

# Thyroidopathy in pregnancy and in the newborn

**Thyroidopathy** or thyroid disease affects a significant proportion of women of reproductive age. Untreated thyroid diseases can be the cause of infertility, complications in pregnancy (miscarriages, premature births, etc.) and may contribute to the delay of psychomotor development of the child. Therefore, early detection and treatment is desirable during pregnancy. According to the recommendations of the Czech Society of Endocrinology from 2018, thyroid stimulating hormone (TSH), free thyroxine (fT4) and antibodies to thyroid peroxidase (TPOAb) should also be collected during the first blood collection in pregnancy (i.e. usually at 9 – 11 weeks). According to some international professional societies, this examination is not necessary in women without risk factors (see below). All pregnant and lactating women (except those with hyperthyroidism) are recommended iodine supplementation (150–200 µg of elemental iodine per day in addition to the normal dietary intake). Beware, however, of excessive iodine intake (>500 µg per day), which can lead to fetal hypothyroidism.<sup>[1]</sup>

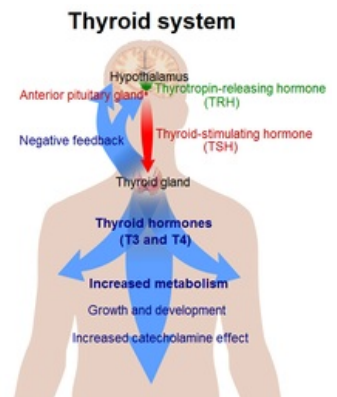


Image: Hormonal regulation of the thyroid gland

## Risk factors of thyroidopathy in pregnancy

- Thyroidopathy in personal or family history;
- Symptoms of thyroid dysfunction or goiter;
- Type 1 diabetes mellitus or other autoimmune diseases;
- Abortion or premature birth in history;
- Positive TPOAb;
- History of head and/or neck irradiation;
- Obesity with BMI  $\geq 40$  kg/m<sup>2</sup>;
- Taking amiodarone, lithium, application of cytokines, recent application of iodine X-ray contrast medium;
- Infertility;
- Living in an area with moderate or severe iodine deficiency.<sup>[1]</sup>

The most common endocrine disease in women is autoimmune thyroid disease – especially chronic lymphocytic thyroiditis (CLT) and Graves-Basedow disease (GB).<sup>[2]</sup>

## Physiology (effect of pregnancy on the thyroid gland)

- during pregnancy, the volume of plasma increases and with it the plasma pool of thyroxine (T4) and triiodothyronine (T3);
- the renal clearance of iodine increases, and part of the iodine also passes through the placenta into the fetal circulation;
- is an accelerated metabolic inactivation of T4 and T3 by deiodase 3 on the inner ring by the enzyme deiodase 3, which is increasingly expressed in the placenta (quantitatively the most important factor);
- the consequence of the above changes is an overall increased need for iodine and thyroid hormones during pregnancy – women with normal iodine stores in the thyroid gland and with normal gland function easily adapt to these changes by increased synthesis of T4 and T3;
- at the beginning of pregnancy, due to the increase in estrogens, the concentration of thyroxine-binding globulin (TBG), which is the main binding protein for T4 and T3, increases → thus the free fraction of T4 and T3 (fT4 and fT3) is temporarily reduced → after increasing synthesis, fT4 normalizes and the bound (and thus total) T4 remains elevated;
- at the beginning of pregnancy, chorionic gonadotropin (hCG) rises sharply, which, among other things, has a stimulating effect on the thyroid gland (similar to TSH – they share a large part of the molecule – the alpha chain) → the secretion of T4 and T3 increases and the secretion of TSH is partially or even completely suppressed by feedback, especially in conditions with high hCG (e.g. twins) – a transient and clinically non-serious condition.<sup>[3]</sup>

The synthesis of thyroxine (T4) and triiodothyronine (T3) is dependent on iodine intake. These hormones are necessary for both preconception and fertilization and throughout pregnancy until several months after birth. In hypothyroidism, fertility is impaired due to increased prolactin levels. The fetus is completely dependent on the production of thyroxine by the mother mainly until the 12th to 16th week, after which the fetal thyrocytes begin their own T4 synthesis, but the mother's supply of T4 is important throughout pregnancy.<sup>[2]</sup>

## Thyroidopathy in pregnancy

### Hypothyroidism

- The most common causes: autoimmune thyroiditis, non-increase in the replacement dose at times of increased demands and relative iodine deficiency; central hypothyroidism (decreased serum fT4) is rare;

- treatment: substitution with levothyroxine (target TSH values are  $< 2.5$  mIU/l) and iodine supplementation.<sup>[4]</sup>
- **Manifest hypothyroidism:** TSH elevation and decreased FT4 or elevation of TSH  $>10$  mIU/l and normal FT4 – indicated for treatment with levothyroxine;
- **Subclinical hypothyroidism:** Elevation of TSH  $\leq 10$  mIU/l and normal FT4 – indicated for treatment with levothyroxine;
- **Isolated positive antibodies:** Positive TPOAb and normal TSH and FT4 – consider treatment with levothyroxine (especially in women with miscarriages, premature births, infertility, decreased FT4, etc.);
- **Isolated hypothyroxinemia:** Decreased FT4 and normal TSH and negative TPOAb – consider treatment with levothyroxine if no adjustment is made after iodine supplementation.<sup>[1]</sup>

### Hashimoto's thyroiditis - chronic autoimmune thyroiditis

- one of the most common autoimmune diseases, it affects about 5% of women of reproductive age;
- arises partly on a genetic basis;
- it develops very slowly as chronic lymphocytic inflammation, mediated mainly by cellular immunity directed against follicular cells of the gland;
- it is also manifested by the production of circulating autoantibodies to the structures of the gland, of which antibodies to thyroperoxidase are of the greatest importance for diagnosis (TPOAb);
- limits the secretory reserve of the gland – functional impairment is of varying severity;
- functional impairment of the gland can be judged by the increase in TSH and in more severe disorders and/or iodine deficiency also by the decrease in free T4;
- ultrasonographic image: coarse structure (dispersion → diffuse), hypoechogenic and hypervascularized.<sup>[3]</sup>

### Hyperthyroidism

- physiological pregnancy may mimic hyperthyroidism clinically and laboratory (increased cardiac output, peripheral vasodilation, increase in total and partially free thyroxine, mild goiter, physiological suppression of TSH due to chorionic gonadotropin);
- however, the prevalence of true peripheral hyperthyroidism in pregnancy is up to 10× lower than in the general population;
- the most common cause is Graves-Basedow disease (in 85% of cases), other causes are rare (hyperfunctional phase of autoimmune thyroiditis, excess iodine, overdose of thyroid hormones, toxic adenoma, polynodular toxic remodeling/goiter);
- untreated or inadequately treated hyperthyroidism in pregnancy increases the risk of premature birth and early miscarriage;
- overdose of thyreostatics in pregnancy leads to fetal hypothyroidism with negative consequences for CNS development and fetal goiter;
- treatment with thyreostatics – in the 1st trimester propylthiouracyl (increased incidence of congenital malformations after methimazole and carbimazole), from the 2nd trimester change to methimazole (higher incidence of hepatopathies after propylthiouracyl), during breastfeeding methimazole;
- the most serious side effects of thyreostatics: agranulocytosis and hepatopathy (monitoring of liver enzymes is indicated).<sup>[4]</sup>
- **Manifest hyperthyroidism:** decreased TSH, increased FT4 and confirmed thyroid etiology (TSH receptor antibody testing (TRAK) and ultrasound), significant clinical signs – indicated for the treatment of thyreostatics (propylthiouracyl in the 1st and methimazole in the 2nd and 3rd trimesters), iodine supplementation is not indicated;
- **Subclinical hyperthyroidism:** decreased TSH, normal FT4 and confirmed thyroid etiology, minimal or no clinical signs – not indicated for the treatment of thyreostatics or iodine supplementation;
- **Transient gestational suppression of TSH:** decreased TSH and normal FT4 of non-thyroid etiology – not indicated for the treatment of thyreostatics but is indicated for iodine supplementation;
- **Isolated hyperthyroxinemia:** elevated FT4, normal TSH and negative TPOAb – not indicated for the treatment of thyreostatics but is indicated for iodine supplementation.<sup>[1]</sup>
- **Newly diagnosed node** palpation or ultrasound ( $>1$ cm) – endocrinological examination indicated.<sup>[1]</sup>

### Consequences of untreated thyropathies in pregnancy

- Abortions;
- Gestational arterial hypertension;
- Preeclampsia/eclampsia;
- Placental abruption;
- Premature births;
- Higher caesarean section frequency;
- Low birth weight;
- Disorders of embryo, fetus, newborn and child development – especially in the central nervous system;
- Postpartum thyroid dysfunction (postpartum thyroiditis).<sup>[4]</sup>

### Postpartum thyroiditis

- a variant of autoimmune thyroiditis that occurs in the first year after childbirth (even after abortion);
- cause: "Rebound" phenomenon of immunotolerance induced during pregnancy by the presence of an antigenically different fetus in the mother's body;
- risk factors: positive TPOAb, type 1 diabetes mellitus and other autoimmune diseases;
- in women with positive TPOAb and DM type 1, screening for TSH is recommended 3 and 6 months after delivery;
- Clinical manifestation:
  - hyperfunction with transition to hypofunction (about 1/3 of the cases),
  - hyperfunction followed by permanent normalization (about 1/3) – hyperfunction is caused by the destruction of thyroid follicles and the release of thyroid hormones into the circulation, so thyreostatics are not effective; resolves spontaneously in 4-6 weeks,
  - hypofunction (about 1/3) – substitution with levothyroxine and iodine supplementation during breastfeeding.<sup>[4]</sup>

## Thyroidopathy in a newborn

### Congenital hypothyroidism

- the most common congenital endocrine diseases (prevalence 1:3000–4000);<sup>[5]</sup>
- thyroid hormones have a key role in brain development, especially up to 8 months of age (a little less until 3 years of age);
- without substitution therapy, irreversible brain damage occurs – with clinical diagnosis, the brain is already irreversibly damaged;
- since 1985, a nationwide neonatal screening – determination of the level TSH;
- etiopathogenesis: 75–80% of *thyroid dysgenesis* (agenesis, aplasia, hypoplasia, hemithyreoidia, cystic malformation, ectopia) or **dysmorphogenesis** (disorder of any stage of hormone synthesis or secretion; neonatal goiter) or rare **isolated congenital central hypothyroidism** (congenital TSH defect – cannot be detected by neonatal screening);
- clinical picture without treatment: initially only prolonged neonatal icterus (due to transplacental transmission of thyroid hormones from the mother), later (in the first 2-3 months of life) failure to thrive, delayed growth rate and bone maturation – late closure of fontanelles, delayed eruption of milk dentition, macroglossia, muscle hypotonia, omphalocele, constipation, hoarse crying, disorders of thermoregulation, anemia; even later growth disorder, psychomotor retardation, sensorineural hearing impairment;
- neonatal goiter or thyroid gland of normal size;
- 2–5 times increased risk of associated congenital malformations compared to the general population → ultrasound examination of the heart, kidneys and CNS is recommended;
- laboratory findings: ↑TSH, ↓fT<sub>4</sub>; (for the central form ↓TSH i fT<sub>4</sub>);
- therapy: lifelong replacement therapy with levothyroxine (started as soon as possible); intestinal absorption of L-thyroxine is aggravated by simultaneous ingestion of fiber, soy milk, calcium or iron preparations and malabsorption as such.<sup>[6][5]</sup>

### Transient hypothyroidism

- causes:
  - in newborns of some mothers with autoimmune thyroid involvement, transplacentally transferred maternal antibodies inhibiting the TSH receptor may;
  - iodine deficiency of the mother;
  - excess iodide in the perinatal period.<sup>[5]</sup>

### Congenital hyperthyroidism

- a rare disorder that can endanger the life of a newborn;
- etiopathogenesis: transplacental transfer of TSH-receptor-stimulating IgG maternal antibodies (aTSHR, TRAK, TRAb) in maternal thyrotoxicosis of the Graves-Basedow type, but also after conditions after thyroidectomy or radioiodine therapy, because antibodies may persist (*autoimmune neonatal thyrotoxicosis*);
- clinical picture in the fetus: tachycardia, arrhythmia, growth retardation (IUGR), goiter;
- clinical picture in the newborn: goiter, increased excitability, tachycardia, more frequent loose stools, failure to thrive despite normal or increased appetite, insomnia, hypertension, hyperthermia, exophthalmus, hepatomegaly and/or splenomegaly, smaller large fontanelle, accelerated bone maturation;
- risk of metabolic disruption and heart failure;
- in a newborn at risk of transplacental transmission of TRAb, thyroid profile (T<sub>4</sub>, TSH, fT<sub>3</sub>) and TRAb are recommended to be examined from umbilical cord blood and then again during the first and second week of life<sup>[5]</sup>
- laboratory findings: ↑fT<sub>4</sub>;
- therapy: antithyroid therapy (thiamazole) until the disappearance of maternal antibodies, i.e. in a descending dose for 2-3 months; Beta-blockers may be needed to influence tachycardia and adrenergic stimulation; After the end of treatment, long-term follow-up is required.<sup>[5][6]</sup>

### Peripheral resistance to thyroid hormones

- peripheral tissue resistance to thyroid hormones → significant elevations of total and free T<sub>4</sub> and T<sub>3</sub>, with TSH levels slightly elevated or normal;

- the most common cause: genetically determined defect of the  $\beta$  subunit of the nuclear receptor for thyroid hormones;
- clinical manifestations very variable: only biochemical abnormalities, picture of hypothyroidism or hyperthyroidism;
- can be detected by neonatal screening (TSH elevation); Otherwise, the reason for examination is goiter, tachycardia and hyperactivity.<sup>[5]</sup>

## Iodine deficiency

- our natural diet is low in iodine → iodization of table salt from the 50s of the 20th century (now potassium iodate), supplementation of pregnant and lactating women, enrichment of baby and toddler nutrition products;
- slight iodine deficiency → decreased production of thyroid hormones → ↑TSH → iodine goiter → discrete cognitive impairment → worse school performance;
- the most severe form: endemic cretinism – eradicated (severe iodine deficiency of pregnant and lactating women → reduced production of thyroid hormones of the fetus and then the newborn with serious consequences for CNS development).<sup>[5][6]</sup>

## Links

### Related Articles

- Thyroid disease • Children's goiter
- Examination of thyroid function

### External links

- Doporučení České endokrinologické společnosti pro screening tyreopatií v těhotenství (2018) (<http://www.endokrinologie.cz/upload/doporuceni-pro-prevenci-endokrinologove-nahled.pdf>)

### Ref

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