



Thyroid Function in Humans



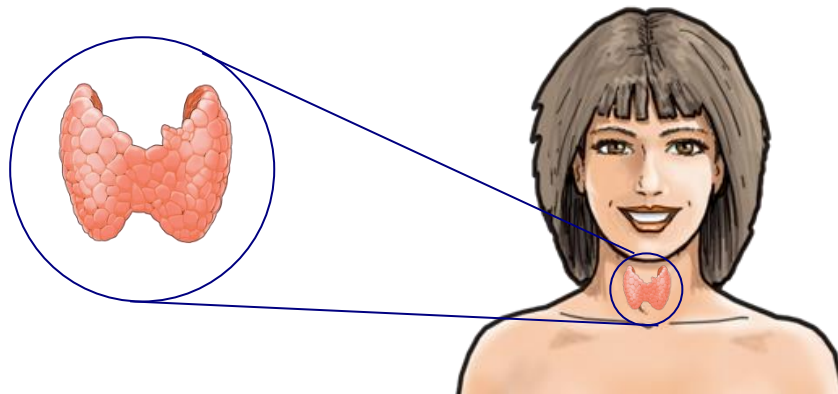


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Introduction

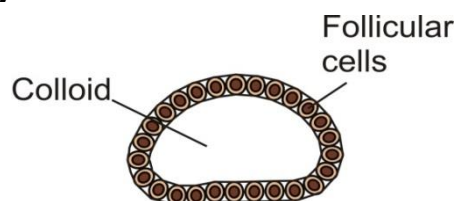
The thyroid gland is one of the largest endocrine glands in the body. This butterfly-shaped gland weights approximately 15-20 grams and it is located in the front of the neck below the thyroid cartilage.

Fig.1: Thyroid gland and its location



The main functional unit of the thyroid gland is the thyroid follicle (see Fig.2). Follicles selectively absorb iodide from the blood and produce thyroid hormones. Each follicle is formed of a single layer of epithelial (follicular) cells and is filled with a secretory substance called colloid, containing a large proportion of proteins, especially thyroglobulin. Thyroid gland primary function is to produce thyroid hormones thyroxine (T₄) and triiodothyronine (T₃). Biosynthesis itself takes place inside the follicular cells.

Fig.2: Structure of thyroid follicle





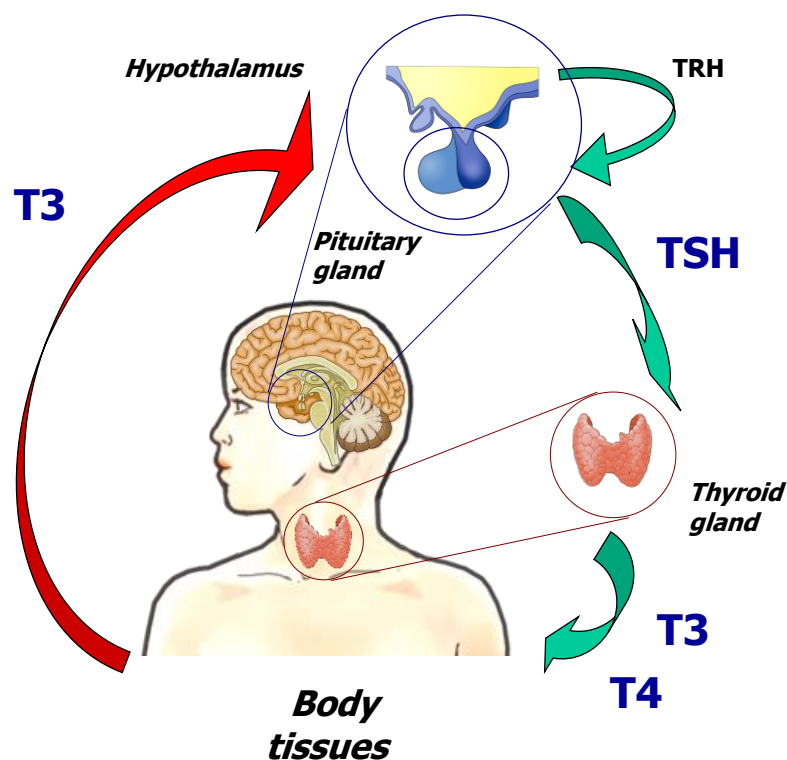
Thyroid hormones control the basal metabolism and are necessary for neural development, normal growth and for sexual maturation.

The thyroid gland also contains another type of cells called parafollicular. These cells produce another hormone, calcitonin, which is involved in calcium and phosphorus metabolism.

Regulation of thyroid hormone synthesis

The production of thyroxine and triiodothyronine is stimulated by thyroid-stimulating hormone (thyrotropin, TSH), released by the anterior pituitary. Production of TSH is induced by the hypothalamic hormone TRH (thyrotropin-releasing hormone). Hormone blood levels are regulated by the negative feedback mechanism (see Fig.3). High T3 and T4 levels have inhibitory effect on pituitary response to TRH. On the contrary, low T3 and T4 levels increase secretion of both TRH and TSH. Only free hormones have ability to regulate the pituitary feedback mechanism.

Fig.3: Hypothalamo-pituitary-thyroid axis





There are other factors playing certain role in stimulation and inhibition of thyroid hormone synthesis, including emotions, stress, immune system, nutrition state of the organism, or other hormonal systems (adrenal hormones, estrogens, somatostatin, dopamin).

Biological availability of the hormones is also managed by maintaining the pool of protein-bound hormones, as well as by conversion circulating T4 to T3 in the periphery.

Thyroid gland hormones, their biosynthesis, transport and metabolism

Hormones thyroxine (T4; 3,5,3',5'-L-tetraiodothyronine) and triiodothyronine (T3; 3,5,3'-L-triiodothyronine) are principal products of thyroid gland. They are produced under the stimulation of the pituitary hormone thyroid-stimulating hormone (TSH).

The thyroid is remarkably efficient in its use of iodide (I^-). Iodide is absorbed from the blood into follicular cells against concentration gradient and stored for future use. Transport across the basement membrane of the thyroid cells is mediated by an intrinsic membrane protein called the Na^+/I^- symporter (NIS), stimulated by TSH. On the other side of the cell, a second I^- transport protein called pendrin moves iodide into the colloid, where it is involved in hormonogenesis (see Fig.4).

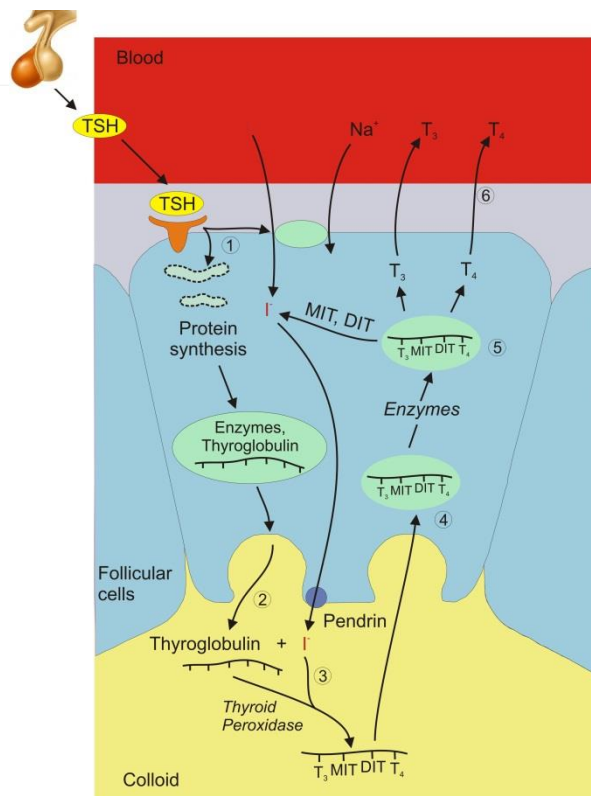
As a result, the concentration of iodide in a normal thyroid gland is approximately 40 times higher than in the blood.

Daily absorption of 150 to 200 μg of dietary iodine (I) is sufficient for normal production of thyroid hormones. If there is a deficiency of dietary iodine, the thyroid enlarges in an attempt to trap more iodine, resulting in goitre.

As iodide is taken in, TSH stimulates the synthesis of thyroglobulin. Thyroglobulin is a big dimeric protein that serves as a reservoir and substrate for thyroid hormone production, and their transport into the follicular colloid. Simultaneously, TSH stimulates synthesis and transport of enzymes participating in thyroid hormone creation. Mechanism is described in Fig.4 and Fig.5.



Fig.4: Follicular cell and thyroid hormone synthesis



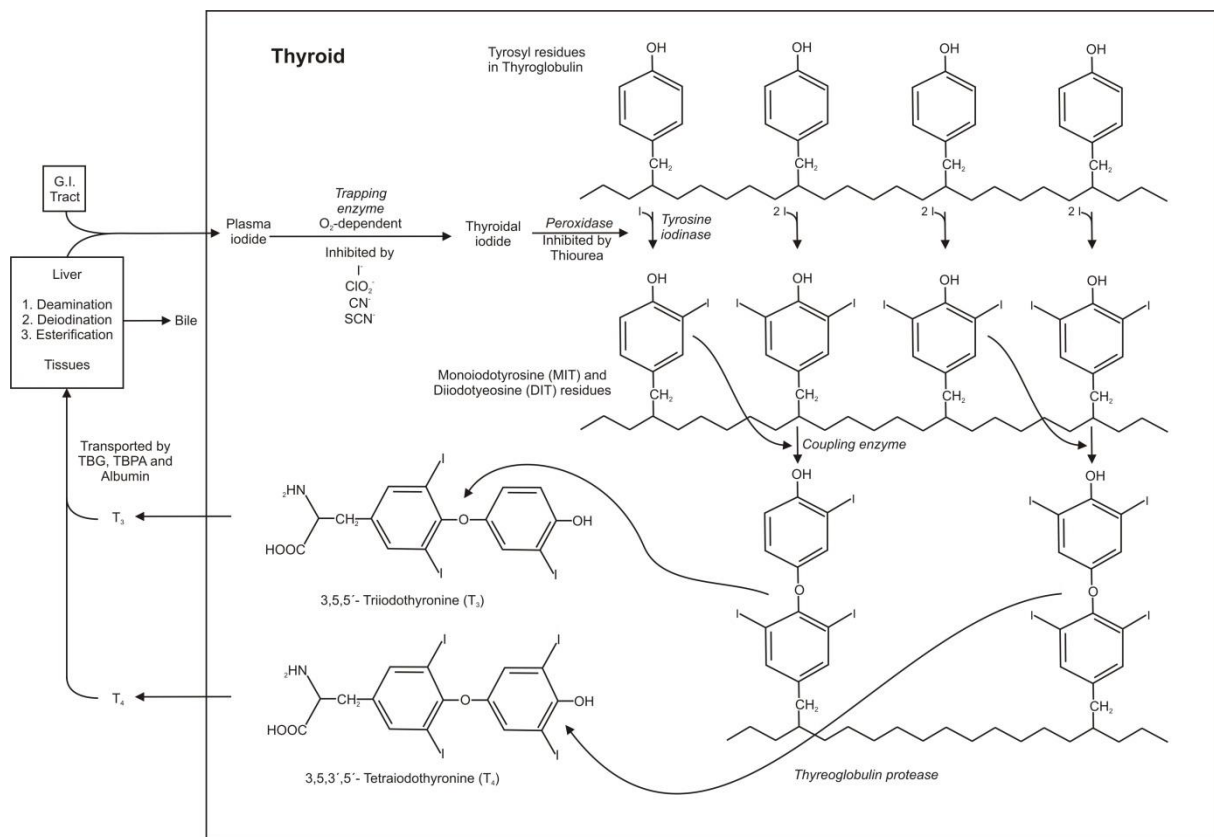
1. TSH binds to its receptor and stimulates intake of iodide and synthesis of thyroglobulin
2. Enzymes and thyroglobulin are transported into the colloid by exocytosis
3. Iodide is bound to the thyroglobulin molecule to create T3 and T4
4. Thyroglobulin is taken back into the cells by endocytosis of the colloid
5. Globules with colloid merge with lysosomes; lysosomal proteases release T3 and T4 from Tg
6. T3 and T4 are transported across the cell membrane and enter circulation

The enzyme called thyroid peroxidase catalyses covalent binding of iodine to tyrosine residues in the thyroglobulin molecule, forming monoiodotyrosine (MIT) and diiodotyrosine (DIT). Thyroxine is created by combining two molecules of DIT; triiodothyronine is created by combining one molecule of MIT and one molecule of DIT. This occurs within the colloid, but mainly at the interface between the follicular cell and the colloid.

Small globules of follicular colloid are endocytosed under the influence of TSH. These globules merge with lysosomes. Proteases present in lysosome digest iodinated thyroglobulin and release T3 and T4 from binding. TSH also mediates the transport of T3 (10%) and T4 (90%) across the thyrocyte membrane into circulation, while the lysosome is recycled back into the follicular lumen.



Fig.5: Formation of thyroid hormones¹



Approximately 40% of T4 is further deiodinated to T3 by peripheral tissues, and around 45% of T4 is deiodinated to rT3 (reverse T3, structural analogue of T3). T3 is 3-4 times more active than T4. It is therefore considered the real, active form of hormone, whilst T4 is considered just as a prohormone. rT3 does not have any biological activity.

Thyroid hormones are bound to various plasma proteins for transport in the blood. Approximately 99.97% of T4 and 99.7% of T3 is carried in the bound form. Only free hormones can enter the cells and are biologically active. Protein-



bound thyroid hormones form a large reservoir that is slowly drawn on when free thyroid hormone is needed. There are four major thyroid-binding proteins: thyroid hormone-binding globulin (TBG), thyroxine-binding prealbumin (TBPA, also called as transthyretin – TTR), albumin and T4 binding lipoprotein (T4 BL). Their proportions are shown in Tab.1.

Tab.1: Proportions of binding proteins in complexes with T4 and T3

Hormon	TBG	TBPA	Albumin	T4 BL
Tyroxine	65-70%	10-15%	15-20%	3-6%
Triiodothyronine	75-80%	10%	10%	3%

Biological half-life of T3 is 0.7 days, biological half-life of T4 is 6.5 days.

As already mentioned, major part of T4 is deiodinated to T3 and rT3. There are three types of enzymes participating in deiodinations:

Type 1: deiodinates at both the 5' and 5 carbon atoms and is found in the liver, kidney, thyroid, pituitary gland and central nervous system, with a high K_m for T4. Its activity is increased in hyperthyroidism and reduced in hypothyroidism.

Type 2: deiodinates only at the 5' position and is found in brain, brown fat, placenta and pituitary gland. With a lower K_m than Type 1, it is considered to maintain intracellular concentrations of T3. This is important in the negative feedback actions of T4 on the pituitary gland. Its activity is decreased in hyperthyroidism and increased in hypothyroidism.

Type 3: deiodinates only at the 5 position and is found only in brain and placenta. As it is incapable of converting T4 to the active T3, it may protect the brain and fetus from excess active T3.

The degradative metabolism of T4 and T3 consist in oxidative deamination and further degradation. T3 and T4 are also conjugated in the liver to glucuronides and sulfates. The conjugates are then excreted via bile. Certain part is hydrolyzed and reabsorbed, the rest pass into stool. Urinary excretion is minor.



Biological function of thyroid hormones

Triiodothyronine enters the cells and binds to a nuclear receptor, causing transcription of specific thyroid hormone responsive genes.

There are two main functions of the thyroid hormones. The first role is to increase metabolism, and the second role is to maintain normal growth and development in children, including mental development and attainment of sexual maturity.

Metabolic rate

Thyroid hormones increase the metabolism of all body tissues except the retina, spleen, testes, and lungs. The basal metabolic rate can increase by 60% to 100% above normal if high concentration of T3 and T4 is present. T3 and T4 increase glucose, fat, and protein utilization. Lipids are mobilized from adipose tissue, and the catabolism of cholesterol by the liver is increased. Muscle proteins are cleaved and used as a fuel. The absorption of glucose from the gastrointestinal tract is increased. Another consequence of increased metabolic rate is increased consumption of vitamins that may develop into vitamin deficiency.

Cardiovascular function

Cardiovascular and respiratory functions are strongly affected by thyroid function. Increased metabolic rate results in a rise in oxygen consumption with high production of metabolic end products. It is accompanied by increased vasodilatation. Blood flow into the skin helps to reduce the body heat caused by higher metabolism. Blood volume, cardiac output, and ventilation all are increased in order to maintain blood flow and oxygen delivery to body tissues. Blood pressure does not change much as the increase in vasodilatation suppresses the effect of cardiac output increase.

Gastrointestinal function

Thyroid hormones enhance gastrointestinal function, their excessive amounts causing an increase in motility and production of gastrointestinal secretions that often results in diarrhea. An increase in appetite and food intake reflects the higher metabolic rate. At the same time, weight loss occurs because of the increased use of calories.

Neuromuscular Effects

Thyroid hormones have significant effects on neural control of muscle, maintaining proper function and tone of the muscles.

Thyroid hormones are also necessary for normal brain development in infants. They enhances cerebration, but their overproduction causes extreme nervousness, anxiety, and difficulty in sleeping.



Altered function of the thyroid gland - Introduction

Disorders of thyroid gland are very frequent; they are the second most frequent endocrinology disorders, after diabetes mellitus.

Increased size of thyroid gland, called goitre, can occur in states associated with thyroid hormone overproduction or insufficiency, but it can occur also in conditions with normal thyroid hormone production. Goitres may be diffuse, involving the entire gland without evidence of nodularity, or they may contain nodules.

Worldwide, over 90% cases (more than one billion) of goitre are caused by iodine deficiency. Such goitre does not appear due to some pathological process. Rather than real disease, this condition appears as a compensatory hypertrophy and hyperplasia of follicular epithelium to overcome thyroid deficiency and keep the body in state of sufficient thyroid hormone supply.

Thyroid gland inflammation (thyroiditis) is heterogenic group of diseases that differ in etiology and clinical picture. It may be classified as one of following four forms:

- **Acute thyroiditis** - very rare, about 0.1-0.7% of all thyroiditis. It is caused by bacterial infection.
- **Subacute De Quervain's thyroiditis** (also known as subacute granulomatous thyroiditis or Giant Cell Thyroiditis)
- **Autoimmune thyroiditis** (Hashimoto's thyroiditis, chronic lymphocyte thyroiditis, postpartum thyroiditis and others)
- **Riedel's thyroiditis** - chronic form of thyroiditis, characterized by a replacement of the normal thyroid parenchyma by a dense fibrosis.

Besides palpation examination, ultrasound, scintigraphy and aspiration biopsy, indispensable part of thyroid gland diagnosis is the determination of biochemical markers - thyroid hormones thyroxine and triiodothyronine, pituitary hormone TSH, and antibodies against different structures on thyroid gland.



From functional point of view, following states may be distinguished:

- Euthyroidism – thyroid hormone production and release is normal
- Hypothyroidism - thyroid hormone production and release is abnormally low
- Hyperthyroidism - thyroid hormone production and release is abnormally high

Subclinical forms are defined on the basis of TSH and FT4 levels: TSH outside range of expected values, FT4 normal.

Typical manifestations of hypo- and hyperthyroism are presented in following table.

Tab. 2: Manifestations of hypo- and hyperthyroidism

	Hypothyroidism	Hyperthyroidism
Basal metabolic rate	Decreased	Increased
Sensitivity to catecholamines	Decreased	Increased
General features	Myxedematous features	Exophthalmos
	Deep voice	Lid lag
	Impaired growth (child)	Decreased blinking
Blood cholesterol levels	Increased	Decreased
General behavior	Mental retardation (infant)	Restlessness, irritability, anxiety
	Mental and physical sluggishness	Hyperkinesia
	Somnolence	Wakefulness
Cardiovascular function	Decreased cardiac output	Increased cardiac output
	Bradycardia	Tachycardia and palpitations
Gastrointestinal function	Constipation	Diarrhea
	Decreased appetite	Increased appetite
Respiratory function	Hypoventilation	Dyspnea
Muscle tone and reflexes	Decreased	Increased, with tremor and fibrillatory twitching
Temperature tolerance	Cold intolerance	Heat intolerance
Skin and hair	Decreased sweating	Increased sweating
	Coarse and dry skin and hair	Thin and silky skin and hair
Weight	Gain	Loss



Statistical data

Although statistical data vary significantly in dependence of the source, there is no doubt that the prevalence and incidence of thyroid disease is very high.

Data suggest that:

- Approximately 200 million people worldwide have a thyroid disorder
- Estimates vary between 20-30 million people affected by a thyroid disease in US, at least a half of them undiagnosed
 - 1 in 8 US women will develop thyroid disease during their lifetime
- 1 per 3 000 – 4 000 newborns are affected by congenital hypothyroidism in North America, Europe, Japan and Australia
- Prevalence of thyroid diseases is much higher in women
 - The likelihood is approximately four times higher than in men in case of Graves' disease, and even five times higher in case of hypothyroid disease
- Prevalence increases with age

Australian data obtained on the bases of Whickham study may serve as good example of relations between sex, age and prevalence of the thyroid disease (see Tab.3).

Tab.3: Estimated prevalence of spontaneous hypo- and hyperthyroidism in Australia

Age	Female		Male		Relative probability of disease Female/Male
	Total number	% of population	Total number	% of population	
<20	16 065	0.60	4 055	0.14	4.29
21-30	26 891	1.91	7 856	0.55	3.47
31-40	50 631	3.46	16 361	1.06	3.26
41-50	83 833	6.28	23 349	1.74	3.61
51-60	107 289	11.25	25 563	2.59	4.34
61-70	136 747	19.30	25 247	3.68	5.42
71-80	166 344	29.22	21 869	4.85	6.02
>80	123 815	41.85	9 504	6.26	6.68
Total	711 614	7.56%	132 831	1.43	5.29



Hypothyroidism

Hypothyroidism is defined as a deficiency in thyroid hormone secretion and action. It is a common disorder that occurs in mild or severe forms in 2-15% of the population. Women are affected more than men, and both sexes are affected more often with increasing age.

Hypothyroidism can occur as a congenital or an acquired defect. Congenital hypothyroidism develops prenatally and is present at birth. Acquired hypothyroidism develops later in life because of primary disease of the thyroid gland or secondary to disorders of hypothalamic or pituitary origin.

- **Primary hypothyroidism** - This disorder results from the destruction or dysfunction of the thyroid gland itself. It is much more frequent than other two types. Synthesis of T₄ and T₃ is impaired, either due to of extrinsic of intrinsic factors. Consequently, concentrations of TSH and TRH increase in order to enhance the stimulation of thyroid gland.
- **Secondary and tertiary hypothyroidism** - Secondary and tertiary hypothyroidism occurs as a result of pituitary or hypothalamic disease that produces a deficiency in either TSH, TRH, or both. TSH levels are decreased, as well as concentration of thyroid hormones T₃ and T₄.

Congenital hypothyroidism

Congenital hypothyroidism is a common cause of preventable mental retardation. It affects approximately 1 of 3 000–4 000 infants. Congenital hypothyroidism may be caused by congenital lack of the thyroid gland or from abnormal biosynthesis of thyroid hormone or deficient TSH secretion. With congenital lack of the thyroid gland, the infant usually appears normal and functions normally at birth because hormones have been supplied in utero by the mother. Thyroid hormone is essential for normal brain development and growth, almost half of which occurs during the first 6 months of life. If untreated, congenital hypothyroidism causes mental retardation and impairs growth. The manifestations of untreated congenital hypothyroidism are known as cretinism. Administration of thyroid hormones prevent from any damage if starts shortly after birth (within first six weeks).



Neonatal screening tests determine the level of TSH, sometimes in combination with FT4, to detect congenital hypothyroidism already few days after the birth. Drop of blood is collected to filtration paper from a heel of the newborn. High TSH levels and low FT4 level suggest congenital hypothyroidism.

Transient forms are known as well. They occur usually after exposure of mother or infant to excessive amount of iodine. Another possible cause is administration of anti-thyroid drugs to mother, as these drugs can cross placenta.

Postnatal hypothyroidism

Hypothyroidism in older children and adults causes a general slowing down of metabolic processes and myxedema. Hypothyroidism affects almost all of the organ systems in the body. The manifestations of the disorder are related largely to two factors: the hypometabolic state resulting from thyroid hormone deficiency, and myxedematous involvement of body tissues.

The most common cause of hypothyroidism is an autoimmune disorder called **Hashimoto's thyroiditis**. Autoimmune reaction is associated with the presence of circulating antithyroid antibodies, and it leads to partial or complete destruction of thyroid gland. Hashimoto's thyroiditis usually start with goitre, hypothyroidism appears later on. Transient hyperthyroid phase may appear due to leakage of thyroid hormones from cells damaged by autoimmune process.

Hypothyroidism may also develop postpartum as a result of subacute thyroiditis, which appears in almost 10% of pregnancies.

Another cause of hypothyroidism is thyroidectomy (surgical removal of thyroid gland) or irradiation.

Hypothyroidism may be also evoked by the intake of large amounts of iodine, contained e.g. in cough syrups, or by administration of iodide-containing radiographic contrast media or the cardiac drug amiodarone. Other drugs suppressing function of thyroid gland are antithyroid drugs propylthiouracil and methimazole, or lithium carbonate, used in manic-depressive states.



Hypothyroidism is characterized by weakness and fatigue, a tendency to gain weight despite a loss of appetite, and cold intolerance. Further, the skin becomes dry and rough and acquires a pale yellowish cast, and the hair becomes coarse and brittle. Gastrointestinal motility is decreased. Nervous system involvement is manifested by lethargy and impaired memory. The face has a puffy look as a result of myxedematous fluid accumulation, the voice is hoarse and husky.

Symptoms of hypothyroidism are summarized in Tab.2.

The most severe and life threatening condition is mixedematous coma. This end-stage of hypothyroidism is characterized by coma, hypothermia, cardiovascular collapse, hypoventilation, and severe metabolic disorders including hyponatremia, hypoglycemia, and lactic acidosis.

Diagnosis of hypothyroidism is based on patient history, physical examination, and laboratory tests.

Low T4 and elevated TSH levels are main characteristic of primary hypothyroidism. Subclinical hypothyroidism corresponds to the condition when thyroid hormone concentrations remain within euthyroid interval, and TSH is elevated. Follow-up is necessary, as the subclinical form frequently develops to manifest hypothyroidism.

Antibodies against thyroid peroxidase typically appear in Hashimoto's thyroiditis.

In secondary and tertiary hypothyroidism, both T4 and TSH concentrations are decreased. A TRH stimulation test may be helpful in differentiating pituitary (secondary hypothyroidism) from hypothalamic (tertiary hypothyroidism) disease.

Hypothyroidism is treated by replacement therapy with synthetic preparations of T4 (sometimes in combination with T3). Adequacy of administered dose is evaluated by the determination of TSH. If it is within the normal range, the treatment is considered satisfactory.



Hyperthyroidism

Hyperthyroidism, or thyrotoxicosis, is defined as a hypermetabolic condition associated with increased amount of thyroid hormones in circulation. The prevalence of hyperthyroidism is relatively low in general population (0.3-0.6%), and women are more prone to this disease than men.

The signs and symptoms of hyperthyroidism are summarized in Tab.2.

The most common cause of hyperthyroidism is Graves' disease. This condition may be accompanied by ophthalmopathy or dermopathy and diffuse goitre. Other causes of hyperthyroidism are multinodular goitre, adenoma of the thyroid gland or inadequate excessive ingestion of thyroid hormones. Similarly to hypothyroidism, hyperthyroidism may be also induced by excessive intake of iodine.

Graves' disease is an autoimmune disorder characterized by presence of autoantibodies and abnormal stimulation of the thyroid gland. Autoantibodies are directed against receptor for TSH, located on the surface of thyroid follicular cells. Thyroid-stimulating antibodies (thyroid-stimulating immunoglobulins; TSI) mimic the effect of TSH and stimulate the follicular cells to create and release thyroid hormones.

Typical onset of the disease is between 20 and 40 years of ages, and women are five times more likely to develop the disease than men.

It may be associated with other autoimmune disorders such as myasthenia gravis and pernicious anemia. Ophthalmopathy, which can cause severe eye problems, occurs in up to one third of persons with Graves' disease. Not all of the ocular changes are reversible with treatment.

Acutely exaggerated manifestation of the thyrotoxic state is called **thyroid crisis**, or thyroid storm. It is life-threatening form of thyrotoxicosis, rarely seen today because of improved diagnosis and treatment methods.



Thyroid storm is manifested by a very high fever, extreme cardiovascular effects (*i.e.*, tachycardia, congestive failure, and angina), and severe CNS effects (*i.e.*, agitation, restlessness, and delirium). Thyroid storm requires rapid diagnosis and treatment.

Many of the manifestations of hyperthyroidism are related to the increase in oxygen consumption and use of metabolic fuels associated with the hypermetabolic state as well as to the increase in sympathetic nervous system activity that occurs.

Weight loss is common despite a large appetite. Other manifestations include tachycardia, palpitations, shortness of breath, excessive sweating, muscle cramps, and heat intolerance. The person appears restless and has a fine muscle tremor. The hair and skin usually are thin and have a silky appearance. About 15% of elderly individuals with new-onset atrial fibrillation have thyrotoxicosis.

The treatment of hyperthyroidism is directed toward reducing the level of thyroid hormone. This can be accomplished by eradication of the thyroid gland with radioactive iodine, through surgical removal of part or the entire gland, or with the use of drugs that decrease thyroid function. Eradication of the thyroid with radioactive iodine is used more frequently than surgery. The β -adrenergic-blocking drugs are administered to block the effects of the hyperthyroid state on sympathetic nervous system function. They are given in conjunction with anti-thyroid drugs preventing the thyroid gland from incorporating iodine to its hormonal form and block the conversion of T4 to T3 in the tissues.



Tumors of thyroid gland

Thyroid carcinoma represents 1.6% of cancers of all ages and 3.8% of cancers that appear before 20 years of age (data from US). Women are affected more than men, in a ratio of more than 3 to 1.

Thyroid neoplasms are classified into three major categories: epithelial, nonepithelial, and secondary. Most primary epithelial tumors of thyroid are derived from follicular cells. These include follicular adenoma and carcinoma, papillary carcinoma and its variants. Other primary epithelial tumors include medullary carcinoma, mixed medullary and follicular carcinomas, insular and poorly differentiated carcinoma, anaplastic carcinoma, and the least common squamous carcinoma.

- **Papillary carcinoma** represents 70-80% of thyroid cancers. Its aggressiveness is relatively low, and it responds well to radioactive iodine treatment.
- **Follicular carcinoma** (10-15% of thyroid cancers) appears in territories with deficit of iodine. Lung and bone metastases that may appear react relatively well to radioactive iodine.
- **Medullary carcinoma** (5-7% of thyroid cancers) originates from parafollicular cells.
- **Anaplastic carcinoma** belongs to the most aggressive tumors. It creates distant metastases and treatment with surgery or radioactive iodine is not very effective.

The nonepithelial tumors are rare; the most common include malignant lymphoma and tumors arising from the mesenchymal elements. The secondary tumors represent metastatic tumors to the thyroid usually originating in lung, kidney, and breast.

Thyroid carcinomas are frequently responsive to treatment with surgery and radioactive iodine. Nevertheless, life-long follow-up is necessary as certain number of patients develop late recurrent disease despite its apparent initial resolution.



Disorders of thyroid gland in pregnancy

Thyroid hormones play an important role in conception, fetal development and postnatal development of the child.

Thyroid disease should be considered in patients undergoing investigation for menstrual problems or infertility.

Hypothyroidism is frequent cause of sterility. Severe hypothyroidism may even cause absolute lack of menstruation (amenorrhea). Nevertheless, decreased fertility and, especially, reduced successfulness of in vitro fertilization (IVF) is associated with anti-TPO autoantibody occurrence, even without pronounced hypothyroidism. Fortunately, once treated adequately, neither hypo- nor hyperthyroidism have a major impact on fertility.

Hyperthyroidism is another possible cause of irregular or absent menses.

A normal pregnancy is associated with a number of important physiological and hormonal changes that alter thyroid function, including:

- Increase of maternal metabolism, in average by 15-20%
- Regulation of thyroid function not only by pituitary gland, but also by placenta (effect of placental hormones hCG, human placental lactogen, placental steroid hormones)
- Transplacental transfer of thyroid hormones
- Changes in T4, T3 and rT3 ratio
- Increase of TBG synthesis, as a result of increased concentration of estrogens
- Increased glomerular filtration that may lead to ioduria (increased loss of iodine by urine)
- Changes in immunity system

During first trimester of pregnancy, TSH suppression due to increasing hCG is observed. hCG can stimulate thyroid gland because receptors for hCG and TSH have 85% analogy. Levels of TT4 and TT3 increase substantially due to rise of estrogens and TBG. FT4 and FT3 levels remain usually normal or can temporarily increase without any risk for a baby or mother.

TSH level normalizes in the second trimester. The level of binding proteins (TBG) continues to increase.



Hyperthyroidism and pregnancy

Transient hyperthyroidism appears due to very high levels of hCG, and manifests as morning sickness (hyperemesis gravidarum).

The most common cause (80-85%) of maternal hyperthyroidism during pregnancy is Graves' disease. It may present initially during the first trimester or may be exacerbated during this time in a woman known to have the disorder. Inadequately treated maternal hyperthyroidism can cause early labor or pre-eclampsia. Additionally, women with active Graves' disease during pregnancy are at higher risk of developing very severe hyperthyroidism known as thyroid storm. Graves' disease often improves during the third trimester of pregnancy and may worsen during the post-partum period.

The risks to the baby from Graves' disease are due to one of three possible mechanisms:

- Uncontrolled maternal hyperthyroidism is associated with fetal tachycardia (fast heart rate), small for gestational age babies, prematurity, stillbirths and possibly congenital malformations.
- Thyroid stimulating immunoglobulins (TSI) cross the placenta and, if the mother's TSI levels are very high, they can interact with the baby's thyroid.
- Anti-thyroid drug therapy (ATD) cross the placenta and can potentially impair the baby's thyroid function and cause fetal goitre.

Mild hyperthyroidism, with slightly elevated thyroid hormone levels and minimal symptoms is often monitored without therapy. When hyperthyroidism is severe enough to require therapy, anti-thyroid medications are the treatment of choice. The goal of therapy is to keep the mother's free T4 and free T3 levels in the high-normal range on the lowest dose of antithyroid medication.

Surgical removal of the thyroid gland is only very rarely recommended in the pregnant woman due to the risks of both surgery and anesthesia to the mother and the baby. Radioiodine is contraindicated to treat hyperthyroidism during pregnancy since it readily crosses the placenta and is taken up by the baby's thyroid gland.

Graves' disease typically worsens in the postpartum period, usually in the first 3 months after delivery.



Hypothyroidism and pregnancy

The most common cause of hypothyroidism is the Hashimoto's thyroiditis. Hypothyroidism can occur during pregnancy due to the initial presentation of Hashimoto's thyroiditis, inadequate treatment of a woman already known to have hypothyroidism, or over-treatment of a hyperthyroid woman with antithyroid medications.

Untreated, or inadequately treated, hypothyroidism can cause maternal anemia, myopathy (muscle pain, weakness), congestive heart failure, pre-eclampsia, placental abnormalities, low birth weight infants, and postpartum hemorrhage.

Most women with mild hypothyroidism may have no symptoms or attribute symptoms they may have as due to the pregnancy.

Untreated severe hypothyroidism in the mother can lead to impaired brain development in the baby. This is mainly seen when the maternal hypothyroidism is due to iodine deficiency, which also affects the baby. However, recent studies have suggested that mild brain developmental abnormalities may be present in children born to women who had mild untreated hypothyroidism during pregnancy. Also, there is increased risk of congenital anomalies and perinatal mortality.

Therefore, it seems advantageous to screen mothers in the first trimester for TSH, FT4, Anti-TPO during the first trimester.

Thyroid disorders, including subclinical hypothyreosis, diagnosed during pregnancy should be treated by replacement therapy with T4.

Subacute thyroiditis, which appears in almost 10% of pregnancies, may develop into postpartum thyroiditis (50% of women with Anti-TPO positivity during pregnancy). Postpartum thyroiditis then develop in permanent hypothyroidism in 25-30% of cases.



Non-thyroid illness

There are a lot of acute disease states which are accompanied by abnormal thyroid hormone values. This may occur as a result from the effects of acute illness and/or the drugs treating illness on the synthesis, transport and metabolism of thyroid hormones. It is therefore necessary to be very cautious when evaluating thyroid function in hospitalized patients. It is recommended to adapt wider range of TSH, and diagnosis should be always confirmed at least six weeks after release from hospital.

Some typical examples are as follows:

- Low serum T3, normal T4. The most common biochemical abnormality, it is seen in approximately 70% hospitalized patients. T3 reduced by about 50%, rT3 increased (except in renal failure) due to its decreased clearance as a result of reduced activity/production of 5' mono-deiodinase Type 1.
- Low serum total T3 and T4. Usually is seen in severely ill patients. Free T4 is normal owing to inhibition of T4 binding or production of altered TBG.
- High serum total T4, normal total T3. It is seen in patients with liver disease producing increased quantities of TBG. Free T3 low or low-normal, rT3 high.
- Increased serum total-T4 and TBG, normal T3 and paradoxical decreases in rT3. It is seen in patients with HIV infection.

Disorders of thyroid gland in elderly

Frequency of thyroid diseases increases significantly with age. Moreover, symptoms of hyperthyroidism and hypothyroidism can be manifested only in a subtle way among older people, or the symptoms may be considered as the manifestation of another disorder. There is a risk that those people escape a proper diagnosis, or they are treated for different disease. According statistics up to 1 in 4 patient in nursing homes may have undiagnosed hypothyroidism. There are continual discussions about the need of some screening program. Determination of TSH, FT4, and Anti-TPO in all women over 50 is one of the possible strategies, but no clear consensus has been achieved yet.



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