ASSOCIATION OF THYROID GLAND DISEASES WITH INTRAUTERINE GROWTH RETARDATION AND FETAL HYPOTROPHY

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Introduction

Hormones of thyroid gland are exceptionally important for normal growth and development of fetus. Thyroid dysfunction of mother can cause severe structural and functional defects of all organs and their function in developing fetus [1]. Particularly sensitive to thyroid function during fetal development is the central nervous system and disturbances of iodine metabolism and thyroid gland function may lead to irreversible neurological damage and mental retardation. One of the serious complications of fetal development associated with thyroid gland diseases is fetal hypotrophy [2].

Fetal hypotrophy (FH) is defined as nonspecific abnormal state of fetus, characterized by growth retardation, nutritional and metabolic defects and chronic hypoxia of fetus. In clinical practice hypotrophy of fetus is defined primarily as weight retardation below the lower margin of the corresponding gestation age. Hypothrophic newborns can be born premature but also in normal delivery term [3, 4].

Marginal values of newborn weight are defined variously by different authors. Some consider it to be below the 5th or 10th percentile of birth weight growth charts and tables. Other authors consider hypotrophy as the arithmetic average minus 2 sigma values and below. Length of newborn fetus and head circumference are used as supplementary criteria. All these parameters are assessed separately by the gender of fetus.

Intrauterine growth retardation (IUGR) is a term associated with fetal hypotrophy but it includes also the developmental aspect. IUGR is defined as “insufficient growth of fetus in relation to length of gravidity” while the term fetal hypotrophy is defined as “complex intrauterine restriction with regard to not only growth but also metabolism and organ functionality”.

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Classification, etiology and consequences of fetal hypotrophy

Fetal hypotrophy can be classified according to its morphology and timing (type I–III) and according to its etiology (maternal, fetal, placental and environmental causes).

Morphological classification

Type I – symmetric, proportional, chronic hypotrophy is caused by insufficient multiplication of cells of fetus and/or placenta function. Fetus suffers from growth restriction from the conception. Growth potential of the whole fetal body is decreased. The condition is evident as IUGR from the 1st trimester.

Type II – asymmetric, disproportional hypotrophy. The condition affects mostly the size of cells and only in lesser amount their number. Retardation concerns primarily the body of fetus, especially the subcutaneous fat and muscles. The growth of head is affected to a lesser extent. This irregular growth restriction of fetus is evident mainly from the 3rd trimester.

Type III – intermediary or mixed hypotrophy is a combination of the two above-mentioned types. Begins during the 2nd trimester, becomes evident usually during the last two to three weeks before delivery.

Etiological classification

The most frequent causes (40% of all cases) of fetal hypotrophy are diseases of the mother [5]. Among them heart disease, hypertension, kidney disease, preeclampsia, thyroid gland diseases, immunological dysfunctions and intrauterine infections are the most common [6–9]. In addition to diseases low or high age of the mother and genetic/epigenetic factors can cause fetal hypotrophy, too. There are also ethnic differences in fetal growth and birth weight but without increased risk of perinatal mortality and morbidity [10] and therefore these are not considered as true hypotrophy.

Fetal causes. Hypotrophy of fetus in healthy mothers and normal placental function may be caused be malformations, chromosome aberrations, inborn anomalies, developmental defects, fetus immaturity and infections (mainly viral) of the fetus. In these cases hypotrophy is only the nonspecific feature of the basic pathological conditions characterized by specific signs. Growth retardation is observed relatively often during multiple pregnancies but in these cases relative placental insufficiency can be present as well [11, 12].

Placental causes. Deficiency of utero-placentary circulation influences the growth of fetus. They can be caused by anatomical irregularities of the uterus and placenta as well as functional defects. Blood vessel diseases of the mother can also decrease utero-placentary perfusion. Absence of one umbilical artery in fetus leads to a serious defect of circulation, too [13].

Environmental factors. Impact of environment in fetal hypotrophy is evident in different forms of dangerous substance abuse as nicotine, alcohol and drugs. In addition cumulative low-dose intoxications with heavy metals like lead, mercury and cadmium, which cross and accumulate in placenta may have negative effect and cause growth retardation. Probably
many other so far unexplained causes including epigenetic factors may contribute to hypotrophy of fetus [14, 15].

Some marginalized groups of population (as the Romani in Central and East Europe) living in poverty and unhealthy conditions are also endangered with fetal hypotrophy by a complex influence of above mentioned factors [16].

Consequences of FH

Growth retardation of fetus is a serious medical problem. It is the most common cause of delivery of a dead newborn. Perinatal mortality of hypotrophic neonates is 8 times higher compared to normal newborns and they suffer from 10 times more from different health problems. This is the reason why observation of fetal growth is important and in case of inadequate development the cause must be identified as soon as possible [17].

Thyroid disorders occurring in fertile period of women associated with IUGR and hypotrophy

Thyroid disorders can be classified according to their morphology (struma) and function (hypo- and hyperfunction). Endemic struma in our region was practically eradicated in the second half of the last century but the possibility of sporadic and/or clinically latent forms cannot be excluded. These can be the consequence of marginal iodine deficiency (and the iodine requirement in gravidity is increased), environmental factors as low dose cumulative accumulation of polychlorinated biphenyls and also smoking [18, 19].

The prevalence of primary (peripheral) hypothyrosis in our region is relatively high and affects women in fertile age. Its most frequent cause is the autoimmune Hashimoto thyroiditis. Secondary (central, hypophyseal) hypofunction caused by destruction of TSH producing cells or tumors is rare.

Hyperthyrosis (Table 1) is mostly occurring as Graves-Basedow disease (60%–85% of all hyperfunctions). It is more common in women and the peak of its manifestation is around the 3rd and 4th decennium. The other cases are connected to the first phase of Hashimoto thyroiditis, Plummer's toxic struma, other inflammatory diseases of thyroid and rarely to hypophyseal overproduction of TSH.

In addition to diseases occurring independently on gestation there are two gravidity specific disturbances of thyroid dysfunction: Gestational transient hyperthyroidism and postpartal thyroiditis. Only the first condition can affect the development of the fetus.

Transitory gestational thyroid hyperfunction is manifesting mostly around the end of the 1st trimester and is often associated with hyperemesis gravidarum. Its pathogenesis is associated with the thyrotropin receptor stimulating effect of choriogonadotropin (hCG) [20]. The differential diagnosis between Graves-Basedow disease and the transitory gestational hyperthyrosis is important not only from the aspect of different treatment and prognosis but also because they have different impact on fetus growth and development. According to [21] gestational hyperthyrosis is induced mainly through the “asialo” form of hCG. This can make a diagnostic problem because standard hCG assays do not detect this form of the hormone. Lack of ophthalmic symptoms and autoantibodies are important features in the differential diagnosis of the two conditions. Antithyroid hormone treatment in gestational hyperthyrosis can be even harmful because in can lead to hypothyroidism.
Postpartal thyroiditis is manifesting between 6th week and 3rd month after delivery and affects 8–10% women after childbirth [22 Gregory Becks a Gerard Bierow]. It can lead to hypothyroidism later and the condition is more frequent in women with type 1 diabetes mellitus as compared to the non-diabetic population. Although it cannot harm the fetus development its can be a warning sign of possible latent thyroid disorder. Careful examination of thyroid function is fully warranted in these women because the recidive rate of this condition is as high as 70% and therefore it can affect the fetus in the next pregnancy.

Table 1

<table>
<thead>
<tr>
<th>Hypothyrosis: 1-2/1000</th>
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<tr>
<td>Women/men: 2-8/1</td>
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<tr>
<td>Age dependent increase up to 20/1000, mostly in women</td>
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<tr>
<td>Unknown number of clinically not manifest cases.</td>
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</table>

| Hyperthyrosis: 27/1000 women, 1.6 – 2.3/1000 men |

FH associated with thyroid dysfunction of the mother

Hypofunction of the thyroid gland is unambiguously associated with IUGR [23–24] but also thyrotoxicosis can be harmful for the developing fetus although in this case the connection is not straightforward. One possibility is the effect of antithyroidal drugs crossing the placenta but according to [25] also thyroid stimulating autoantibodies can cross the placental barrier.

Kilby et al. [26] examined the function of thyroid gland in fetuses and the placcental expression of thyroid hormone receptors in women with normal gravidity and in women where gravidity was associated with IUGR. In the group of normal gravidity an increase of free thyroid hormones (FT_4 and FT_3) was observed between the 2nd and the 3rd trimester, while fetuses in IUGR group had serum concentration FT_4 and FT_3 significantly lower in the same period. Levels of serum TSH exhibited no notable difference between the two groups.

Immunocytochemical examination of placenta revealed differences in the expression for thyroid hormones alpha1, alpha2 and beta1. In normal placenta levels of all receptors increased alongside with advancing gravidity and the increase was significantly higher in placenta from women with IUGR fetuses. This study unveils the tight association between thyroid metabolism of mother and fetus a hitherto not fully elucidated topic [27].

In accordance with these findings are also results of investigations which proved that IUGR is associated with altered thyroid function [28]. In a study of blood samples from 49 small fetuses between the 21st and the 38th week of gestation significantly increased TSH levels were accompanied by decreased FT_4. The hormone level was associated with the degree of hypoxemia and acidemia of fetuses with IUGR [29]. Preterm infants also exhibit low levels of T_3 and T_4 in umbilical cord blood and they remain low during the first two to three weeks of life. This is case of temporary hypothyroxinemia or temporary
hypothyroidism in preterm newborns [30]. The condition is more serious the more premature the delivery was. With time the levels are adjusted to the values of those newborns from normal deliveries. The significance of this hypothyroxinemia in preterm period (without increase of serum TSH) remains controversial. However, serious hypothyroxinemia is invariably specifically associated with restricted development.

Ligand binding studies have revealed presence of high affinity nuclear receptors for $T_3$ in placenta and human fetal brain after the 10th week of gestation. It was confirmed that $T_3$ in human placenta stimulates production of 17-estradiol and epidermal growth factor. This suggests an important role of thyroid hormones in trophoblast development and a possibility of the alteration of this function during IUGR [32].

**Conclusion**

The association between the normal (and abnormal) thyroid function and fetal growth and development is a very important but not fully elucidated one. There are huge gaps in our understanding of the fetal thyroid development and its association with the iodine metabolism and thyroid function of the mother.

From practical point of view the situation is less complicated. Thorough investigation of the thyroid function in all cases with imminent or manifest IUGR as well as careful monitoring of fetal growth in all women with thyroid dysfunction together with subsequent therapeutic intervention can prevent any unwanted pathological condition of mother and fetus in these conditions.

**Abbreviations**

<table>
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<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>FH</td>
<td>Fetal hypotrophy</td>
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<td>IUGR</td>
<td>Intrauterine growth retardation</td>
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<tr>
<td>TSH</td>
<td>Thyroid stimulating hormone</td>
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<tr>
<td>T3, T4, FT3, FT4</td>
<td>Trijodthyronine (thyroxine), Tetrajodthyronine and their free forms</td>
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<td>hCG</td>
<td>Human chorionogonadotropic hormone</td>
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<td>TBG</td>
<td>Thyroid hormone binding globulin</td>
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**References**


