patients [6]. Maintaining euthyroid status is important for the best effectiveness of rhGH therapy. The incidence of revealing hypothyroidism should be taken into account while starting rhGH therapy, as hypothyroidism may worsen the poor response to the therapy. It seems that assessment of TSH and FT4 concentration after rhGH therapy onset should be performed earlier and more often - for example every 3 months. It seems important to establish, if possible, the threshold values of pre-rhGH treatment TSH and/or FT4 levels for revealing hypothyroidism during rhGH therapy [7].

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A11
The development of guidelines for management of thyroid diseases in pregnancy – current status

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The increasing awareness of the importance of the proper maternal thyroid function for fetal development prompted the development of guidelines on thyroid diseases in pregnancy. They have been created based on trial results as well as the personal experience of experts. The main differences between guidelines published by the Endocrine Society (ES, 2007, revised in 2012), the American Thyroid Association (ATA, 2011) and the Polish Society of Endocrinology (PSE, 2011) are further discussed. It has to be mentioned that other national guidelines also exist. Physiological changes in thyroid function during gestation influence test results, making the application of general population thyroid hormones reference values for pregnant women the most controversial. Commercially available free thyroid hormones assays tend to give values lower than the actual ones, particularly during the 3rd trimester of pregnancy. The Endocrine Society stresses a need to establish the trimester-specific reference values for each laboratory, however, the American Thyroid Association defines TSH reference values of 0.1-2.5, 0.2-3.0, and 0.3-0.3 µIU/ml for the 1st, 2nd and 3rd trimester of pregnancy, respectively, if such site-specific TSH reference is not available. The results of a multi-centre study on thyroid hormone reference values for Polish pregnant women are in press.

In pregnancy, there is an approximately 50% increase in daily iodine requirement. All societies recommend daily iodine intake of 250 µg during pregnancy and lactation, which should be obtained by additional supplementation with formulas containing 150 µg of iodine.

The endocrine societies are concerned with careful management of both overt and subclinical hypothyroidism in pregnant women and in women of childbearing age, especially because the number of such cases has increased significantly during the last decade. Moderate-to severe maternal hypothyreosis is associated with maternal and fetal adverse outcomes. The endocrine societies agree that a dose of L-thyroxin has to be adjusted to maintain TSH level within the trimester-specific reference range. The pregnant woman should be followed with TSH measurements every 4-6 weeks. ATA strongly recommends against therapy other than L-thyroxin preparations, including T3. After delivery L-thyroxin should be reduced to the pre-conception dose (ATA, ES, PSE) and TSH checked 4-6 weeks postponed. Consequences of mild maternal hypothyroidism, as well as the level of TSH requiring intervention, are still a matter of debate. According to current guidelines, TSH levels in hypothyroid women of childbearing age should be maintained below 2.5 µIU/ml to reduce the risk of TSH increase in early pregnancy. There is no need to monitor of the thyroid function in foetuses and newborns of hypothyrotic mothers (ATA) – in Polish newborns a congenital hypothyroidism screening with TSH is routinely performed. Some issues are still debated, i.e. the necessity to treat isolated hypothyroxinaemia during pregnancy or L-thyroxin administration in women with normal thyroid function and positive anti-thyroid antibodies. The lack of unequivocal data supporting the treatment of such cases during pregnancy is also stressed by the PSE.

The differences in management of hyperthyroidism during pregnancy mainly concern the use of anti-thyroid drugs: according to the ATA propylthiouracil (PTU) should be used during the first trimester and patients treated with methimazole (MMI) should be switched to PTU at the moment the pregnancy is confirmed; following the first trimester consideration should be given to switching to MMI. The Endocrine Society recommends the use of PTU as first line therapy in the first trimester as MMI is potentially responsible for congenital abnormalities; if PTU is not available or it is not tolerated MMI should be administered. Moreover, the ES states that decision which anti-thyroid drug is given should be also driven by the practitioners’ own experience. Monitoring of the liver function in patients treated with PTU is recommended by the ES only.

The universal screening of asymptomatic pregnant women or women in childbearing age for thyroid dysfunction remains controversial. The ES guideline does not recommend the universal screening suggesting that aggressive case finding should be rather considered. However there was no agreement between all members of the Guideline Committee - some of them recommended screening of all pregnant women for serum TSH abnormalities by the ninth week of gestation or at the time of their first visit. The ATA does not recommend the universal screening. Routine TSH screening is recommended at the 4th-8th week of gestation (first prenatal visit) and in women planning pregnancy by the PSE. Screening for thyroid autoimmunity is not recommended but may be considered if appropriate, e.g. in recurrent spontaneous abortion or miscarriage.

The frequency of nodular goitre in pregnant women is up to 20-30%, and differs between populations. The formation of new thyroid lesions during pregnancy is observed in 10-20% of women. The management of the nodular goitre in pregnancy does not differ from the general population (thyroid function assessment, a TPO in hypothyroid women, ultrasound and biopsy if needed). There are no essential differences in medullary and anaplastic thyroid cancer management in pregnant women. In case of differentiated thyroid cancer (DTC) the surgery can be performed after delivery as it is recommended by the ATA. If DTC is diagnosed before the 24th week of gestation – thyroid surgery should be considered before the end of the 2nd trimester, particularly for rapidly enlarging lesions (ES, PSE recommendation). If the patient is to be managed conservatively, the surgery should be performed within 4 weeks after delivery. The ATA recommends maintaining TSH values between 0.1-1.5 µIU/ml, and the ES – suppressed TSH and FT4 or total T4 in the upper normal range for pregnancy.

Mothers with anti-TPO positivity are at increased risk of thyroid illness after pregnancy. The discussed guidelines differ slightly in screening indications for postpartum thyroiditis. The lack of evidence for anti-thyroid drug use in
thyrotoxicosis phase is unquestionable. During hypothyreosis phase careful control is necessary and the treatment with l-thyroxin of all women planning next pregnancy is recommended.

Summing up, it should be stressed that despite a huge progress which has been made in our understanding of thyroid physiology and pathology in pregnancy there are still important areas of uncertainty and further research is needed to optimize the management of thyroid diseases in pregnancy. The new version of the joint ATA and the ES guidelines is to be released in 2016. The Polish recommendations also need to be revised.

References

A12
Antithyroid drugs
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Antithyroid drugs were introduced into medical practice in 1945. These are tioamidine derivatives that contain a sulphydryl group - preparations include methimazole (MMI) and carbimazole (CMI) or thiourea derivatives - preparation propylthiouracil (PTU). CMI is an inactive form that is converted in the body to MMI. Both MMI and PTU are available in Europe and Asia and in some countries CMI is available too. In the USA, only MMI and PTU are available. Administered orally, they reach maximum serum concentration after 1-2 hours. MMI does not bind to serum proteins and remains in the free form, while 80-90% of PTU binds to serum proteins. These drugs actively accumulate in the thyroid gland against the gradient concentration. The metabolic effect of PTU lasts 12-24 h, therefore this drug has to be administered 1-2 times per day. MMI maintains biological activity for more than 24 hours, and in this context may be administered once a day. Both preparations inhibit iodination of tyrosyl residues in thyroglobulin driven by thyroid peroxidase, thereby inhibiting the synthesis of thyroid hormones. They only block formation of new thyroid hormones but do not remove thyroid hormones which are already in the thyroid or in the blood stream. Antithyroid drugs also have an immunosuppressive effect, which is manifested by reduction of TSH receptor antibody (TRAb) serum level, induction of intrathyroidal lymphocytes apoptosis, increasing of the number of suppressor T cells and reduction of the number of helper T cells as well. This facilitates achievement of remission of Graves’ disease. PTU may also act in the peripheral tissues by inhibiting conversion of thyroxine to triiodothyronine.

Antithyroid drugs are recommended for treatment of hyperthyroidism caused by overproduction of hormones in children, adults and pregnant women. Antithyroid treatment should be used as a long-term essential treatment for Graves’ disease and as a short-term treatment to prepare the patients with Graves’ disease or toxic nodular goiter for thyroid surgery or radioiodine. In adults, the treatment of Graves’ disease usually lasts 12-18 months but it also is possible to order longer administration of low doses of antithyroid drugs. The initial dose of the antithyroid drugs depends on the severity of hyperthyroidism, the size of the thyroid gland and the supply of iodine. Starting dose of MMI is usually 15-30 mg administered in a single dose, or equivalent by 150-300mg PTU in three divided doses. After 4-12 weeks euthyroidism is usually achieved and antithyroid drug dose can be reduced to 5-10mg MMI or 100-200mg PTU. Further treatment with low doses is continued for 1.5 years or longer. Long lasting remission is achieved in approximately 30% of patients. Relapse of hyperthyroidism occurs usually in the first 6 months after cessation of treatment. Then the recurrence rate decreases, and reaches 50-60% of patients after 1-2 years following cessation of treatment. A particular high risk of relapse concerns patients who remain TRAb positive at the end of therapy.

The purpose of preparation for radioiodine therapy or thyroid surgery is to bring to the euthyroid state, confirmed by normal free triiodothyronine (FT3) and free thyroxine (FT4) serum levels, which usually takes a few weeks or months.

The initial dose of antithyroid drugs in children depends on the body weight and do not exceed 0.5-1 mg/kg MMI or 5-10 mg/kg/kg PTU. Antithyroid treatment in children should be continued for many years, at least for 24 months. Antithyroid drug therapy is associated with the risk of side effects. Minor side effects involving 15% patients are itching, rash, urticaria, joint pain, swelling, abnormal sense of taste or smell, nausea, or vomiting. These symptoms are not life-threatening and do not require discontinuation of antithyroid drug. Switching to another drug, dose reduction or antihistamine addition may be helpful. Major side effects are potentially life-threatening or even lethal and occur in less than 1% of patients. These include agranulocytosis, which can occur during therapy with MMI in 0.35% of patients, and with PTU in 0.3-7%. Occasionally, aplastic anemia and vasculitis or hepatitis develop after PTU, particularly in children. For this reason the MMI is the first choice drug for treating hyperthyroidism. In cases of serious side effects antithyroid drugs must be immediately discontinued and such patient should be hospitalized. Case report side effects are pancreatitis and hypoglycemia after MMI. This latter condition is connected with the appearance of anti-insulin antibodies.

Both drugs may have teratogenic effects. During the first trimester of pregnancy PTU is preferred because of lower risk of fetus defects. Congenital malformations associated with the use of MMI during pregnancy are called methimazole embryopathy, which include aplasia cutis congrena, choanal atresia and intestinal anomalies. Antithyroid drugs are secreted in breast milk in low concentrations and therefore the therapy is not contraindicated in breastfeeding women.

Antithyroid drugs are used to treat the thyroid storm. In such cases high doses of MMI reaching 120 mg/d or PTU reaching 1200 mg/d are recommended.

References

A13
Contemporary application of classical techniques in thyroid scanning
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Thyroid Research 2015, 8(Suppl 1):A13
The thyroid consists of two lobes that are connected by an isthmus. It is located anterior to the trachea between the cricoid cartilage and the suprasternal notch. It produces two related hormones, thyroxine (T4) and triiodothyronine (T3). Benign nodules and thyroid cancer are relatively common and amenable to detection by physical examination. Nuclear medicine is a part of medicine that uses radioisotopes for the diagnosis and treatment of diseases. Technetium-99m-pertechnetate is widely used for imaging the thyroid gland. 99mTc is trapped by thyroid, but unlike iodine, it does not undergo organification and remains in the gland for a relatively short period. Imaging is done 30 min after administration of radiotracer. 123Iodine has a short physical half-life of 13 h. Both tracers are pure gamma emitters.

Iodine is worse for imaging (except metastases in thyroid differentiated cancer) because it gives a high absorbed radiation dose related to the long physical half-life of 8 days and beta emissions. It is ideal for the treatment of thyroid disease, and used in the management of differentiated thyroid cancer. Graves’ disease, and toxic nodular goitre.

Indications for thyroid scintigraphy and RAI uptake are: differential diagnosis of thyrotoxicosis, before treatment with radioliodine 131I, measuring of goitre volume, ectopic goitre, congenital hypothyroidism. Other indications are metastases of well-differentiated thyroid cancer (e.g. papillary or follicular cancer). Very rarely, ovarian goitre is present.

The normal image of thyroid scan shows the typical butterfly shape (a shield shape according to the ancient Greeks), the position in the anterior neck area, the regular contour, without any interruption or mismatches. The distribution of the radiotracer is homogenous with intense, usually warm color in the middle of each lobe related to its thickness. The margins have a less intense color because of the decreased quantity of thyroid tissue. Physiologically the right lobe is often larger than the left one. There is imaging on the scan of the salivary glands.

Nuclear imaging of Graves’ disease is characterized by an enlarged gland and increased tracer uptake (usually more than 55%) that is distributed homogenously. Toxic multinodular goitre shows irregular distribution of tracer and a normal or factitious thyrotoxicosis are also associated with low uptake. The irregular tracer distribution is consistent with heterogeneity in cell function and growth, and the presence of micro- and macronodules. Large and discrete hyperfunctioning nodules may be associated with poor uptake in the extranodular thyroid tissue. The latter consists of suppressed normal tissue with less tracer accumulation. After 131I treatment, the areas that were cold may appear warm.

Although the use of fine needle aspiration biopsy (FNAB) has diminished the use of thyroid scans in the evaluation of solid thyroid nodules, the functional features of thyroid nodules have some prognostic significance. So-called cold nodules, which have diminished or no tracer uptake, are usually benign. However, these nodules are more likely to be malignant (5-10%) than hot nodules, which are almost always benign.

Subacute thyroiditis is associated with very low uptake because of follicular cell damage and TSH suppression. Drug-induced thyrotoxicosis or factitious thyrotoxicosis are also associated with low uptake.

Thyroid scanning is used in the follow-up of thyroid cancer. After thyropectomy and ablation using 131I, there is diminished tracer uptake in the thyroid bed, allowing the detection of metastatic thyroid cancer remnants that retain the ability to transport radiiodine. Whole body scans using 18F-FDG or 123I-MIBG [1-3] are performed after thyroid hormone withdrawal to raise the TSH concentration or after the administration of rhTSH.

Radioiodine 131I may be also used for treatment benign or malignant thyroid disorders.

A14
New methods of nuclear medicine in thyroid
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Thyroid Research 2015, 8(Suppl 1):A14

Since radioiodine was first introduced in the therapy of hyperthyroidism in the 1940s, in the 21st century, thyroid has become the arena of development of nuclear-molecular biology imaging. SPECT and PET techniques allow the visualization of small particles like peptides and their receptors. In PET with 18F-FDG we can assess metabolic activity of thyroid tumours. If there is higher metabolic activity, the tumour is more aggressive and the prognosis poorer. These novel methods let us observe the primary lesion and metastatic processes in iodine avid differentiated thyroid cancer (DTC) and medullary thyroid cancer (MTC). Potentially, each particle triggered with a radioisotope which is involved in a cell structure and/or its metabolism can be useful in molecular imaging. The first group of molecules used in radiotopicoidine molecular imaging is peptide receptors agonists and antagonists. Somatostatin receptors are overexpressed in DTC and MTC. Therefore, somatostatin analogues triggered with radioisotopes are used in imaging (99mTc-Technetium, 111Indium, Gallium) or treatment (90Ytrium, 177Lutetium) of these malignancies.

Implementation of appropriate chelator allowed the creation of radiopharmaceuticals conjugated with either SPECT or PET isotopes. It seems that the best method for visualization of MTC is PET with 18F-DOPA uptill now. Recently, new radiolabelled tracers for MTC visualizations are under investigation: cholecystokinin – 2 (CCK-2) gastrin receptor ligand radiolabelled with 111Indium and glucagon – like peptide 1 (GLP – 1) labelled with 99mTcTechnetium.

References

A15
Thyroid dysfunction during pregnancy
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Thyroid Research 2015, 8(Suppl 1):A15

Pregnancy is characterized by specific changes in thyroid physiology. First, the requirements for dietary iodine increase substantially, which is due to the increased thyroid hormone formation, the enhanced iodine metabolism, the increased loss of this nutrient, etc. According to the current recommendations, the supply of iodine during gestation, and also during lactation, should be at least 250 micrograms daily. Therefore, additional iodine supplementation is advised at the level of at least 150 micrograms daily to be administered to every pregnant and lactating woman. According to current recommendations, this additional iodine supplementation is also recommended in women who are going to be pregnant. Thyroid hyperstimulation, caused by human chorionic gonadotrophin (hCG) at the end of the first trimester, is another physiological change during pregnancy. Concerning thyroid disorders in pregnant women, thyroid dysfunctions, i.e. hypo- and hyperthyroidism, are most frequent. The diagnosis is based on abnormal values of thyroid hormones and thyrotrpin concentrations, although reference ranges differ substantially from those accepted for general population. Thus, the interpretation of obtained results are difficult. According to the current recommendations, the estimated upper limit of TSH concentration during pregnancy and pregnancy is 2.5 mU/L, however still some difficulties in the interpretation of results occur mainly in the first trimester. In turn, the lack of reference ranges for thyroid hormones is associated with severe diagnostic problems especially in the 2nd and 3rd trimesters. Thyroid antibodies should be screened before and/or during pregnancy and possibly monitored in subjects with thyroid dysfunction, especially with hyperthyroidism. Both thyroid dysfunctions are predominantly of
autoimmune etiology, with hypothyroidism occurring much more frequently. The prevalence of hypothyroidism, especially of its subclinical form during preconception and gestational state, is estimated at the level of 10-15% or possibly higher.

The etiology of hypothyroidism is usually associated, as in the general population, with Hashimoto’s thyroiditis. Replacement therapy with levothyroxine (L-thyroxine) is the treatment of choice in hypothyroidism. Hypothyroid patients on L-thyroxine replacement should be carefully monitored to keep TSH and thyroid hormone concentrations in recommended ranges before conception and during pregnancy. Patients with pre-existing hypothyroidism generally require increased L-thyroxine doses during pregnancy. In turn, hypothyroidism in pregnancy is usually associated with Graves’ disease. Medical treatment in hyperthyroid pregnant women is the management of choice, with propylthiouracil being the preferred antithyroid drug in the first trimester and thiamazole being recommended in the 2nd and 3rd trimesters. Careful control of maternal thyroid function is required during antithyroid drug treatment to avoid fetal hypothyroidism. The increased concentration of HCG in the first trimester assumes relatively frequently the form of gestational transient thyrotoxicosis. This form of thyrotoxicosis constitutes the separate entity: it usually needs no treatment, although in some patients with severe clinical symptoms the treatment with antithyroid drugs may be useful. Summing up, the diagnostic and treatment procedures in pregnant women with thyroid dysfunction are characterized by certain specificity and should be updated due to results of ongoing epidemiological studies, especially those on establishment of reference ranges of thyroid hormones.

A16
Comparing the effectiveness of stimulation using rhTSH and thyroid hormone withdrawal in the treatment of thyroid cancer
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Thyroid Research 2013, 8(Suppl 1):A16

Thyroid cancer (TC) is the most common neoplasm of the endocrine system. In 2011, the standardized incidence rate in Poland was 7.4 for women and 1.7 for men [1]. This rate is characterized by a steady increase. However, it is not accompanied by an increase in mortality [2,3]. On the contrary, a significant reduction is observed due to diagnosing cancer at earlier stages and improved treatment effectiveness [4]. Over 90% of all TC are differentiated thyroid cancers (DTC), which are characterized by favorable prognosis, i.e. 10-year survival in 90-95% of cases [5]. As a result of treatment, more than 80% of patients recover, although in 15% of cases local recurrence is observed, with distant metastases being diagnosed in 5-10% of cases. Relapse frequently occurs within the first five years, but there have been reports of recurrences or distant metastases even 40 years later; therefore, lifetime oncological follow-up is required [6].

Taking into account the very good prognosis and the need for long-term monitoring, patients should be offered the safest and most comfortable procedures. The biggest burden for patients with DTC resulting from oncological treatment and follow-up is the use of a radioiodine (131I) and periods of hypothyroidism required to evaluate TSH-stimulated thyroglobulin (Tg) - a sensitive and specific marker for DTC.

The use of 131I is associated with a dose-dependent increase in the risk of secondary neoplasms: leukemia, bone cancer, stomach and colorectal cancer, salivary gland cancer and soft tissue tumors. Compared to the general population, in patients treated with 131I an overall 2% increase in the risk of other tumors was observed. The adverse effects of 131I are also manifested as impaired function of salivary glands, and parotid glands in particular [7,8].

Periods of hypothyroidism lasting for approximately 4-6 weeks are associated with disturbances in the patients’ symptoms of hypothyroidism, deterioration of physical, intellectual and social functioning. Additional treatment is often needed due to exacerbation of comorbid conditions and inability to work [9].

The introduction of recombinant human TSH (rhTSH) was a breakthrough in the care of patients with DTC. Recombinant human TSH (rhTSH) is a protein produced by the ovarian cell lines of Chinese hamsters transfected with DNA that encodes both subunits of the protein. The bioactivity of recombinant TSH depends on the degree of saturation of the carbohydrate component with the sialic acid residues, and is as high as for endoTSH in overt hypothyroidism and significantly higher than for endoTSH in the state of hormonal balance. Recombinant TSH strongly stimulates iodine uptake as well as Tg and thyroid hormone synthesis in both thyrocytes and DTC cells. The results of studies evaluating the impact of rhTSH on 131I pharmacokinetics are of great importance, indicating a decrease in isotope radiotoxicity (reduction of exposure dose for the bone marrow by a third) by accelerating the renal clearance of iodine and reduction of the effective half-life of 131I in the whole body from 0.54 +/- 0.1 day to 0.43 +/- 0.1 day. At the same time, the effective half-life of 131I is extended in the thyroid gland residues, which is a beneficial effect that determines effectiveness of the treatment [10-12].

Registered indications relate to the use of rhTSH for ablation in patients after total thyroidectomy with no evidence of distant metastases, as well as in monitoring the course of the disease. Numerous studies [13,14] confirm the equal effectiveness of ablation for 131I at 1100 MBq and 3700 MBq regardless of the method of stimulation: rhTSH or thyroid hormone withdrawal (rH - T1-T3, N0, N1, M0; ESTIMABL - T1-T2, N0, N1, M0).

The results of multicenter studies in patients with T4 carried out by Bartenstein et al. and published in 2013 also confirmed the high efficacy of ablation using rhTSH in the higher risk group [15].

The results of a ten-year follow-up study in patients undergoing ablation using TSH, presented by Malinoro et al., demonstrated equal frequency of recurrence episodes, distant metastases and persistent disease compared with patients treated with thyroid hormone withdrawal [16].

Recombinant human TSH has not been registered for the treatment of patients with metastatic diseases; however, such attempts are being made. The first reports of a successful treatment with 131I after rhTSH stimulation in patients with distant metastases were published in 2000 by Luster [17] et colleagues, and in 2003 by Jarzab et al. [18]. Studies conducted by Tai et al. demonstrated equal 5-year survival rates in patients with DTC metastases to the lungs and bones, regardless of the method of preparation for the 131I therapy: rhTSH or thyroid hormone withdrawal [19].

An important indication for the use of rhTSH is disease monitoring. The first assessment concerning the effectiveness of ablation therapy is carried out 6-12 months after radioiodine treatment. The assessment includes rhTSH-stimulated Tg levels, anti-Tg antibodies levels, thyroid ultrasound and whole-body scintigraphy. In more than 80% of patients, serum Tg levels reach the highest values at day 5 after administration of rhTSH. Evaluation of serum Tg levels after TSH stimulation is the most effective method of disease monitoring. The sensitivity of Tg measurement during the treatment with L-T4 is definitely lower: in 20% of patients with metastases to the lymph nodes and in 5% with distant metastases it may be false negative [20].

Periodic monitoring of patients with complete remission of the disease must be carried out over a period of many years. In patients with a low risk of relapse, in the absence of anti-Tg, it is possible to omit the whole-body scintigraphy and only to evaluate the stimulated Tg and perform the ultrasound examination of the neck and chest X-ray [20].

The use of rhTSH in preparing patients for the treatment of metastatic disease is justified if the patient’s condition does not allow a break in L4T administration in fear of exacerbation of the symptoms of neoplasm or comorbidities, and if it is impossible to achieve endogenous stimulation due to hypopituitarism or hormonally active metastases.

New opportunities for the implementation of rhTSH include: improvement of the efficiency of imaging patients using FDG PET/CT after rhTSH administration, diagnosis of congenital hypothyroidism, treatment of nodular goiter with 131I, assessment of thyroid reserve in elderly patients, testing of TSH-dependent immune system genes, evaluation of differences in the metabolism of adipose tissue and secretion of adipokines [21].

Summary: • Diagnosis and treatment with 131I is equally effective regardless of the method of TSH stimulation: with rhTSH or with rhTSH withdrawal.
• Recombinant human TSH extends the effective half-life of radioiodine in the thyroid residues, which may increase the effectiveness of the treatment.
• Minimized radiotoxicity of 131I may reduce the risk of secondary malignancies.
Assistance is required in avoiding hypothyroidism and related symptoms, deterioration of quality of life and inability to work professionally.

Despite the high price of rhTSH, the total economic analysis of the cost/benefit ratio suggests that its use is favorable. 

Despite the high price of rhTSH, the total economic analysis of the cost/benefit ratio suggests that its use is favorable.


Tala H, Robbins R, Gagin JA, Larson SM, Tuttle RM. Five-year survival is similar in thyroid cancer patients with distant metastases prepared for radioactive iodine therapy with either thyroid hormone withdrawal or recombinant human TSH. J Clin Endocrinol Metab 2011, 96(7):2105-2111.

References


A18 Pendulum swings from hypo- to hyperthyroidism: thyrotoxicosis after severe hypothyroidism after neck irradiation in a patient with a history of Hodgkin’s lymphoma

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Thyroid Research 2015, 8(Suppl 1):A18

Case presentation: A 27-year old female presented with clinical and biochemical thyrotoxicosis (TSH 0.01 µU/mL; ref. range: 0.27-4.2 µU/mL); FreeT4 1.58 ng/dL (ref. range 0.98-1.63 ng/dL); FreeT3 4.56 pg/mL (ref. range 2.6-4.4 pg/mL). Clinical examination revealed tachycardia at about 100 beats/minute and no obvious goitre. Autoimmune profile was suggestive of Graves’ disease (anti-TSH-receptor antibodies (aTSHR) 16.69 IU/L (ref. 0-1.75), anti-thyroid peroxidase antibodies (aTPO) 1780 IU/L (ref. 0-34 IU/mL). The patient had a history of Hodgkin’s lymphoma, diagnosed and treated with chemo- and radiotherapy (including the neck) at the age of 18. At the age of 20 she developed severe hypothyroidism (TSH=100 µU/mL), though with high titres of both aTPO (150 IU/mL) and aTSHR (37.56 IU/mL) antibodies. Thyroid function tests normalised after treatment with L-thyroxine (100 µg od). At the age of 26 she became “anxious” and experienced “heart palpitations”. She was found to have suppressed TSH, that remained suppressed even when the dose of L-thyroxine was reduced and then discontinued. After further four months she was found to have raised free T3 (see above). Thyroid scintigraphy revealed a normal and homogenous iodine uptake (41%). The patient responded very well to treatment with low dose thiamazole (10 mg od). As subclinical thyrotoxicosis persisted after discontinuation of thiamazole, she was eventually referred for treatment with radioiodine.

Discussion: Thyroid dysfunction is one of the most common abnormalities seen after radiotherapy for Hodgkin’s disease that includes the neck [1]. Primary hypothyroidism, the most common radiation-induced thyroid dysfunction, appears in 20–30% of patients who had therapeutic radiotherapy administered to the neck region, and usually occurs within the first 5 years after therapy [peak 2-3 years after treatment] [1]. Irradiation of the thyroid may also increase the risk of Graves’ disease [relative risk 7.2-20.4%], or Graves’ ophthalmopathy, thyroiditis, benign adenomas and thyroid cancer. The aetiology of radiation-induced thyroid dysfunction includes vascular damage, parenchymal cell damage and autoimmune reactions [1]. According to some authors, thyroiditis observed in Hodgkin’s disease may be the result of immune regulation disorders in Hodgkin’s disease [2]. Our case illustrates that after neck irradiation, severe hypothyroidism can be followed by thyrotoxicosis. In both situations, aTSHR were elevated. There are two types of aTSHR: thyroid stimulating antibody (TSAb) and TSH-stimulation blocking antibody (TSBAB). TSAB blocks TSH-stimulation of the thyroid and causes hypothyroidism. TSAB stimulates the thyroid and causes Graves’ hyperthyroidism. In our opinion, change of thyreometabolic state is possible, because in this case there was a gradual switch from a TSH receptor blocking antibodies (TSBAB) into TSH receptor stimulating antibodies(TSAB). In some patients, TSAB and hyperthyroidism develop unexpectedly after hypothyroidism that is caused by TBAbs [3]. Also, in some hypothyroid patients after irradiation of the neck with Hodgkin’s disease developed hyperthyroidism [4]. This shift in thyroid function occurs rarely [3,4]. A number of mechanisms may be involved in switching from TBAbs to TSABs. Significantly, thyroxine treatment in some patients is associated with increased TSAB that in extreme cases might lead to development of hyperthyroidism in hypothyroid patients [3]. There are reports that after neck irradiation Graves’ disease may develop in patients receiving thyroxine, and 33% of the patients with Graves’ hyperthyroidism had received thyroxine before its onset [4]. Therefore thyroid hormone-replacement therapy in patients with hypothyroidism after irradiation of the neck does not eliminate risk of later thyroid abnormalities.

Acknowledgement: Verbal consent was obtained from the patient for presentation of the above case for postgraduate and student training purposes.

References


A19 Ultrasound and cytological diagnostics of thyroid - its proper application in case of coexisting disturbing clinical signs and symptoms, suggestive of active proliferative lesion

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Thyroid Research 2015, 8(Suppl 1):A19

Currently, the most important clinical issue for a practicing endocrinologist is to answer the question whether the detection of a thyroid nodule/nodules during physical examination or thyroid focal lesion/lesions in the ultrasound (US) scan provides the basis for referring the patient for surgery. The fine-needle aspiration biopsy (FNAB) performance is recommended for each case of:

1) a palpable nodule corresponding to focal lesion with diameter of 5 mm or more, revealed during US examination,
2) an impalpable lesion with a diameter of 10 mm and more,
3) a lesion with suspicious US features, suggesting the malignancy (see: Table 1).

At the present stage, US examination still cannot be conducted with such precision so that it alone will be able to document the occurrence of malignancy and constitute a definitive diagnosis of thyroid cancer. Simultaneous visualization of even a few suspicious US features, as well as demonstration of enlarged cervical lymph nodes, together with observations of changes with time of thyroid lesions and of lymph nodes, can only bring us closer to a final diagnosis. The most suspicious feature is the shape of a nodule/US focal lesion. Accordingly, “standing egg” or “taller-than-wide” shape - on transverse or longitudinal planes - can much more likely be related to the presence of
malignancy [4]. This feature is estimated to be present in approximately 90% malignant cases [5]. This is due to the fact that malignant lesions grow across the normal tissue plane in a centrifugal manner [6]. We have grouped the individual US features into mnemonics, to facilitate their permanent memorising. Mnemonics are made up of the first letters of the names of these characteristics. Our experience allows us to propose a system that is based on assigning the points to each US feature. The principle of assessment is to add points, which will allow classification of the lesions to particular groups of a different risk of malignancy (Table 2).

Two signs/symptoms presented in the bottom of Table 2 are of crucial importance is information on inherited diseases, with particular stress on dystrophic), in contrast to the absence of calcifications (the latter suggesting benign nature of lesions);

The occurrence of almost all of these symptoms by itself requires the execution of all possible diagnostic tests, followed by treatment implementation. In any case, a reassuring outcome of US and FNAB examination should not cause failure to the appropriate diagnostics and treatment.

Table 1(abstract A19) Definitions of suspicious US features (the, so-called, US patterns), in contrast to US patterns speaking for a benign nature of lesion [1]

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcifications</td>
<td>- assessed especially as the presence of microcalcifications, also their coexistence with other forms of calcifications (e.g. dystrophic), in contrast to the absence of calcifications (the latter suggesting benign nature of lesions);</td>
</tr>
<tr>
<td>Orientation</td>
<td>- “taller-than-wide” shape on transverse and longitudinal planes, in contrast to all other shapes;</td>
</tr>
<tr>
<td>Doppler</td>
<td>- the presence of increased irregular chaotic central blood flows; this group includes also hypoechoic lesions when accompanied by a total absence of blood flow; in contrast to the peripheral, subcapsular blood flow (suggesting benign lesions);</td>
</tr>
<tr>
<td>Echogenicity</td>
<td>- hypoechogenicity, defined as “darker” than normal thyroid echogenicity, and described as similar to the echogenicity of muscles surrounding the gland, especially sternocleidomastoid muscles;</td>
</tr>
<tr>
<td>Halo</td>
<td>- uneven thickness of halo (outer shell that surrounds the lesion) or absence of halo, in contrast to thin halo, regularly surrounding the lesion;</td>
</tr>
<tr>
<td>Echostucture (composition)</td>
<td>- solid lesions, also mixed lesions with cystic portion not exceeding 10% of the volume, in contrast to mixed lesions with cystic parts greater than 10% of total volume, as well as to lesions with solely cystic composition;</td>
</tr>
<tr>
<td>Largeness (size)</td>
<td>- the size of lesion greater than 3 cm in diameter, in contrast to smaller lesions;</td>
</tr>
<tr>
<td>Margin</td>
<td>- poorly defined and irregular, sometimes infiltrated border, in contrast to a well-differentiated regular margin;</td>
</tr>
<tr>
<td>Augmentation</td>
<td>- the enlargement of lesion by at least 20% in two dimensions, i.e. at least 50% by volume (for the lesion in diameter of less than 10 mm - minimum 2 mm in two dimensions) in a period of time shorter than 1.5 years [2,3];</td>
</tr>
<tr>
<td>Lymph node invasion</td>
<td>- the presence of lymph nodes, suspicious in US evaluation and of the size larger than 5-8 mm in the smallest dimension [3];</td>
</tr>
</tbody>
</table>

Table 2(abstract A19) The scoring system of US features (patterns) assessed in thyroid nodules/focal lesions. Low risk US pattern - 0 < 3 points; intermediate risk US pattern - ³ 3 < 7 points; high risk US pattern - ³ 7 points (note scoring system modification when compared with ref. [1])

<table>
<thead>
<tr>
<th>CODE (each feature – 1 point)</th>
<th>HELM (each feature – 0.5 point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Califications Max. no. of points – 4</td>
<td>H Halo Max. no. of points – 2</td>
</tr>
<tr>
<td>O Orientation</td>
<td>E Echogenicity</td>
</tr>
<tr>
<td>D Doppler</td>
<td>L Largeness</td>
</tr>
<tr>
<td>E Echogenicity</td>
<td>M Margin</td>
</tr>
</tbody>
</table>

Table 3(abstract A19) Disturbing signs and symptoms that require invasive intense diagnostics, regardless of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) category and US pattern [1]

<table>
<thead>
<tr>
<th>HARM</th>
<th>HASH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heredity</td>
<td>Hoarseness</td>
</tr>
<tr>
<td>Age</td>
<td>Ache</td>
</tr>
<tr>
<td>Radiation</td>
<td>Swallow</td>
</tr>
<tr>
<td>Male</td>
<td>Hardness</td>
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</tbody>
</table>

According to our opinion, introduction of the scoring system for the disturbing symptoms and signs is useless because their assessment can be simply achieved by applying common sense. In other words, the occurrence of almost all of these symptoms by itself requires the execution of all possible diagnostic tests, followed by treatment implementation. In any case, a reassuring outcome of US and FNAB examination should not cause failure to the appropriate diagnostics and treatment.

Most authors assume that FNAB of the thyroid is a basic procedure for qualifying the patient for surgery or clinical observation. Generally accepted classification of FNAB diagnostic categories is shown in Table 4 [7]. However, one must be aware of aspiration cytology limitations, resulting from the specificity of FNAB technique itself. This entails the risk of false negative results of a few percent, and less - false positives results. Even a diagnosis of "benign lesion" (category II acc. TBSRTC), assuming a proper sample collection from the tested lesion, is still associated with a risk of cancer but less than 3% [7]. Nevertheless, the authors of recent study suggest that repeated FNAB in the category in question can be performed only after 2 to 4 years, if the first FNAB indicated benign character of the lesion; the above recommendation applies to lesions in asymptomatic patients with no risk factors [8].
FNAB limitations result also from the nature of an assessed lesion itself, especially in situations when the final diagnosis can be formulated only on the basis of histopathological examination - e.g. follicular thyroid carcinoma (FTC). Diagnoses of “follicular lesion of undetermined significance (FLUS)/atypia of undetermined significance (AUS)” (category III TBSRTC) \[6\] or of “follicular-neoplasm/suspicious for follicular neoplasm” (category IV) relate - in most cases - to hyperplastic nodules or follicular adenoma rather than to FTC. In practice, it means that follicular adenoma and FTC cannot be distinguished on the basis of cytological examination. According to TBSRTC recommendations \[7\], category III should only be used in exceptional situations when it is not possible to establish a more precise cytological diagnosis since cytological findings are not convincingly benign to be classified as category II, yet the degree of cellular or architectural changes is not sufficient for an interpretation of category IV and - even more - of category V (“suspicious for malignancy”). Moreover, the authors of recent study suggest that the patients with cytological diagnosis - AUS (within category III TBSRTC) should be qualified to surgery much more often than the patients with FLUS (also category III), because of significantly higher risk of malignancy \[9\]. Not every FNAB result may precisely identify what type of treatment should be applied; all non-diagnostic or unsatisfactory smears are assigned to category I. Such a result is an indication for repeat biopsy, usually within 3-6 months, sometimes sooner, because the risk of malignancy is not quite small and it is rated for a few percent. The most important objective of our presentation is to propose an algorithm of diagnostic and therapeutic management in thyroid nodules/US focal lesions which is based on the information from both US image and FNAB cytology. In Figure 1 we have presented the modified version of our earlier algorithms \[1,4\]; for modification we have taken into account the recent reports of other authors \[8,9\].

**References**

1. Lewiński A, Adamczewski Z: Decision making for surgery in the suspect thyroid nodule. (Proper application of ultrasound (US) and fine needle aspiration biopsy (FNAB)). Thyroid Research 2015, 8 (Suppl 1) 1-15.

**Table 4** (abstract A19) The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) – according to Cibas and Ali \[7\]

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Risk of malignancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Nondiagnostic or unsatisfactory</td>
</tr>
<tr>
<td>II</td>
<td>Benign</td>
</tr>
<tr>
<td>III</td>
<td>Atypia of undetermined significance or follicular lesion of undetermined significance</td>
</tr>
<tr>
<td>IV</td>
<td>Follicular neoplasm or suspicious for follicular neoplasm</td>
</tr>
<tr>
<td>V</td>
<td>Suspicious for malignancy</td>
</tr>
<tr>
<td>VI</td>
<td>Malignant</td>
</tr>
</tbody>
</table>

---

**Figure 1 (abstract A19)**

- Patient with thyroid problems
  - Qualification to US thyroid examination
  - Ultrasound (US) pattern (CODE + HELM + AL)
  - Indications for FNAB
    - Low risk US pattern 0 < 3 points
    - Intermediate risk US pattern ≥ 3 < 7 points
    - High risk US pattern ≥ 7 points
  - Any lesion, any US pattern
  - FNAB TBSRTC category
    - I, II, III, IV
  - Management
    - Observation
    - Observation and FNAB examination after 3-6 months
    - Observation and FNAB examination after 18-24 months
    - Observation or consider surgery
    - Repeat FNAB examination after 3 months (sometimes sooner) or consider surgery
    - Observation and FNAB examination every 12 months
    - Recommend surgery
  - Presence of other essential disturbing clinical signs and symptoms
    - H - Heredity
    - A - Age
    - R - Radiation
    - M - Male
    - S - Swallow
    - H - Hardness
  - Inquisitive intense diagnostics of any type, appropriate treatment, in most cases - the radical

**References**

1. Lewiński A, Adamczewski Z. Decision making for surgery in the suspect thyroid nodule. (Proper application of ultrasound (US) and fine needle aspiration biopsy (FNAB)). Thyroid Research 2015, 8 (Suppl 1) 1-15.
aspiration biopsy (FNAB) completed but do not replace coexisting worrying clinical signs and symptoms. *Thyroid Intern* 2013, 1:3-18.


4. Adamczewski Z, Lewiński A. Proposed algorithm for management of patients with thyroid nodules/focal lesions, based on ultrasound (US) and fine-needle aspiration biopsy (FNAB); our own experience. *Thyroid Res* 2013, 6:6.


A20 Acromegaly and the thyroid gland

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*Thyroid Research* 2015, 6(Suppl 1):A20

Acromegaly is a chronic disease caused by hyperecretion of growth hormone (GH), most frequently from a pituitary somatotropic adenoma. Its prevalence was estimated at 60–70 cases per million people, but in recent years it seems to be higher (even 86 cases per million). Approximately 3-4 new cases of acromegaly are annually diagnosed per million people. In acromegalic patients, the mortality rate is 2-4 times higher than in the general population. The most common causes of death in patients in question are cardiovascular and/or respiratory complications, or neoplastic diseases.

Data indicating the increased risk of the development of benign and malignant tumors of various organs, particularly of the colon, thyroid gland, breast, and prostate, are reported in numerous studies. An elevated level of IGF-I seems to be responsible for the increased risk of cancers. It is to be recalled that IGF-I is a mitogenic, anti-apoptotic and angiogenesis-promoting factor. Prevalence of cancers in acromegal patients remains controversial: some authors describe the increased prevalence, in contrast, others do not. The difference among studies may be due to a lower incidence of acromegaly per se, retrospective nature of studies or to differences in study designs. In most studies, patients with cancers diagnosed prior to acromegaly were excluded [1].

The presence of IGF-I receptors was shown in both normal and neoplastic thyroid tissue in humans, a long time ago. There are numerous scientific evidence that IGF-I reveals an important, TSH-independent effect in growth processes in humans thyroid [2,3]. Moreover, there are a lot of studies describing the increased prevalence of goitre (both diffuse and nodular) in acromegalic patients, and many authors have demonstrated a positive correlation between the thyroid volume and serum IGF-I concentration. Large meta-analysis published recently by Wolinski et al. [4] has confirmed that both thyroid nodular disease and thyroid carcinoma are significantly more frequent in acromegalic patients than in general population (Table 1). Accordingly, these results demonstrate that the repeated thyroid ultrason (US) examination and careful evaluation of possible lesions (together with cytological assessment) should be important part of follow-up in patients with acromegaly. Wolinski et al. [4] documented that in newer studies on acromegalic subjects, thyroid disorders were reported more frequently - in studies published after year 2008, thyroid nodular disease occurred in about 65% of patients whereas in older studies approx. in 54%. Similar phenomenon could be recorded for case of thyroid carcinomas – 6% patients in newer reports published after 2008 vs. 3% in older studies, published before 2008. These results speak for the hypothesis that the improvement in diagnostic methods and therapy of acromegaly extends the survival time of patients, what - in turn - increases the prevalence of benign and malignant neoplasms possible to detect.

Result of selected studies on acromegaly and thyroid disorders, published in recent years, are presented in Tables 2 and 3.

References


<table>
<thead>
<tr>
<th>Table 1 (abstract A20) Studies with control group included in meta-analysis – the table taken from the study by Wolinski et al. [4], modified. Asterisk (*) - persons with non-functioning or PRL secreting adenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies with control group</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>dos Santos et al, <em>Pituitary</em> 2013;16:109-114</td>
</tr>
<tr>
<td>Herrmann et al, <em>Clin Endocrinol Diabet.</em> 2003;112:225-230; retrospective</td>
</tr>
<tr>
<td>Gaspen et al, <em>J Endocrinol Invest.</em> 2002;25:240-245</td>
</tr>
<tr>
<td>Popovic et al <em>Clin Endocrinol (Oxf)</em> 1998;49:441-445; retrospective</td>
</tr>
<tr>
<td>Barlay et al, <em>Arch Intern Med.</em> 1991;151:1629-1632; retrospective</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
**Table 2 (abstract A20)** Results of the retrospective study by Turkish authors [1], including 64 acromegalic patients who were subjected to thyroid US examination and thyroid function tests (distribution of thyroid diagnoses)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multinodular goitre</td>
<td>31</td>
<td>48.4%</td>
</tr>
<tr>
<td>Simple nodule</td>
<td>6</td>
<td>9.4%</td>
</tr>
<tr>
<td>Toxic multinodular goitre</td>
<td>1</td>
<td>1.6%</td>
</tr>
<tr>
<td>Hurthle cell adenoma</td>
<td>1</td>
<td>1.6%</td>
</tr>
<tr>
<td>Diffuse goitre</td>
<td>9</td>
<td>14.1%</td>
</tr>
<tr>
<td>Thyroid carcinoma</td>
<td>5</td>
<td>7.8%</td>
</tr>
<tr>
<td>No thyroid disease</td>
<td>11</td>
<td>17.1%</td>
</tr>
</tbody>
</table>

**Table 3 (abstract A20)** Results of the retrospective study by Brasil, including 106 acromegalic patients, who were subjected to thyroid US examination and thyroid function tests (distribution of thyroid diagnoses)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multinodular goitre</td>
<td>34</td>
<td>32.5%</td>
</tr>
<tr>
<td>Simple nodule</td>
<td>8</td>
<td>7.5%</td>
</tr>
<tr>
<td>Unspecified abnormalities</td>
<td>22</td>
<td>20.6%</td>
</tr>
<tr>
<td>Diffuse goitre</td>
<td>11</td>
<td>10.4%</td>
</tr>
<tr>
<td>Normal US</td>
<td>31</td>
<td>29.9%</td>
</tr>
</tbody>
</table>


**A21 Selected genetic aspects in the pathogenesis of the thyroid diseases**

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According to genetic ethiopathogenesis, thyroid diseases may be divided into monogenic and polygenic (multifactorial) thyroid diseases.

**Monogenic thyroid diseases are the following:**

1. Congenital defects of thyroid hormones biosynthesis as a result of dysmorphogenetic (majority goitrous) primary congenital hypothyroidism;
2. Genetic familial defects of thyroid underdevelopment, including thyroid agenesis, thyroid hypoplasia and ectopia;
3. Genetic protein-binding defects, including thyroxine-binding globulin (TBG) defects, albumin and prealbumin defects;
4. Congenital resistance to thyroid hormone syndrome;
5. Genetic non-autoimmune hypothyroidism;
6. Medullary thyroid carcinoma (MTC) (familial type of the MTC, and multiple endocrine neoplasia MEN 2 A and B), caused by RET gene mutations and inherited as the autosomal dominant mode.

About 10-15% of all cases of primary congenital hypothyroidism (CH) are associated with either a goitre or a normal thyroid gland. This type of CH has been linked to a number of defects in thyroid hormonogenesis and is caused by mutations in the following thyroid-specific genes: *HNIS*, *Tg*, *TPO*, *PDS*, *THOX2*, *DEHAL*. It is inherited by the autosomal recessive mode. Only about 2% of primary congenital hypothyroidism cases (CH) due to the defects of the thyroid underdevelopment are familial with genetic background. This type of CH is associated with mutations in genes responsible for the growth or development of thyroid follicle cells such as *TSHR*, *TTF1*, *TTF2*, *PAX 8*, *NKK2*, or *HOXA3*. Except for defect caused by a mutation of the *TSHR* gene, such inborn thyroid dysgenesis is associated with an increased incidence of birth defects (such as: respiratory distress, ataxia, muscle hypotony, choreoathetosis, cleft palate, bilateral choanal atresia, hypoplastic epiglottis, spiky hair).

In addition, mutations in the *GNAS* 1 gene may give congenital hypothyroidism associated with hypogonadisms and Albright’s osteodystrophy, which is the part of pseudohypoparathyroidism type IA and II (pseudopseudohypoparathyroidism).

The next group of monogenetic thyroid diseases with less or more evident thyroid function disorder: the following:

1. TBG partial or complete deficiency and TBG excess due to TBG gene defects with X-linked inheritance pattern;
2. Generalized, peripheral and pituitary resistance to thyroid hormones mainly caused by TRbeta gene mutations, inherited by the autosomal recessive.

The second group of thyroid diseases are the multifactorial (polygenic) ones. Among them the most frequent are:

1. Graves’ hyperthyroidism;
2. Autoimmune thyroiditis;
3. Thyroid carcinoma derived from thyroid follicle cells such as papillary and follicular thyroid carcinoma.

Although autoimmune thyroid diseases (AITD), including autoimmune thyroiditis and Graves’ hyperthyroidism with thyroid ophthalmopathy (TAO), are still unclear, they are defined as polygenic diseases resulting from genetic and environmental factors. The environmental factors which play a role in the development of AITD include iodine excess (with amiodarone treatment), selenium deficiency, stress, interferon alpha, bacterial and viral infections and, in the case of Graves’ hyperthyroidism, and tobacco smoking.

There are some genes whose polymorphisms have been confirmed in the development of and susceptibility to AITD. These are the following: 1. thyroid-specific genes such as the *Tg* gene and 2. genes modulating the immune system, such as HLA antigens, *CTLA4*, *PTPN22*, genes encoding proinflammatory cytokines, such as: IL10, TGF beta, IL 6, IL 4, IL1 beta, IL10, and others.

On the other hand, among the many genes involved in the development of differentiated thyroid carcinoma derived from thyroid follicle thyroid cells (papillary and follicular one), *BRAF* and *RET-PTC* seem to be the most important.

**A22 Personal experiences in ultrasonography and sonoelastography of thyroid gland**

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Thyroid Research 2015, 8(Suppl 1):A22

In recent decades, thyroid ultrasonography has become one of the most important procedures performed in daily endocrinological practice. This convenient, fast, non-invasive and cheap procedure benefits in many aspects on determination of thyroid morphology.
The advantages of thyroid US include measurement of thyroid volume, evaluation of its echogenicity with visualization of parenchyma vascularisation. Also, thyroid ultrasonography is necessary for selection of so-called suspicious features of potential malignancy among thyroid lesions. According to numerous studies, combination of some specific sonographic features indicate higher risk of malignancy, and indicate necessity for fine needle aspiration biopsy (FNAB).

Sonographic features of the lesion, that rise the suspicion of malignancy include: decreased echogenicity; irregular, diffused boarders; microcalcifications; local limphadenopathy; taller than wider orientation in parenchyma; increased vascular pattern in the center; documented, rapid growth of the lesion [1-3]. However, according to a recent meta-analysis by Brito et al., evaluating predictive values of different combination of those features, ultrasonography does not benefit in satisfactory values of sensitivity and specificity (table 1) [4]. Similar results were obtained in recent meta-analysis performed in our center, in which newer publications had been evaluated and slightly different criteria for inclusion in the study had been used [5]. Only prospective studies were included. We have excluded studies focusing only on particular subgroups of patients and nodules – e.g. surgical or pediatric patients only, follicular lesions or lesions with previous non-diagnostic result of FNAB only etc. Finally, we analyzed the data of 5439 thyroid lesions. Just like in the paper of Brito, we have revealed the usefulness of some sonographic features in selecting potential malignant lesions. Studies revealed significant value of "taller than wider feature" with positive predictive value of 76%. Different, independent features of higher risk of malignancy included hypoechogenicity, and the presence of microcalcifications. According to both metaanlyses, the value of Doppler analysis of the nodule vascularisation in prediction of thyroid malignancy, seems doubtful. (table 2, graph 1). We have also performed another meta-analysis dedicated specifically to sonographic features medullary thyroid cancers (MTCs); according to the pool results, MTCs presents similar sonographic appearance than other thyroid cancers (TCs); however, most markers of malignancy were less common for MTCs than papillary TCs (PTCs). Some features turned out to be important factors decreasing risk of MTC – e.g. none of the 157 included MTCs were hypoechogenic [6].


However, as the values sensitivity, specificity, PPV and NPV of thyroid ultrasonography as an independent procedure, are unsatisfactory, this procedure is not recommended for determination of thyroid malignancies and fine needle aspiration biopsy remains the "gold standard". This invasive procedure, despite nowadays being the most accurate, it also has some disadvantages. Firstly, it's invasive. Secondly, the whole diagnostic process, which includes ultrasonography, obtaining the material with the needle, fixation of the specimen and eventual cytological assessment by the pathologist is time consuming and quite expensive. Finally, there is a significant amount of indeterminate or inconclusive results (follicular lesions and smears inconclusive for adequate evaluation) [7]. Thus, exploration for new methods seems desirable.

Recently sonoelastography has been introduced in endocrinology practice, as an additional tool for ultrasonographic evaluation. This modern, non-invasive method, uses the acoustic radiation force in the assessment of the elasticity of examined tissue. Its value has been previously proven in the diagnosis of non-thyroidal oncologic conditions, such as breast cancer [8]. The first paper, describing its potential in thyroidology was published by Lyshchik et al. [9]. The researchers performed the procedures with the use of static, free-hand elastography, which demanded specific kind of compression, thus the results depended on the experience of the sonographer. Also, static elastography was time-consuming and did not provide adequate measurements of cystic and calcified lesions. As it did not let for quantitative measurement of the force needed for effective compression of the nodule, it was very subjective. Also, first generation of elastography was not reliable in selection of potential malignancies in multinodular goiter.

In 2010 Sebag et al., estimated the accuracy of shear wave elastography in non-invasive diagnosis of thyroid malignancies [10]. New method provided simultaneous quantitative and qualitative real time measurements without the need for manual compression of the tissue. Thusly, it was operator independent and highly repeatable. Sebag et al revealed very promising results, indicating high accuracy of SHE in the determination of thyroid malignancies. Recent years brought another information about potential use of SHE in monitoring the therapy of the subjects with acute, and subacute thyroiditis [11,12].

The potential of SHE in the diagnosis of thyroid malignancies had also been studied in detail in our center. The paper by Szczepanek-Paulewska et al. included 122 patients with multinodular goiter (393 lesions) referred to our clinic prior total thyroidectomy [13]. Before the surgery each lesion was described in details, including the presence of suspected sonographic features and its elasticity. After the surgery, obtained specimens of each lesion was analyzed by an experienced pathologist. Basing on histopathological description, the study group included 18 papillary, two follicular, 1 medullary and 1 anaplastic thyroid carcinoma.

For the malignant lesions, the cut-off value of >50kPa was revealed as the most sensitive (OR 40.8, sensitivity 95%, specificity 70%). (table) Also SHE was found to be highly effective in the diagnosis of malignant lesions, with the use of quantitative color scale. Other sonographic markers of malignancy appeared to be significantly less accurate. (table 3).

Table 1(abstract A22) The main characteristics of studies included in the meta analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>Mean age</th>
<th>Nodules</th>
<th>Malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azizi et al.</td>
<td>2012</td>
<td>706</td>
<td>women – 48.5, men – 47.7</td>
<td>912</td>
<td>86</td>
</tr>
<tr>
<td>Bougna et al.</td>
<td>2012</td>
<td>99 women, 39 men</td>
<td>520</td>
<td>158</td>
<td>21</td>
</tr>
<tr>
<td>Rossi et al.</td>
<td>2012</td>
<td>1439 women, 417 men</td>
<td>52</td>
<td>2421</td>
<td>233</td>
</tr>
<tr>
<td>Trimboli et al.</td>
<td>2012</td>
<td>438 women, 138 men</td>
<td>530</td>
<td>498</td>
<td>126</td>
</tr>
<tr>
<td>Bhatia et al.</td>
<td>2011</td>
<td>89 patients*</td>
<td>not given</td>
<td>89</td>
<td>19</td>
</tr>
<tr>
<td>Merino et al.</td>
<td>2011</td>
<td>89 women, 14 men</td>
<td>58</td>
<td>106</td>
<td>10</td>
</tr>
<tr>
<td>Ünlütürk et al.</td>
<td>2011</td>
<td>157 women, 37 men</td>
<td>women – 43.7, men – 47.5</td>
<td>237</td>
<td>58</td>
</tr>
<tr>
<td>D'Souza et al.</td>
<td>2010</td>
<td>151 women, 49 men</td>
<td>not given</td>
<td>200</td>
<td>26</td>
</tr>
<tr>
<td>Friedrich-Rust et al.</td>
<td>2010</td>
<td>37 women, 13 men</td>
<td>women – 54, men 52</td>
<td>53</td>
<td>7</td>
</tr>
<tr>
<td>Gietka – Czernek et al.</td>
<td>2010</td>
<td>42 women, 10 men</td>
<td>45</td>
<td>71</td>
<td>22</td>
</tr>
<tr>
<td>Yunus et al.</td>
<td>2010</td>
<td>58 women, 8 men</td>
<td>not given (range 18 – 75)</td>
<td>78</td>
<td>25</td>
</tr>
<tr>
<td>Asteria et al.</td>
<td>2008</td>
<td>54 women, 12 men</td>
<td>women – 51.3, men – 60.5</td>
<td>86</td>
<td>17</td>
</tr>
<tr>
<td>Brunelle et al.</td>
<td>2008</td>
<td>264 women, 79 men</td>
<td>41.2</td>
<td>479</td>
<td>66</td>
</tr>
<tr>
<td>Rubaltelli et al.</td>
<td>2008</td>
<td>25 women, 15 men</td>
<td>55</td>
<td>51</td>
<td>11</td>
</tr>
</tbody>
</table>
Another problem in endocrine practice is the issue of the selection of nodules for FNAB in case of multinodular goiter where the amount of lesions can be high and it is not possible to puncture all nodules. Study performed in our department showed that SWE is also valuable tool in the selection of lesions for FNAB [14]. All analyzed cancers turned out to be the least elastic lesions in particular goiters; even ones which were not very stiff in absolute values were stiffer than other lesions present in the same goiter.

Despite many benefits and high diagnostic value in differentiation of benign and malignant thyroid lesions SWE is not free of limitations. Some features were described as interfering results of sonolastographic examination and potentially leading to overestimation of the cancer risk. According to the study performed by Bhatia et al. [15] partially cystic lesions were less elastic than solid ones; stiffness was also positively correlated with the diameter of the nodule. Study performed in our department brought the first, systematic analysis of biochemical and ultrasonographic parameters influencing elasticity of thyroid nodules [16]. According to our results, numerous parameters can increase stiffness of the lesion. Most important among them were micro- and especially macrocalcifications, cystic components, isthmal location; stiffness was also correlated with the maximal diameter of the lesion.

In conclusion, conventional sonographic markers of malignancy seem to be valuable for the preliminary assessment of thyroid nodules; however, these features do not benefit in satisfactory values of sensitivity and specificity. Elastography and particularly SWE seems to be important advance of conventional ultrasonography allowing for the more reliable distinction between benign and malignant thyroid nodules as well as better selection of lesions for FNAB in case of multinodular goiter. However, SWE can be not credible in case of some lesions (e.g. partially cystic, with calcifications, etc.). Also data about usefulness of SWE in case of some particular types of thyroid cancer – such as follicular and medullary TCs are very limited. Altogether, there is still a need for further techniques allowing for more reliable distinction between benign and malignant thyroid nodules as well as further studies on the available techniques.

References


<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>median</th>
<th>P</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q-box max [kPa]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>174.2</td>
<td>90.4</td>
<td>191.3</td>
<td>&lt;0.0001</td>
<td>14.1-299.9</td>
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<tr>
<td>Benign</td>
<td>55.6</td>
<td>59.3</td>
<td>35.1</td>
<td>1.3-298.1</td>
<td></td>
</tr>
<tr>
<td>Q-box mean [kPa]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>139.3</td>
<td>83.1</td>
<td>142.6</td>
<td>&lt;0.0001</td>
<td>7.8-294.0</td>
</tr>
<tr>
<td>Benign</td>
<td>35.1</td>
<td>30.6</td>
<td>25.3</td>
<td>1.2-180.9</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1(abstract A22) Pooled odds ratios with 95% confidence intervals for analysed sonographic markers of malignancy. On the basis of: Wolitski K, Szkudlarek M, Szczepanek-Parulska E, Ruchała M. Usefulness of different ultrasound features of malignancy in predicting the type of thyroid lesions: a meta-analysis of prospective studies. Pol Arch Med Wewn. 2014; 124: 97-104


A23 The effect of Selenium on thyroid physiology and pathology
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Selenium (Se) is an important trace element for human physiology. It has anti-inflammatory, anti-neoplastic and anti-aging properties and protects from oxidative stress [1]. It is present in muscles, liver and kidneys, but reaches its highest concentration in the thyroid gland [2]. Selenium is incorporated in the molecular structure of a class of proteins called selenoproteins and the following well-characterized selenoproteins are found in the thyroid gland: glutathione peroxidases and thioredoxin reductases, protecting thyroid against free radicals, and deiodinases type I and II, participating in the synthesis of thyroid hormones [2]. Selenium status appears to have an impact on the development of several thyroid pathologies; autoimmune thyroid diseases, including Hashimoto disease and Graves-Basedow disease, thyroid orbitopathy, goiter, nodules and thyroid cancer.

Low concentrations of Se were shown in patients with Graves’ disease [3]. Higher serum Se levels were seen in patients who went into remission and remained euthyroid during a 2-year follow-up period when compared with patients who did not receive permanent euthyreosis [4]. Results of these studies encourage the implementation of supplemental Se in the treatment of hyperthyroidism together with antithyroid drugs as well as to continue further research into new selenium-rich thyrostatics. The clinical study GRASS comparing the effectiveness of thyrototoxicosis treatment with thyrostatics alone and that accompanied by Se is just being carried out [5]. There are some data about the role of Se in the treatment of thyroid orbitopathy. Serum Se levels are lower in patients with orbitopathy when compared with Graves’ disease patients without orbitopathy [6]. Selenium supplementation has proven to prevent deterioration of mild Graves’ ophthalmomopathy [7]. In the single study Se was shown to be effective in the prevention of the post-partum surge of TPO-Ab and thyroid dysfunction [8], however the data about Se effect in Hashimoto disease are conflicting; according to the Summary of a Cochrane Systematic Review the evidence to support or refute the efficacy of Se supplementation in people with Hashimoto’s thyroiditis is incomplete and not reliable to help in clinical decision making [9]. The influence of Se on goitrogenesis and carcinogenesis in the thyroid gland is still unclear. The data on effect of low Se levels in patients with goiter and thyroid nodules are divergent [1,10]. In vitro study showed that Se is able to decrease thyroid cancer growth [11]. In one study Se was inversely correlated with stages of thyroid cancer [12], but in a post-diagnosis study there was no association between fingernail selenium levels and thyroid cancer risk [13].

Conclusive results about the undisputable role of Se in the treatment of thyroid related diseases, including hyperthyroidism or thyroid orbitopathy, on a wider scale are still unavailable and further research is both required and recommended.

References

A24 Diabetes and the thyroid
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Thyroid disorders are more common in diabetic patients than in the general population. Abnormal thyroid function can be found in as many as 11% to 30% of patients with diabetes mellitus (DM) type 1 or 2. Thus, the Polish Society of Endocrinology and Polish Diabetes Association recommends screening for thyroid dysfunction in all patients with DM. According to these recommendations, concentrations of thyrotropin (TSH) and thyroid peroxidase antibodies (TPOAb) should be measured in every patient with newly diagnosed DM1, and in all patients with DM1 who have never undergone thyroid function tests. In exactly the same situations, patients with DM2 require TSH assessment, while TPOAb titer should be measured only if TSH reaches ≥ 2.0 mIU/L. In diabetic patients with TSH concentration ≥ 2.0 mIU/L and elevated TPOAb level, free thyroxin level should be assessed and – if normal – subsequently TSH should be monitored once a year. If the TSH concentration ≥ 2.0 mIU/L co-occurs with TPOAb titer within the reference range, TSH assessment should be repeated every other year. Patients with TSH < 2.0 mIU/L and normal TPOAb titer should undergo TSH testing every five years. Diabetic patients with a family history of chronic autoimmune thyroiditis require TSH testing once a year. If TPOAb titer is elevated in patients with DM2, the type of DM should be reassessed by measuring the level of antibodies against glutamic acid decarboxylase.

Special attention should be paid to women who are pregnant or planning pregnancy. In preconception period, TSH concentration should be measured in every woman with DM, and in DM1 patients together with TPOAb level. When pregnancy is confirmed, assessment of TSH and TPOAb is advised at the first obstetrician appointment (before 9th week of pregnancy). In all pregnant diabetic patients with a past medical history of Graves’ disease, anti-TSH receptor antibodies (TRAb) should be additionally measured at the first obstetrician appointment and repeated at the end of the second trimester (before the 22nd week of pregnancy). If carbohydrate balance is unimpaired, hyperthyroidism is rarely accompanied by hyperglycemia. Abnormal fasting or postprandial glucose levels in patients with hyperthyroidism indicate increased risk of developing diabetes. In such patients, oral glucose tolerance test (OGTT) should be performed once the euthyroidism is achieved. In diabetic patients, hyperthyroidism causes deterioration of metabolic control of DM and leads to all the systemic consequences of hyperglycemia, including increased risk of ketoacidosis. Additionally, even slight thyroid hormone excess significantly increases the risk of cardiovascular disease in patients with DM. Thus, both overt and subclinical hyperthyroidism should be treated in this group of patients. In diabetic patients with thyroid orbitopathy, the risk of optic neuropathy is increased, and intensive anti-inflammatory treatment should be introduced in every active disease except for the mild course cases. On the other hand, administering high steroid doses in patients with DM adversely influences the metabolic control of diabetes. Hence, in patients treated with oral anti-diabetic medications, periodic insulin therapy should be introduced along with steroid administration.

In diabetic patients, also the hypothyroidism is proven to be an independent risk factor for cardiovascular episodes. Therefore, treatment of subclinical hypothyroidism is strongly recommended in this condition. Hypoglycemia or reduced insulin requirement in diabetic patients may indicate concomitant development of hypothyroidism and/or – especially in patients with DM1 – adrenal insufficiency, and polyglandular autoimmune syndrome. Unexplained hypoglycemic states always require hormonal testing to exclude these endocrine disorders.

References

Neurological symptoms and signs in thyroid disease
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Neurological symptoms and signs in thyroid disease

A25

Numerous complex regulatory mechanisms influence the development and function of the peripheral and central nervous system. Among them, hormones belong to the most potent regulatory factors. Various particles known for their hormonal activity serve as neurotransmitters. Additionally, hormones secreted systematically modulate the function of the nervous system both on the brain level and in peripheral organs. Thyroid function has been shown to play a crucial role in the proper cognitive development but also in many other aspects of nervous system activity, in mechanisms involving direct interaction with intrinsic regulatory circuits or indirectly by systemic effects exerted e.g. on the circulatory system or metabolic pathways. Due to these close relations with the nervous system functioning, disturbances of thyrometabolic state are associated with a vast spectrum of neurological signs and symptoms including: mood and cognitive disorders, headache, ophthalmoplegia, tremor and other movement disorders, muscle weakness etc. Both hyper- and hypothyroidism may cause psychiatric symptoms like depressive or anxiety disorder, memory deficits, executive inability and even psychosis. The severe decompensated hypothyroidism may result in myxoedema coma - a life-threatening condition with sequentially progressing encephalopathic symptoms. Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAAT) represents another form of encephalopathic disorder associated with thyroid disease and causing potentially serious clinical complications. In the responsive hyperthyroid patients, the thymometabolic disturbances may affect both central nervous system and periphery, the thyrometabolic disturbances may affect both central nervous system and periphery, the thyrometabolic disturbances may affect both central nervous system and periphery, the thyrometabolic disturbances may affect both central nervous system and periphery, the thyrometabolic disturbances may affect both central nervous system and periphery, the thyrometabolic disturbances may affect both central nervous system and periphery, the thyrometabolic disturbances may affect both central nervous system and periphery, the thyrometabolic disturbances may affect both central nervous system and periphery, the thyrometabolic disturbances may affect both central nervous system and periphery.
thyroglobulin and thyroid peroxidase. In Graves-Basedow’s disease, TSH receptor is the main autoantigen against which the antithyroid antibodies are directed. High titres of ATG and anti-TPO may suggest the coexistence of Hashimoto’s disease. In 80% cases of Graves-Basedow’s disease, TSHR antibodies are stimulatory (thyroid stimulating immunoglobulins – TSI). In some cases, antibodies that inhibit thyrotropin binding to thyroid cells are produced (thyrotropin binding inhibiting immunoglobulins – TBI), which may lead to the development of hypothyroidism. In Hashimoto’s disease, cytotoxic lymphocytes, able to destroy thyroid follicular cells, receive considerable stimulation. Apart from cytotoxic lymphocytes, macrophages and the phenomenon of programmed cell death (apoptosis) also take part in the process of thyrocyte destruction. Clinical diagnosis of Graves-Basedow’s disease is based on the detection of evenly enlarged thyroid gland with tactile fremitus and/or audible vascular murmur and the occurrence of the typical ophthalmic changes. Some patients also suffer from pretibial myxoedema and thyroid acropathy. Ultrasonography is a very useful imaging tool in the diagnosis of Graves-Basedow’s disease – the thyroid gland is usually enlarged and has a homogenous, hypoechoic structure. Scintigraphy is not obligatory in each case of Graves-Basedow’s disease, but it is very helpful in patients with the features of nodular structure and in the form without the goitre in which diagnostic difficulties occur. In the classical form of Hashimoto’s disease, a painless goitre of intensified cohesion presents with a butterfly-like shape, because of the palpable pyramidal lobe. Patients complain of pressure and feeling of obstruction within the neck, and can report swallowing disorders and hoarseness. Chronic autoimmune thyroiditis can also occur in the atrophic, focal and juvenile form. Additionally, there are two variants of Hashimoto’s disease: postpartum thyroiditis and silent, painless thyroiditis. High anti-TPO antibody concentrations confirm the diagnosis of Hashimoto’s disease or any of its variants. The absence of antibodies in serum does not exclude lymphocytic thyroiditis as they are provided by intrathyroid lymphocyte infiltrations. Some authors attribute a special diagnostic significance to fine-needle aspiration biopsy in seronegative forms. Ultrasound thyroid examination is helpful in establishing correct diagnosis. Heterogeneous and distinctly hypoechoic structures of the thyroid gland are typical sonographic manifestations.

A27
Are the normal values of thyroid gland in children fulfilling the role attributed to them?
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It has always been very difficult to precisely define a goitre. The borderline cases, when a distinction between healthy and abnormal thyroid has to be made, are especially problematic. Imperfection of goitre classifications is connected with high variability of thyroid palpation, both interobserver and intraobserver – this variability increases with diminishing thyroid volume and decreasing goitre incidence.

Application of ultrasound examination of the thyroid has significantly decreased variability of obtained data, however, repeatability of this examination also depends on many factors, including the thyroid volume, position in which the assessment is being performed, width of the probe, as well as experience and number of the researchers.

Before final analysis, results thus obtained are interpreted by comparison of the measured thyroid volume to the value considered as borderline. For years, the borderline values, which could be universally used in such evaluations, had been searched for. However, presented reference values were very often disappointing as they proved to be either too restrictive or too liberal. This is one of the reasons why assessment of goiter incidence based even upon ultrasound examination has been losing its significance, giving way to assessment of ioduria, which seems to be more objective evaluation of iodine intake in the examined population.

Having analyzed the suggestions for ultrasound reference ranges in children we came to the conclusion that their inadequacy resulted from erroneous assumptions, which had been made during their development.

Examined population: A question arises whether reference ranges developed for children living in a region with adequate iodine intake can be universally used for classification of children residing in a different area?
No, this could only be possible if the thyroid size depended merely on the iodine intake. Although it is the iodine deficiency that is the most frequent cause of goiter, other factors can also influence the size of the thyroid. They include goitrogenic agents, naturally occurring in the environment (flavonoids and humus substances deriving from organic debris in the soil), as well as factors connected with pollution. Many inorganic (like thiocyanates, chlorides, nitrates) and organic (like phenols, hydrocarbons, phthalic acid esters) compounds have goitrogenic activity. Diet of the examined population is also important, as long-term consumption of cruciferous vegetables (from Cruciferae sp. or poorly cleaned cassava, which contains large quantities of glucosides releasing cyanides metabolized to thiocyanates, can result in significant enlargement of the thyroid gland. On the other hand, consumption of large amounts of saltwater fish or algae provides large, often supra-physiological supply of iodine. A large amount of iodine in ingested food does not always correlate with its high absorption by an organism. Although erythrosine, widely used in food industry as a colouring agent (e.g. in cereals), contains large amounts of iodine, its bioavailability for the human body is low. When analyzing the results, one should also consider the genetic predisposition of the examined population (its ethnic background) as well as the incidence of autoimmune disorders, which might influence thyroid size too.

The assumption that the size of the thyroid depends only on iodine supply leads to errors, which must be realized when using reference ranges developed so.

Metrical and anthropometric data: The reference ranges have the character of discrete/non-continuous (grouped) data. Depending on the age or BSA (body surface area) value, the thyroid size of an examined child is compared to the reference group. Groups’ ranges are quite wide and equal: for age – 8.3%-16.7% of the lower value of the range, for BSA – 6.25%-14.3%. Therefore, errors resulting from rounding, can be as high as 8.35% in children of the 6-year-old group and 7.15% in the group of children with BSA of 0.7 m2 (these are the youngest and smallest children, in whom the thyroid size is the smallest, so they constitute the group with the highest intra- and interobserver variability).

There is no doubt how to compare the obtained results with the reference ranges based on BSA (given reference value constitutes the middle of the range), however, interpretation of the result obtained on the basis of the age may encounter difficulties. Age should be determined based on the date of the examination and the date of birth. However, frequently it is defined by the age declared by the parents in the questionnaire, which leads to an error resulting from rounding the real data.

Moreover, ages given in the reference values might be interpreted in two ways – as the middle of the range (like BSA) – in such situations children aged 11.5-12.49 would fit in the 12-year-old group or the inclusion in the 12-year-old group is possible only when the child turns 12 years (an 11.5-year-old child is still in the 11-year-old group). One should also be aware of the phenomenon of acceleration, as it makes it difficult to compare data from different time points, as well as in the populations inhabiting different latitudes.

Regardless of the different interpretations of the data, it should be remembered that the result obtained based on reference ranges set for the groups, contains an error resulting from rounding (conversion of continuous data into discrete data).

Variability in iodine intake: Iodine supply in the population is not a constant value and it may change over time. The consumption of iodine in the society is influenced not only by iodine prophylaxis, but also by education policy, aimed at presenting the consequences of iodine deficiency and the necessity of prevention of deficiency of this element in the surrounding environment. The integration processes between countries and more and more expanding free trade and movement of people affect the iodine intake in the population, as well. Foodstuffs (especially imported on a large scale) do not necessarily fully meet the standards of the iodine content set by a given country. Models of iodine prophylaxis differ among particular countries – they do not need to be based of obligatory use of iodized salt, like in Poland. Moreover, in recent years a lot of effort has been made to decrease salt intake, which is still the most common carrier for iodine. These are all constant processes, changing the iodine supply in a population. There are examples of countries in which iodine
deficiency problems, once solved by introducing preventive measures, reappeared.

Once developed, standards may become outdated over time.

**Conclusions:** During the analysis of the results one should use as little rounding and generalizations as possible, because these are subject to error. The data should be processed as little as possible, they should be analyzed as continuous data, and not discrete. Acquiring them should be burdened with the least intra- and interobserver variability.

The analysis should be based on a comparison of the thyroid gland to the parts of the body (like thumb phalanx or BSA) instead of age, due to high variability during the growth period.

Analysis of thyroid volume to BSA (V/BSA) is in our opinion the best estimation of the size of the thyroid gland in the study population. Potential error is only burdened with the error resulting from the measurements (intra- and interobserver variability), like ioduria level determination.