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Hormonal Disorders in the First Year of Children's Life: Causes and Risks of Development

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ABSTRACT

The article discusses the causes and risks of hormonal disorders in children in the first year of life. Normal thyroid function is important for the development of the nervous system in fetuses and newborns. It is known that thyroid hormones play a leading role in the development necessary for the development and maturation of the brain, which continues in the neonatal period. If the functions of the thyroid gland in children with a weight deficit are disrupted in the first months of life, then irreversible damage to CNS may occur, which in the future will lead to the development of mental retardation. However, these complications can be avoided by conducting an appropriate diagnosis in the neonatal period.

The main purpose of diagnosing the disorders discussed above in newborns is to avoid brain damage in patients. In addition to the main goal, it is also possible to ensure the possibility of normal development of children with this diagnosis when conducting timely diagnosis of the disease and taking appropriate measures.

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INTRODUCTION

The increase in the incidence of congenital hypothyroidism (CH) in the world is about 1 case per 1,400-1,700 newborns born alive. Congenital hypothyroidism is one of the preventable causes of mental retardation. Newborn screening was designed to prevent such complications associated with the development of the nervous system. Different methods are used for screening; most newborn screening protocols involve measuring TSH in a dry blood spot sample, others require measuring the level of total thyrotoxin (T4) in a dry blood spot sample and measuring TSH levels based on the results, and others require an initial measurement of both TSH and T4.

MATERIALS AND METHODS

The analytical method and comparative research methods are used in the work. The analysis of sources and literature covering the issues of hormonal disorders in the neonatal period was carried out.

RESULTS

The thyroid gland develops during the entire period of fetal formation. In the first trimester, the T4 circulating in the baby's body comes from the mother, since the baby does not produce enough T4 until the second half of pregnancy. From this point on, there is an increase in the concentration of T4 due to the production of thyroxine-binding globulin (TBG) by the liver and the production of T4 by the fetal thyroid gland stimulated by TSH.

The concentration of T4 increases from 2 mcg/dl at 12 weeks to 10 mcg/ dl in full-term newborns, the concentration of free thyroxine (FT4) from 0.1 ng/ dl at 12 weeks to 2 ng/ dl at term and triiodothyronine (T3)

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and free triiodothyronine (FT3) concentrations do not increase in the fetus due to the activity of placental deiodinase.[1]

In addition, iodine, which is necessary for the fetus to synthesize hormones, comes from the mother and is transferred through the placenta, while the needs of the fetus are 250-300 mcg / day.

The thyroid gland is smaller in premature infants, which leads to a decrease in the production of thyroid hormones and a decrease in the ability to accumulate iodine, which leads to a violation of thyroid function at a time when hormone needs are changing rapidly.

In the period after birth 30-60 minutes, due to the colder environment and the clamping of the umbilical cord, the production of thyrotropin (TSH) by the infant increases to 60-80 mU/L before then decreasing to 20 mU/L after 24 hours and after birth and 6-8 mU/L approximately 1 week after delivery. There is also an increase in T4 and FT4 levels (up to 10-22 mcg/dl and 2-5 ng/dl, respectively) 24-36 hours after birth. T3 levels also increase due to increased secretion and conversion of T4 to T3 in tissues.

Levels of T4, FT4 and T3 gradually decrease in the first 4 weeks after delivery to 7-16 mcg/dl T4, 0.8-2 ng/dl FT4 and 0.5-6 mU/L TSH.

After birth, premature infants also have a similar increase in TSH and thyroid hormone levels, but to a lesser extent compared to full-term infants.[2]

The researchers analyzed changes in the hypothalamus-pituitary-thyroid (HPT) axis in the first 24 hours after birth in infants born at 24 and 34 weeks. They found that the peak of TSH occurring during childbirth was weakened in the group born at 24-27 weeks; T4 levels also decreased in the first 24 hours in this group, whereas it increased in the more mature group. As in full-term infants, T4 values decrease in the first week of life, but this decrease is greater in children with PT and VLBW, since the clearance of T4 occurs faster.

There are several possible causes of thyroid dysfunction in young children:

- Violation of the transmission of maternal T4 through the placenta;
- Limited thyroid reserves due to small size;
- Preservation of the metabolism of thyroid hormones of the fetus;

1. Predisposition to diseases not related to the thyroid gland.

Experts analyzed the thyroid gland function in 75 healthy infants born at 30 to 35 weeks of gestation before the first year of life, compared with full-term children of the same postnatal age. The average concentration of TSH 24 hours after birth in children was significantly lower. In addition, the levels of T4 and T3 at 1 and 24 hours were significantly lower, and the level of reverse triiodothyronine (rT3) at 24 hours was significantly higher in infants on PT. 1 week after delivery, the values obtained in thyroid function tests were in the same range in both groups.

Thyroid function may be impaired in premature infants with hyaline membrane disease or respiratory distress syndrome, manifested in the form of euthyroid disease syndrome. The expected increase in TSH, T4 and T3 concentrations at birth does not occur, and levels may not increase until the baby recovers, and this will happen very slowly. There is also an inverse correlation between FT4 levels and the severity of the disease in these infants.

Premature infants with a weight deficit also show special changes in thyroid function. Their TSH levels increase at birth, but remain within the normal range, and they have higher thyroid hormone needs in the long term, like all premature babies, and therefore they should be monitored at regular intervals.[3]

Maturation of the HPT axis in newborns with PT and SGA with an increase in TSH occurs between 2 and 6 weeks after birth. Despite these differences and the presence of factors affecting thyroid function in premature infants, the thresholds used to diagnose thyroid function are the same as in full-term infants, which increases the likelihood of false negative screening results.

In infants with very low or critical birth weight, thyroid disorders are often observed, such as a delayed increase in thyrotropin levels, transient hypotheroxinemia. These deviations may be temporary or persistent.

In recent years, there has been evidence of an increase in the incidence of CH in premature newborns, which may exceed the incidence in full-term newborns, reaching 1 case per 400 premature births. It is unclear whether this increase is real, or whether it is due to the more frequent detection of moderate or transient forms of such disorders in young children.

Premature babies may experience a delayed increase in TSH levels, and in this case, newborn screening will not detect a problem. There is evidence that newborn screening results may be normal in 5-10% of infants with VLBW or ELBW.

The delay in increasing TSH levels in low-weight newborns has not been fully studied, and the question of whether this is a transient disorder due to immaturity of the axis continues to be discussed.

There are international recommendations for the detection of CH in these cases, among which the following should be highlighted:

1) In a paper published jointly by the American Academy of Pediatrics, the American Thyroid Association and the Lawson Wilkins Pediatric Endocrine Society in 2006, the authors recognized that delayed TSH elevation is more common in premature infants, but also discussed the difficulties of implementing a universal screening program with routine second-sample testing and stated the need for longitudinal studies to assess the long-term results of these measures. An alternative option is to limit this approach to screening to patients at high risk of CH, such as newborns with very low body weight (frequency of CH, 1 case per 250 births), infants with low body weight (frequency of CH, 1 case per 1589 births). In the case of persistent hyperthyrotropinemia after 6 weeks, the guidelines suggest starting treatment and retesting after 3 years;

2) The consensus recommendations of the European Society of Pediatric Endocrinology, published in 2014, recommended re-screening in the following cases:

- Premature newborns with a gestational age of less than 37 weeks;
- newborns with low and very low body weight;
- Sick and premature newborns admitted to the neonatal intensive care unit–
- Collection of samples during the first 24 hours of life;
- Multiple births, especially in the case of same-sex twins.[4]

They recommended taking a second sample 2 weeks after delivery or 2 weeks after the initial screening. However, the authors acknowledged that this approach is not used in every neonatal unit, and stressed the difficulty of implementing the recommendation of repeated testing with venous blood samples instead of samples of dry blood spots.

The data were obtained as a result of the implementation of special programs for repeated screening of thyroid function in premature infants. The observed frequency of CH was higher in newborns after childbirth compared with full-term infants, with a frequency of 1 in 579 births at 32-36 weeks of gestation compared with 1 in 1488 births at 37 weeks or more.

The incidence was higher in infants born at 32 weeks or earlier: 1.56% among infants with low birth weight, 1.9% among infants with very low birth weight and 3.7% among infants with low birth weight.

These studies have found application in clinical practice. For example, one group of researchers collected whole blood samples weekly for 37 weeks after the adjusted age or discharge from the hospital. The authors emphasized that 27 (50.9%) infants born before 33 weeks of gestation and diagnosed with CH had a delayed increase in TSH levels detected between 8 and 48 days after birth (an average of 13 days), which would not have been detected at the initial stage. From all these patients, 12 (40.7%) had decompensated hypothyroidism (FT4 <10 pmol/L) and 4 had severe hypothyroidism (FT4 <5.5 pmol/L). In this study, repeated screening was also analyzed, as a result of which 6 cases (22%) of permanent high blood pressure and 8 (29%) of transient high blood pressure were identified. In 13 newborns (48%), an increase in TSH levels was detected after 15 days, and in 7 of them the FT4 concentration was below 10 pmol / L. In addition, 25% of infants with a delayed increase in TSH levels were exposed to iodine.[5]

Another group of authors screened blood samples from the heel injection after 2 weeks, 4 weeks and at discharge with testing of venous samples for confirmation. They diagnosed high blood pressure in 49 newborns, 92% of whom had a delayed increase in TSH levels. Testing of samples obtained after 2 weeks revealed the majority of cases (n = 18), and it is worth noting that in 15 patients the concentration of TSH was higher than 100 mU/L, and that in 1 patient with an early increase in TSH and in 19 patients with a delayed increase in TSH was free, the concentration was T4 less than 0.8 ng/dl, which apparently justifies monitoring with repeated testing at different points in time.[6]

Thus, given the high incidence of abnormalities in these patients and the potential impact on their outcomes, it seems reasonable to recommend a reassessment of thyroid function and patient follow-up, since the long-term impact of diagnosis or treatment in these cases is unknown.

Transient hyperthyroidism can be caused by various factors: maternal thyroid disease (treatment of the mother with antithyroid drugs, transfer of maternal antibodies to the TSH receptor, gene variants (heterozygous variants of the *DUOX-2* gene or the *TSHR* gene encoding the TSH receptor), prenatal/postpartum exposure to high doses of iodine (povidone-iodine, iodine-containing contrast agents), areas of natural iodine deficiency, factors associated with the severity of the disease or the use of drugs listed in Table 1.

In recent years, improvements in the treatment and management of perinatal diseases (antenatal steroid therapy, non-invasive ventilation, reduction in the use of pharmaceuticals, etc.) have reduced the incidence of hypothyroxinemia in premature infants and delayed hyperthyrotropinemia in infants with extremely severe course.

A steady increase 2 weeks after delivery at a TSH concentration of more than 10 mU/L or a FT4 concentration of less than 0.8 ng/dl is an indication for treatment recognized in most guidelines. There is less consensus on the approach to intermediate TSH values from 6 to 10 mU/L, which will depend on several factors, and in these cases the decision is made jointly by the doctor and parents.[7]

According to the agreed recommendations of the European Thyroid Association, infants with persistent TSH concentrations above 10 mU/L about 1 month after birth are eligible for treatment under the age of 3 years with subsequent reassessment. Thyroid imaging is recommended to assess the presence of structural abnormalities that confirm the diagnosis of permanent hypertension. Identification of genetic changes associated with hyperthyrotropinemia can also determine the decision on treatment and predict the course of the disease. Genetic research is widely used in other areas of medical practice, and fundamental developments that are relevant today.[8-11]

DISCUSSION

Premature newborns are more likely to develop hypothyroxinemia (low T4 / FT4, normal TSH), which is detected in the first weeks of life in almost 50% of children born before 28

Table 1: Medications that affect thyroid function

Decrease or increase in thyroid hormone secretion	*Medicinal preparations*
Reduces TSH secretion	Iodine
	Amiodaronum
Increase TBG (Trophoblastic beta 1-glycoprotein) concentration	Estrogens
Reduce TBG (Trophoblastic beta 1-glycoprotein) concentration	Glucocorticoids
Displacement of the protein binding site	Furosemide
	Salicylate
Increases metabolism in the liver	Phenobarbital
	Phenytoin
	Carbamazepine
Decreased activity of T4 5'-deiodinase	Propylthiouracil
	Amiodaronum
	Beta blockers
	Glucocorticoids

weeks. Such children may have neonatal conditions associated with abnormal thyroxine concentrations:

- Acute respiratory distress syndrome;
- Bronchopulmonary dysplasia;
- Sepsis with early and late onset;
- Pneumothorax;
- Asphyxia;
- Persistent pulmonary hypertension;
- Necrotizing enterocolitis;
- Open arterial duct.

Most cases are transient, but in the early stages it may not be easy for a clinician to determine whether hypothyroxinemia represents a secondary or tertiary form of hypothyroidism (hypothalamic-pituitary) or is caused by a deficiency of TBG (Thyroxine-binding globulin). Current scientific evidence is also insufficient to prove that levothyroxine for the treatment of hypothyroxinemia in newborn infants can improve long-term outcomes of the development of the nervous system.

There are several randomized trials conducted on small samples (10-100 premature infants), with heterogeneity in the characteristics of the participants and the protocols used (levothyroxine doses range from 4 to 20 mcg/ kg/day, duration from 2 to 6). weeks), which makes it difficult to interpret the data.

Some evidence suggests that hormone replacement therapy may be useful for children with an extremely severe phase of pregnancy. Other studies have found a link between T4/ T3 levels and patient outcomes (mortality, cardiovascular complications, etc.), although it would be difficult to establish a causal relationship.

Thyroxine treatment remains controversial, and the available data do not support the recommendation of its continued use for the treatment of children with transient hypothyroxinemia. More data is needed to determine the cases in which treatment may be beneficial, the best time to start treatment and its ideal duration based on optimal thresholds for circulating thyroid hormone levels.

Some authors recommend starting treatment in the case of hypothyroxinemia associated with an increased TSH concentration of more than 10 mU/L or a persistent increase (FT4 <0.8 ng / dl in two dimensions with an interval of 1-2 weeks) with a decision to treat on an individual basis in high-risk patients, such as infants born before 28 weeks of pregnancy or with a body weight of less than 1000 g, especially with severe disease.[12]

It is important to differentiate transient hypothyroxinemia of premature infants from hypothyroxinemia associated with abnormalities in the hypothalamic-pituitary axis. Persistent low FT4 levels combined with TSH levels below or below normal indicate a central CH. This is most often associated with another pituitary hormone deficiency (congenital panhypopituitarism) and can manifest itself with prolonged neonatal hypoglycemia and prolonged jaundice. There is also the possibility of isolated central hypothyroidism, which occurs infrequently, with a frequency of 1 in 30,000 births and cannot be detected by screening newborns for TSH levels.

After analyzing the specific characteristics of thyroid function in premature newborns, it becomes obvious that screening for hypothyroidism is different than in full-term infants.

The authors recommend measuring thyroid hormone levels (TSH/FT4) in venous blood samples after 2 weeks, 4 weeks after reaching a weight of 1500 g or at discharge. In addition, the researchers recommend repeated testing in infants weighing ≥ 1500 g if they continue to be in critical condition. Ideally, screening will consist of measuring TSH and FT4 in venous blood or measuring TSH in a dry blood spot in centers where this method is available.[13]

Risk factors for CH should be assessed, and therefore it is important to learn about the use of medications that may affect thyroid function, about the use of povidone-iodine or iodine-containing contrast. The examination is completed by testing free T4, but the start of treatment is not postponed, at the same time, the thyroid gland should be visualized using scintigraphy (with or without a perchlorate isolation test), ultrasound or both.

It is also necessary to re-evaluate in case of TSH concentration in veins from 10 to 20 mU/L. Since some cases are temporary, repeated testing is recommended after 1-2 weeks, considering the possibility of treatment if abnormal results persist.

If abnormal results persist at a TSH concentration of 5-10 mU/L 3-4 weeks after delivery or before discharge, it is necessary to expand the examination (thyroid imaging, serum thyroglobulin) and consider treatment with levothyroxine with repeated testing at the age of 2 years. or 3 years or even earlier in patients with a need for levothyroxine of less than 3 mcg/kg/ day, given that many of these cases are temporary.

CONCLUSION

Thus, it can be concluded that infants born before 32 weeks of pregnancy and infants with low body weight are at risk of thyroid dysfunction. The normal concentration of TSH during newborn screening, carried out in the first days after birth, does not exclude CH in newborns.

Due to the risk of false negative results of the examination of newborns for CH and the risk of thyroid dysfunction, it is necessary to repeat the examination 2 weeks after delivery, 4 weeks after delivery, when reaching a weight of 1500 g or at discharge.

Current data do not support the recommendation for mandatory treatment of transient hypothyroxinemia in infants on PN. Initiation of treatment is recommended in cases where hypothyroxinemia is associated with an increase in TSH above 10 IU/L or a persistent increase in TSH, with individual treatment of premature newborns with a serious disease from a high-risk group.

A TSH concentration of 20 mU/L or higher in combination with any FT4 concentration is considered a violation and requires treatment at a dose of 10-15 mcg / kg / day. TSH levels from 10 to 20 mU/L at normal FT4 levels require reassessment with a more thorough examination by an endocrinologist (including imaging) and consideration of the possibility of treatment if they persist.

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