

HYPOTHYROIDISM IN PREGNANCY – MATERNAL-FETAL IMPLICATIONS

DAN MIHU¹, NICOLAE COSTIN¹, CARMEN GEORGESCU²,
LIGIA BLAGA³, SEPTIMIU CIUCHINĂ¹, MIHAELA OANCEA¹,
ANDREI MĂLUȚAN¹

¹Department of Obstetrics and Gynecology II

²Department of Endocrinology

³Department of Neonatology

“Iuliu Hațieganu” University of Medicine and Pharmacy Cluj-Napoca

Abstract

The incidence of hypothyroidism in pregnancy is 2% and clinical forms develop in 0.5% of all patients. The thyroid function undergoes certain physiological changes during pregnancy, which are related to TBG, low iodine availability, placental hormones. The biological diagnosis of hypothyroidism in pregnancy is based on plasma TSH values higher than 2.5 mIU/L. In the context of hypothyroidism, an increase in the incidence of preeclampsia, premature birth, premature separation of normally inserted placenta, postpartum hemorrhage is found. Thyroid hormone deficiency in the first trimester of pregnancy can cause intrauterine growth retardation, intellectual deficit or spastic motor deficit in the fetus. Iodine deficiency is one of the main causes of hypothyroidism in pregnancy. The detection of hypothyroidism during pregnancy requires the initiation of early L-thyroxine treatment in doses of 2-4 µg/kg/day. In the context of hypothyroidism in pregnancy, some dilemmas need to be clarified: the necessity to evaluate thyroid function in all pregnant women or only under certain conditions, as well as the necessity to prevent iodine deficiency. Maternal and fetal hypothyroidism can have important adverse effects on fetal development. For these reasons, maternal hypothyroidism should be avoided during pregnancy. Iodine replacement is recommended in doses of 100 µg/day before conception and 200 µg/day during pregnancy.

Keywords: hypothyroidism, thyroid hormones, iodine, L-thyroxine, pregnancy.

HIPOTIROIDISMUL ÎN SARCINĂ – IMPLICAȚII MATERNO-FETALE

Rezumat

Incidența hipotiroidismului în sarcină este de 2%, iar formele clinice se constituie la 0,5 % dintre paciente. Funcția tiroidiană suferă anumite modificări fiziologice în cursul sarcinii, legate de TBG, disponibilitatea scăzută de iod, hormonii placentari. Diagnosticul biologic al hipotiroidismului în sarcină se bazează pe valori ale TSH-ului plasmatic peste 2,5 mUI/l. În contextul hipotiroidismului se constată o creștere a incidenței preeclampsiei, nașterii premature, dezlipirii premature de placenta normal inserată, hemoragiilor în postpartum. Deficitul hormonilor tiroidieni în primul trimestru de sarcină poate determina asupra fătului întârziere de creștere intrauterină, deficit intelectual sau deficit motor spastic. Carența de iod este una dintre principalele cauze ale hipotiroidismului în sarcină. Decelarea hipotiroidismului în cursul sarcinii impune instituirea unui tratament precoce cu L-tiroxină în doză de 2-4 µg/kg/zi. În contextul hipotiroidismului în sarcină se impune elucidarea unor dileme: necesitatea bilanțului funcției tiroidiene la toate femeile însărcinate sau doar în anumite condiții, precum și necesitatea prevenției carenței de iod. Hipotiroidismul

matern și fetal pot avea efecte adverse importante asupra dezvoltării fătului. Din aceste motive hipotiroidismul matern trebuie evitat în cursul sarcinii. Substituția cu iod este recomandată preconcepțional în doze de 100 µg/zi, iar în cursul sarcinii în doze de 200 µg/zi.

Cuvinte cheie: hipotiroidism, hormoni tiroidieni, iod, L-tiroxină, sarcină.

Primary hypothyroidism is common, affecting 3-10% of all women, and it frequently develops during the fertility period.

It is considered that 1-25% of all pregnant women need levothyroxine therapy for hypothyroidism. Epidemiological studies show that 0.4% of all pregnant women have serum thyrotropin concentrations higher than 10 µU/ml at 15-18 WA [1].

Physiological changes in the maternal thyroid function during pregnancy

The thyroid function undergoes physiological changes during pregnancy. The main adaptive thyroid mechanisms in pregnancy are [2,3,4]:

- The titer of Thyroxin Binding Globulin (TBG), a transport protein with an affinity for thyroid hormones, is increased in the context of hyperestrogenemia that stimulates the hepatic synthesis of this protein.

This increase is responsible for an enhanced binding of T_3 and T_4 to TBG (3/4 of T_4 is bound to TBG during pregnancy, compared to 2/3 in non-pregnancy). This mechanism mediates an increase in thyroid hormone production, total T_3 and T_4 concentrations being 1.5-fold higher. The free fraction (free T_4), which represents a biologically active fraction and is routinely measured, is slightly changed. This is why thyroid hormone values during pregnancies are difficult to interpret, requiring specific norms depending on gestational age.

- Iodine availability is low due to transplacental passage (fetal requirements) on the one hand, and to increased renal iodine clearance on the other hand.

So, there is a relative iodine deficiency during pregnancy. Iodine deficiency favors hypothyroxinemia, contributing to the increase of maternal thyroid volume. In the fetus, the thyroid is functional during the second half of the pregnancy and the decrease in iodine availability reduces the synthesis capacity. These findings require supplementation with 200 µg iodine/day during pregnancy.

- Chorionic gonadotropin or placental HCG has a thyrostimulating effect due to its similar structure to TSH. HCG binds to TSH receptors, stimulating thyroid hypertrophy and causing T_4 to increase. The increase in HCG during the first trimester of pregnancy causes a mirror decrease in TSH: a 10,000 IU increase in HCG determines

a 0.6 pmol/L increase in T_4 and a 0.1 m IU/L decrease in TSH. In the second half of the pregnancy, the titer of TSH is restored to the values prior to gestation.

- The placenta secretes desiodase type 3, which determines an increase in inactive T_3 .

All these biological changes are responsible for an approximately 30% increase in the volume of the thyroid gland.

The fetal thyroid gland is functional starting with the second half of the pregnancy and hormone synthesis starts at 18 WA. Before this gestational age, the thyroid hormones detected in the amniotic fluid compartment result through the transplacental passage of maternal hormones. This transfer of maternal hormones occurs throughout the pregnancy. In the fetus, the role of thyroid hormones is crucial for adequate neurological development. At cerebral level, fetal desiodase type 2 transforms maternal T_4 into T_3 , an active hormone. Consequently, maternal T_4 levels should be normal in order to maintain a normal cerebral T_3 titer in the fetus.

The adaptive changes in the thyroid function in pregnancy are more obvious in the first trimester and are subsequently stabilized in the absence of thyroid pathology or iodine deficiency.

Diagnosis

Approximately 2% of all pregnant women have hypothyroidism, most frequently subclinical forms. The incidence of clinical hypothyroidism is 0.5%. The two main causes are iodine deficiency and Hashimoto autoimmune disease, frequently associated with antiperoxidase and antithyroglobulin antibodies [2].

Hypothyroidism may precede pregnancy or can be detected during pregnancy. The clinical diagnosis of hypothyroidism is difficult to make during pregnancy, because signs can be attributed to pregnancy itself: weight gain, muscle cramps, asthenia, constipation, bradycardia, hair loss, dry skin. The biological diagnosis is based on the increase in plasma TSH levels. Normally, there is a physiological decrease in TSH at the onset of pregnancy. TSH values higher than 2.5 mIU/L confirm the diagnosis. Free T_4 can be normal or low [2,6,7].

Maternal consequences of hypothyroidism

An increase in the incidence of preeclampsia, premature birth, premature separation of normally inserted placenta and postpartum hemorrhage is found in hypothyroidism. These obstetric pathology aspects might be determined by an early alteration of placentation, the

implication of thyroid hormones in the normal development of the placenta being demonstrated. Complications occur particularly in the case of severe hypothyroidism, but they have also been reported in subclinical hypothyroidism [8]. A new fascinating topic in the field of autoimmunity in pregnancy is that of fetal microchimerism: this represents the migration of fetal cells into the maternal blood during pregnancy and the prolonged persistence of fetal progenitor cells in the maternal tissues. Recent studies have confirmed that microchimerism develops in the thyroid gland of women with Hashimoto and Graves disease. Even if the functional consequences of persistent fetal microchimerism are not known, fetal cells present in maternal tissues might play a role in the etiopathogeny of autoimmune thyroid diseases and probably in the modulation of autoimmunity during pregnancy [9].

Fetal consequences of hypothyroidism

During the first two trimesters of pregnancy, fetal thyroid hormone requirements are met by the transplacental passage of maternal hormones.

In the case of hypothyroidism of maternal origin, fetal development may be normal. At the same time, it has been shown that thyroid hormone deficiency in the first trimester of pregnancy may induce intrauterine growth retardation, intellectual deficit or spastic motor deficit in the fetus. The development of fetal brain (multiplication, migration and architectural organization of neurons) during the second trimester of pregnancy corresponds to a stage in which the necessary thyroid hormones for the growing fetus are almost exclusively of maternal origin. During the subsequent stages of development of the fetal brain (multiplication, migration and myelination of glial cells), which develops starting with the third trimester of pregnancy, the necessary thyroid hormones for the fetus are mainly of fetal origin. Thus, while severe maternal hypothyroidism in the second trimester of pregnancy will determine an irreversible neurological deficit, maternal hypothyroxinemia that appears during the later stages of pregnancy will cause less severe and partially reversible fetal brain damage [9].

Three situations should be considered in hypothyroidism:

1. For newborns with an ontogenetic deficit of the thyroid gland, which causes congenital hypothyroidism, the participation of maternal hormones in the fetal circulating titer of T_4 remains unaffected and thus, the risk of brain damage exclusively results from fetal thyroid hormone insufficiency.

2. When only the maternal thyroid is deficient, maternal hypothyroidism influences the development of the fetal brain.

3. In iodine deficiency, both maternal and fetal thyroid function is affected. In these cases, the degree and the stage of iodine deficiency in pregnancy determine the

potential repercussions for fetal neurological development.

The first prospective study was reported by Haddow et al. [10] in 1999. The authors retrospectively studied the intellectual quotient of children aged 7-9 years, whose mothers had increased TSH levels and low free T_4 levels during the second trimester of pregnancy. The IQ of children born to mothers with hypothyroidism during pregnancy was lower. The benefits of hormone replacement therapy were also evaluated. The children whose mothers were not treated with L-thyroxine had a 7 point lower IQ compared to the reference group, and 19% of these had an IQ lower than 85. In 2004, Rovet et al. [11] studied the cognitive performance of 66 children born to mothers who had hypothyroidism treated with L-thyroxine during pregnancy. This treatment was aimed at obtaining a TSH value of 5-7 mIU/L. The results evidence altered cognitive performance (memory), which supports the need for maintaining an adequate balance of the thyroid function during pregnancy.

Iodine deficiency is one of the main causes of hypothyroidism during pregnancy. This deficiency causes maternal and fetal morphological thyroid changes such as thyroid hyperplasia and goiter. This iodine deficiency can also alter fetal cognitive performance, with a 10-13 point reduction in the IQ. Hormone replacement therapy may improve these deficiencies in children. In autoimmune thyroid disorders, the dosage of TSH anti-receptor antibodies is required in the 6th month of pregnancy. The same measure is recommended in the case of a history of thyroidectomy. A high antibody titer shows an increased risk of passive transfer to the fetus, with a risk of transient hyper- or hypothyroidism at birth [12].

Treatment of maternal hypothyroidism during pregnancy

The detection of hypothyroidism during pregnancy requires the initiation of early treatment with L-thyroxine in a morning fasting dose of 2-4 $\mu\text{g/kg/day}$. This dose should be adapted so as to obtain a TSH value lower than 2.5 mIU/L. For patients with hypothyroidism prior to pregnancy, treatment should be adapted [13]. It is considered that L-thyroxine doses should be increased by approximately 30% once the diagnosis of pregnancy has been made (between 4 and 8 weeks of amenorrhea). Serum TSH and free T_4 levels should be measured every 2 months. T_4 requirements will most likely increase with the evolution of pregnancy. This increase might also be caused by an inadequate intestinal absorption of the hormone due to ferrous sulfate administered in pregnancy. This is why L-thyroxine and ferrous sulfate should be administered 4 hours apart [14].

Strategies for the detection of hypothyroidism in pregnancy

A number of dilemmas need to be clarified:

Is an evaluation of the thyroid function necessary in all pregnant women?

A recent consensus of endocrinologists [6,15] recommends the detection of maternal hypothyroidism only in the following situations:

- A personal or family history of thyroid disease
- A family history of diabetes mellitus
- Goiter
- Presence of anti-thyroperoxidase antibodies
- Presence of clinical signs of thyroid disease (hypo- or hyperthyroidism)
- Presence of an autoimmune disease
- A history of irradiation of the cervical region
- Patients with infertility
- Patients with abortions or premature delivery

The incidence of hypothyroidism in pregnancy is approximately 2%, clinical forms developing in 0.5% of all patients. At the same time, 30% of the patients with increased TSH levels have no personal or family history, which is why systematic detection can be recommended. Systematic detection involves the measurement of plasma TSH levels. In the case of suggestive clinical signs, the dosage of free T_4 will also be performed. If the diagnosis of hypothyroidism is made, etiological evaluation will include the dosage of anti-thyroperoxidase antibodies [16,17].

Should iodine deficiency be prevented?

Iodine deficiency is defined as ioduria lower than 100 $\mu\text{g/L}$ and may occur in up to 75% of all pregnant women. Iodine deficiency is accompanied by a reduction in thyroid hormone synthesis resulting in hypothyroxinemia. The decrease in T_4 causes an increase in TSH, which induces an increase in the thyroid volume with the development of goiter.

The prevention of iodine deficiency is imperative before and during pregnancy. The intake recommended by WHO is 200 $\mu\text{g/day}$. Iodine is available in sea salt, sea fruit, fish. Iodine replacement therapy is provided by the administration of potassium iodide tablets.

In this sense, the following measures related to the prevention and treatment of hypothyroidism during pregnancy are mentioned [2,18]:

Before conception

- Potassium iodide 100 $\mu\text{g/day}$

Pregnancy and breastfeeding

- Systematic potassium iodide 200 $\mu\text{g/day}$
- Thyroxine, morning fasting doses
- In the case of hypothyroidism prior to pregnancy

→ increased doses

- Thyroxine doses should be increased by approximately 30%

▪ TSH control every 4-6 weeks after changing the replacement medication dosage

- The aim is a TSH value lower than 2.5 mIU/L
- Decrease of the dosage after delivery (Fig. 1)

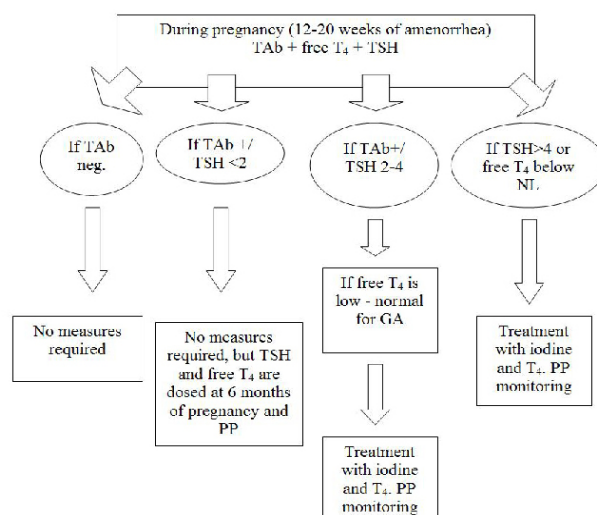


Fig. 1. Algorithm proposed for the systematic screening of thyroid autoimmunity and hypothyroidism during pregnancy, based on the measurement of thyroid antibodies (TAB), thyroid stimulating hormone (TSH), and free T_4 concentrations in the first half of the pregnancy. GA = gestational age; NL = normal limits; PP = post-partum.

Conclusions

1. The evaluation of the thyroid function seems to play an important role in women in the preconception period and during pregnancy. This evaluation should be recommended to all women with a personal or family history of thyroid disease or autoimmune disorders.

2. There is no unanimously accepted concept regarding the systematic evaluation of the thyroid function in women at the age of procreation. Recent studies emphasize the importance of a systematic detection of thyroid dysfunctions during pregnancy.

3. In all cases, the iodine replacement dose recommended in the preconception period is 100 $\mu\text{g/day}$ and during pregnancy, 200 $\mu\text{g/day}$.

4. It is known that both maternal and fetal hypothyroidism has important adverse effects on the fetus. This is why maternal hypothyroidism should be avoided.

5. If hypothyroidism has been diagnosed before pregnancy, the adjustment of the L-thyroxine dose is recommended in the preconception period, so as to reach a maximum TSH level of 2.5 mU/ml.

6. T_4 therapy should be generally introduced at 4-6 weeks of amenorrhea. A 30-50% increase in the dose is required.

7. If hypothyroidism is diagnosed during pregnancy, thyroid function tests (TFT) should be normalized as rapidly as possible. L-thyroxine doses should be adjusted in order to maintain a serum TSH level lower than 2.25 $\mu\text{U/ml}$ in the first trimester of pregnancy and 3 $\mu\text{U/ml}$ in the second and third trimesters of pregnancy. Thyroid function tests should be reevaluated within 40-60 days.

8. Women with thyroid autoimmunity who are

euthyroid at the beginning of the pregnancy have an increased risk to develop hypothyroidism and should be monitored by the measurement of TSH values.

9. Subclinical hypothyroidism (serum TSH concentrations above the upper limit of the reference interval with normal free T_4) determines a reserved maternal and fetal prognosis. It has been shown that treatment with T_4 can improve obstetrical prognosis, but does not change the long term neurological development of the fetus. Under these conditions, T_4 replacement therapy is however recommended.

10. After delivery, the majority of women with hypothyroidism require a decrease in the L-thyroxine dose that has been administered during pregnancy.

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