

Iodine intake and neonatal thyroid function: A never-ending story

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ABSTRACT

Iodine deficiency in pregnant women can lead to abortion, dysgravidy, intrauterine growth restriction, premature birth, low birth weight, which places the pregnant woman in a group with increased vulnerability to the lack of adequate amounts of iodine. Iodine deficiency in pregnancy can lead to increased perinatal and infant mortality and the prevalence of congenital anomalies. All these aspects shed new light on the many side effects of iodine deficiency during pregnancy. The present paper aligns with the general trend of assessing the maternal-fetal thyroid hormone status and establishing the most accurate indicators for its quantification and taking into account the degree of iodine deficiency and prematurity.

Keywords: iodine intake, thyroid function, neonatal

INTRODUCTION

Thyroid hormones were the first hormones to appear on the evolutionary scale, being the first to occur during fetal development (1). Almost simultaneously with the development of the thyroid gland, the development of the central nervous system begins since the nerve cells are supplied with a constant reserve of thyroxine, which in turn is dependent on a constant supply of iodine (2).

Since the thyroid first appears in the development of the fetal endocrine system, it can be hypothesized that thyroxine is involved in controlling all endocrine organs, as is expected if the thyroid controls the genome (3).

Pregnancy is characterized by several important hormonal changes that result in an increase in iodine requirements, especially in iodine-deficient countries, translated into an increase in thyroid volume, according to studies by Rasmussen, Glinoyer, and Filteau (4-6). Glinoyer showed that hormonal changes play an important role in producing thy-

roid hormones, which depend on increased iodine intake (2).

Pregnancy increases maternal T4 requirements, causing a 25-50% increase in maternal T4 production in euthyroid women. In women with hypothyroidism or in women from endemic regions with iodine deficiency, the normal development of the fetal brain requires the maintenance of maternal free T4 serum concentrations during gestation by supplementation with iodine. The transplacental passage of T4 does not seem to be sufficient in all cases to protect the brain of fetuses with hypothyroidism. In this situation, early intensive treatment of newborns with obvious signs of intrauterine hypothyroidism will lead to normalization of IQ levels in childhood. Thus, the placental barrier of maternal iodothyronines, even in the third trimester of pregnancy, does not appear to be impermeable to the transplacental passage of maternal thyroid hormones (7,8).

Even in small quantities, these concentrations can represent a significant source of thyroid hor-

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mones qualitatively to ensure adequate development of the maternal-fetal unit. Its most important function is the transplacental transport of both hormones from mother to fetus and thyroid and adrenal function substances.

Garnica and Chan suggested that placental activity is modulated by fetal signals, this interrelationship being well highlighted in intrauterine growth restriction (IUGR). Regardless of the low placental permeability to thyroid hormones, the rate of thyroid hormone transfer from mother to fetus has been found to be altered by several factors, such as protein that binds thyroid hormones in maternal serum, maternal thyroid status, impaired fetal thyroid function, the stage of gestation (transfer of thyroid hormones before the onset of fetal thyroid function and near term), and the intensity of enzymatic deiodination of iodothyronine in the placental tissues (9).

The autonomy of the fetal pituitary-thyroid axis does not seem to be completely independent of the status of the maternal thyroid and the transfer of maternal thyroid hormones, which can occur when the fetal thyroid is affected. These results support the hypothesis that enzymatic deiodination of thyroid hormones forms a barrier that reduces the transplacental passage of hormones, and the fetal slope of the placenta is the primary factor in the mechanism of hormone transfer regulation (10,11).

Despite the presence of the barrier, there is an adequate maternal supply of thyroid hormones to the fetus at the beginning of pregnancy, which suggests that the enzymatic mechanism is influenced to some extent by the thyroid status of the fetus. The presence of type III deiodinase at the maternal-fetal interface modulates the thyroid status of the human fetus, and the expression at the endometrium suggests the important local regulation of thyroid status in the implantation process. Pregnancy is characterized by maternal-fetal gradients of free T4 and T3, attributed to the placental expression of type III deiodinase (D3) (12).

Thus, the development of the fetal thyroid is mainly independent of maternal influences. Even the limited transfer of thyroid hormones from mother to fetus can protect the fetus from hypothyroidism. At the level of placental tissues by the local conversion of T4 to T3, T4 to rT3, and T3 to T2, better regulation is made regarding the exposure of the fetus to the action of maternal thyroid hormones. It also provides a source of iodine for the needs of the fetus. At the fetal level, rT3 is the major metabolite of T4, produced by deiodination of the inner ring of T4 by deiodinase III. The concentration of rT3 in the fetal serum is three times higher than the maternal serum concentration (12).

Fisher showed that circulating thyroid hormones in the fetus are both maternal and fetal, and

their presence depends on the proper functioning of the placenta for the transport of T4 and an adequate supply of iodine. Most of T4 is diverted in the placenta, but significant amounts of T4 are still transferred (13).

According to the studies of Polk et al. the placenta is permeable to iodine and TRH but impermeable to TSH (14). Maternal HRT plays an important role in controlling fetal thyroid function before the maturation of the near-term hypothalamic-pituitary-thyroid axis. The placenta is relatively impermeable to thyroid hormones under euthyroid conditions. The free fraction of T4 proved to favor this transfer. During pregnancy, fetal serum levels of T3 and the free fraction of T3 are lower than maternal levels (7,15,16).

FETAL THYROID HORMONES AND PREGNANCY

The physiology of the maternal and fetal thyroid differs, but the systems interact through the placenta and amniotic fluid, which modulate the transfer of iodine and minimal but functionally important amounts of thyroid hormones from mother to fetus (3).

During trimesters 2 and 3, marked maternal-fetal gradients of T4 and T3 free fractions were observed. T3 seems to cross the placenta more easily than T4; therefore, serum fetal T3 concentrations are normally low. Transplacental transfer of thyroid hormones to the fetus has been shown to be of particular importance, but this passage is not quantitative enough, acting more as a trigger for fetal thyroid development.

The logical explanation in clinical trials of the T4 passage may be due to thyroid status, which probably regulates T4 transfer by modulating placental enzymatic activity. Another explanation would be the transfer of T4 via the extraplacental chorioamniotic pathway.

In the period before the onset of fetal thyroid function, the transfer of T4 from mother to fetus has been estimated that more than 40% of the T4 value measured at birth in the umbilical cord is still of maternal origin.

Iodine transfer is difficult to quantify, but it is considered that the iodine contained in the fetal thyroid increases progressively from less than 2 µg at 17 weeks of gestation to more than 300 µg at term, so that at term the iodine responsible for T4 is likely to increase at a value of 500 µg, and the substitute dose of T4 in hypothyroid newborns is 50-75 µg/day, and it can be estimated that the transfer of iodine from mother to fetus is about 50 µg/day. It has been estimated at 75 µg/day by the WHO (17,18).

Clinical studies have shown the possibility of sporadic hypothyroidism in the fetuses of mothers

with normal thyroid function, suggesting that the transfer of thyroid hormones from mother to fetus cannot prevent the onset of fetal hypothyroidism. Measurements of the total umbilical cord T4 in newborns with thyroid atresia showed that T4 levels are about 30% of those found in normal newborns. This supports the idea of maternal thyroid hormone transfer to the fetus throughout pregnancy.

Late in pregnancy, the fetal swallowing process is thought to be responsible for most of the thyroid hormones transferred from amniotic fluid to the fetal circulation (7,19,20).

The fetal thyroid function is autonomous, as evidenced by the “impermeability” of the placenta for thyroid hormones and TSH. The human placenta actively accumulates iodine on the fetal side so that during the second and third trimesters, the fetal thyroid concentrates iodine in a much larger amount than the maternal thyroid.

Decreased thyroid hormone levels delay brain biochemical maturation, with decreased brain oxidative enzymes and myelin synthesis. According to research by Hetzel’s team, iodine deficiency decreases the transfer of maternal thyroid hormones to the fetal brain in the first months of pregnancy. In addition, serum concentrations of free T4 increase between 18-20 and 35-37 weeks of pregnancy, an increase caused by increased secretion of thyroid hormones. These changes in serum thyrotropin and free T4 levels were caused by increased pituitary thyrotropin stimulation by TRH and increased thyroid sensitivity to thyrotropin (3,21).

Monitoring of a fetus at risk of thyroid dysfunction is performed by performing ultrasound examinations, which may reveal the presence of fetal goiter. The clinical relevance of this finding is that the presence of goiter can be an obstacle to the upper airways during expulsion. Cordocentesis is used to determine the fetal thyroid status and is used for a correct assessment of girls at risk of thyroid dysfunction.

Thyroid hormones are essential for fetal and neonatal development, but little is known about their role during pregnancy. They are necessary for the development of the fetal brain, for the maturation of other organs and systems, some being important in achieving a better transition to extrauterine life. The end of the second trimester and the beginning of the third trimester represent a critical transition period of the metabolism of fetal thyroid hormones, which can be interrupted by premature birth, thus contributing to postnatal thyroid dysfunction. Maternal-fetal T4 transfer during pregnancy is essential before the fetal hypothalamic-pituitary-thyroid axis becomes effective and can continue to varying degrees throughout pregnancy.

The postnatal response of the hypothalamic-pituitary-thyroid axis to preterm infants generally follows a pattern described in full-term infants, albeit in an attenuated manner. In preterm infants, Jacobsen et al. have indicated that TRH stimulates TSH secretion at week 20 of pregnancy, indicating the presence of pituitary TRH receptors beginning at this gestational age.

Thyroid stress can be detected, and the size of the thyroid gland can be measured using ultrasound. Thyroid enlargement of physiological causes found in areas with low iodine intake occurs during childbirth. These hypertrophies are good indicators of iodine supplementation, indicating the degree of iodine deficiency, but at the same time illustrating the increased need for thyroid hormones during the period of physiological stress, which occurs during intrauterine life.

IODINE AND NEONATAL THYROID PHYSIOLOGY

Iodine is both an essential element in the biosynthesis of thyroid hormones and an antioxidant. In the body, the transport of iodine in the thyroid gland is under the action of enzymes such as: Na⁺/K⁺ATPase, sodium iodine symporter, and apical iodine transporter (22). The World Health Organization has been implementing the iodine prophylaxis strategy since 1991, under the name of universal salt iodination (23).

The main functions of iodine in the human body are: use for the production of thyroid hormones, trigger of apoptosis (cell death programming) in normal and abnormal cells – fetal source of apoptotic mechanisms during fetal development, reacts with tyrosine and histidine to inactivate enzymes and denature proteins, possible initial source of thyroxine in early fetal development.

In pregnant women, renal clearance of iodine increases due to increased glomerular filtration rate, and iodine and iodothyronine are transferred to the fetus. As a result, serum concentrations of inorganic iodine decrease. Women living in areas where iodine intake is at the limit (< 50 µg per day) may have an absolute or relative iodine deficiency, as well as thyroid goiter. Even in areas without iodine deficiency, thyroid volume increases by 10-20% during pregnancy. Fetal needs increase iodine levels as fetal thyroid hormone production increases in the second half of pregnancy. In addition to transporting iodine along the placenta, monodeiodination of placental iodothyronines provides increased amounts of iodine to the fetus as the placenta enlarges (5,24,25).

Early pregnancy increases renal blood flow and glomerular filtration, leading to an increase in plasma iodine clearance. This results in a decrease in

plasma iodine concentrations and an increase in iodine requirements in the diet. In women with iodine deficiency, it is a problem in terms of thyroid function due to the mandatory increase in renal iodine losses because the intrathyroid deposits of iodine are full at the time of conception and remain unchanged during pregnancy.

Maternal and fetal thyroid physiology differ, but the systems interact through the placenta and amniotic fluid, which modulate the transfer of iodine and small but important amounts of thyroid hormones from mother to fetus. The immediate neonatal needs of thyroxine, and implicitly those of iodine, are increased in relation to the calculated intrathyroidal reserve of thyroid hormones which is low.

Intrathyroid regeneration of T4 requires adequate and rapid iodine supplementation, but the concentration of iodine and thyroglobulin in the thyroid of preterm infants is low and does not increase until the age of 42 weeks of pregnancy. The iodine content of thyroglobulin in the thyroid gland is related to maternal iodine status, and the potential iodine reserves of premature infants may be decreased in iodine-deficient mothers.

The recommended dose of iodine in preterm infants is 30 mg/kg/day, and an increase in dose to 40-50 mg iodine/kg/day in high-grade preterm infants does not affect serum iodothyronine levels (21,24,26).

Plasma inorganic iodine (PII) concentrations, 24-hour urinary iodine levels, and thyroid function (total T4, thyroglobulin-TBG, and TSH) were measured in several pregnant women. The results showed a wide variability of PII values and urinary iodine concentrations, but there was no tendency for PII concentrations to decrease during pregnancy. In regions without iodine deficiency, pregnancy has no major influence on circulating iodine levels. In regions where iodine intake is near or low, the situation is different, and significant changes occur during pregnancy. In addition, there is an increase in iodine requirements due to the transplacental transfer of iodine required for iodothyronine synthesis by the fetal thyroid, which becomes progressively functional after the first trimester (27,28).

The need to increase iodine intake has been demonstrated in many studies; thus, a pregnancy evolved in the conditions of a borderline iodine intake, the reason for which there were increases of both the volume of the maternal thyroid and of the fetal thyroid, in case it was not supplemented with iodine during the pregnancy. This is in opposition to the idea that there may be a small change in the fetal thyroid during pregnancy in regions without iodine deficiency.

If there is an adequate iodine intake in pregnant women, with a median urinary iodine concentra-

tion of 100-150 µg/l, the profile associations in the USA and Europe recommend supplementation, while the WHO recommends an iodine intake of 250 µg/day (29).

Iodine transfer is difficult to express, but it is considered that the iodine content of the fetal thyroid increases progressively from < 2 µg at 17 weeks of gestation to > 300 µg at term so that at term the average concentration of T4 is about 500 µg. The estimated daily transfer of iodine from mother to fetus is 50 µg.

THE FETAL THYROID AND FETAL DEVELOPMENT

The fetal thyroid is extremely sensitive to the inhibitory effect of iodine, and iodine contamination is the major cause of transient neonatal hypothyroidism. Therefore, in the absence of other sources of iodine, premature infants who are dependent on parenteral nutrition are now vulnerable to iodine deficiency.

The fetal thyroid by week 20 is totally dependent on maternal thyroxine intake, not being fully functionally active. As a result, maternal thyroxine production increases 1.5 times (30). The daily requirements for T4 to maintain euthyroid status in hypothyroid women should be increased from 10 to 150% during pregnancy, with an average value of 40-50%. This represents a daily supplement of T4 between 75 and 150 µg, which in terms of iodine intake corresponds to a dose of 50-100 µg.

Transfer of T4 from mother to fetus before the onset of fetal thyroid function has not been quantified. It has been estimated that more than 40% of the T4 measured from the umbilical cord at birth is still of maternal origin.

In full-term infants, the serum level of thyroxine (T4) increases postnatal, while in preterm infants, especially in high-grade preterm infants (< 30 weeks gestation), the serum level of T4 may decrease transiently, which results in a period characterized by hypothyroidism. In addition, hypothyroidism is associated with increased perinatal mortality and morbidity, prolonged oxygen therapy and mechanical ventilation, increased incidence of ventricular hemorrhage, and cerebral white matter lesions (10).

According to Hill's research, fetal development and growth depend on endocrine, paracrine, and autocrine mechanisms that occur in the fetoplacental unit. Insufficiency of this fetoplacental unit results in IUGR, with fetuses having a cerebral weight relative to that of the body, while other organs such as the liver are significantly reduced. Kilby et al. have shown in utero that fetuses with IUGR have significantly lower blood levels of free T4, free T3, and a small increase in TSH (31).

Klein et al. have shown that very low birth weight infants have low serum T3 and T4 concen-

trations (32). According to the studies of Kilby et al. this is accompanied by a reduction in the expression of all forms of thyroid hormone receptors in the cerebellum and cortical substance in girls with IUGR. Premature infants less than 30 weeks gestational age (not necessarily with IUGR) may have a period of hypothyroidism with a serum collapse of the T4-free fraction without an increase in TSH (31).

According to data provided by Van Wassenaer et al., these newborns have problems with self-regulation of iodine intake in the thyroid and immaturity of the hypothalamic-pituitary-thyroid axis, which results in the inability to compensate for the loss of maternal T4 intake in a short time (21). Comparing the concentrations of the free T4 fraction of premature newborns with those of fetuses *in utero*, with the same gestational age, Ares et al observed a difference of 50% smaller, a phenomenon that is not observed in full-term newborns (33).

Chowdhry et al. have shown that this difference is carefully viewed by many neonatologists as a physiological response, because the additional intake of thyroid hormones in premature infants has not shown any clear benefit in long-term neuropsychiatric development (34).

It is well established that the thyroid status of newborns has a significant long-term impact on their behavior, locomotor ability, speech, hearing and knowledge. Delaying the restoration of thyroid hormonal status in newborns can lead to irreversible disorders. Prompt thyroid supplementation resulting from the diagnosis of neonatal hypothyroidism may restore neuronal development to normal values. These imply that the brain's development may be partly due to sensitivity to the action of thyroid hormones in the neonatal period, but also before birth.

The development of different cortical areas has been associated with the distribution and duration of thyroid hormone deficiency, suggesting that there are critical periods during which various cortical regions are sensitive to thyroid hormone intake. Even when the fetus begins to produce thyroid hormones in the second trimester of pregnancy, maternal thyroid hormones contribute to endocrine supplementation in the fetal brain.

Sinha et al. demonstrated the correlation between maternal serum T4 concentrations, fetal T4 brain levels, and maternal iodine in premature

birth (35). Early recognition of a potentially treatable fetal thyroid condition often depends on detecting abnormal growth of the fetal thyroid gland (36).

CONCLUSIONS

Iodine deficiency in pregnant women, revealed by iodine dosage, falls within the limits of mild deficiency. However, the current dietary iodine intake does not cover the iodine requirement in pregnancy. Iodine deficiency remains a public health problem for pregnant women in Romania. In the general population, pregnant women are a high-risk group regarding iodine deficiency due to an imbalance between intake and needs (high needs and low intake).

The iodine deficiency in the newborn, revealed by the dosing of the blood TSH at birth, falls within the limits of the average deficiency, which accentuates the pathogenetic risk.

Improving the severity of iodine deficiency was highlighted by comparing iodine deficiency in pregnant women with that of the newborn; it is found that the degree of deficit in the mother compared to the newborn is lower. The variations of the iodine deficiency recommend periodic monitoring, with the intervention modalities to the ascertained situation.

The results obtained regarding the maternal-neonatal thyroid hormonal status require the additional administration of iodine for the prevention of deficiency. In pregnant women, iodine deficiency is a topical public health problem due to its severity and potential adverse effects on the fetus.

The possibility of monitoring neonatal hypothyroidism by dosing blood TSH at birth immediately after the expulsion of the fetus and ultrasound examination of its thyroid to prevent early development of developmental deficiencies and the establishment of appropriate therapy.

Establishing reference intervals for thyroid hormones, considering both the degree of iodine deficiency and gestational age, may be particularly important in diagnosing and conducting fetal thyroid disorders (e.g. hypothyroidism).

The status of thyroid hormones and thyroid volume in newborns and their mothers are dependent on the severity of iodine deficiency and, to a lesser extent, on the degree of prematurity.

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