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Impact of hypothyroidism on pregnancy

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ABSTRACT: It is estimated that more than 2% of pregnant women have hypothyroidism and that the incidence of treated hypothyroidism prior to pregnancy is around 0.3% of pregnancies. In the majority of cases, hypothyroidism is mild and is due to an autoimmune mechanism, as evidenced by the presence of anti-TPO or antithyroglobulin antibodies. Pregnancy may be indicative of a fruste form, related to asymptomatic autoimmune thyroiditis, which is unable to increase its hormone production to meet the specific needs of pregnancy. It can also be the consequence of moderate or severe iodine deficiency. Moreover, thyroid balance during pregnancy is essential for good fetal brain development. In fact, several studies have shown that children born to mothers who are not or insufficiently substituted for hypothyroidism have lower intelligence quotients than the general population. In addition, other maternal consequences (gravid hypertension, pre-eclampsia, etc.) and fetal consequences (IUGR, intellectual deficit) of hypothyroidism during pregnancy have been described. Although current recommendations suggest targeted screening of patients at risk of hypothyroidism, it is desirable that, in the near future, this screening becomes systematic as soon as the diagnosis of pregnancy is confirmed. L-thyroxine treatment should then be rapidly initiated (or adapted in the case of known hypothyroidism prior to pregnancy) with the aim of achieving a TSH of less than 2.5 mIU/l. In all cases, iodine supplementation should be offered from the preconceptional period through to breastfeeding.

KEYWORDS: Hypothyroidism; Pregnancy; Iodine deficiency; Antithyroid antibodies, Thyroid autoimmunity.

1 INTRODUCTION

Despite the apparent clinical latency, both pregnancy and the postpartum period are challenging for the thyroid gland. The thyroid gland possesses significant adaptive capacities which, on the whole, enable it to cope with the increased hormonal requirements and the depletion of the iodine load. However, imbalances are possible, which has consequences for the maternal and foetal situation. Indeed, it has been shown that certain thyroid dysfunctions such as hypothyroidism can increase the risk of spontaneous miscarriage, be responsible for alterations in brain development and increase the risk of obstetric complications such as preterm delivery.

2 PHYSIOLOGICAL CHANGES IN MATERNAL THYROID FUNCTION DURING PREGNANCY

Thyroid function is physiologically altered during pregnancy [1,2,3]. Indeed, many thyroid adaptations occur:

- The level of Thyroxin Binding Globulin (TBG), a transport protein with a very high affinity for thyroid hormones, is increased due to hyperestrogenism. Indeed, hyperestrogenism stimulates the hepatic synthesis of TBG and increases its sialylation, which increases its half-life. This increase is responsible for an increase in the binding of T3 and T4 to TBG (three quarters of T4 is bound to TBG during pregnancy, compared to two thirds outside of pregnancy), which in turn leads to an increase in thyroid hormone production. Thus, total T3 and T4 concentrations are increased during pregnancy and stabilise at 1.5 times the normal value. In contrast, the free fraction (free T4), which represents the biologically active fraction and is the one usually measured, is little changed. It should be noted, however, that there may be variations due to haemodilution and iodine deficiency (20-30% decrease in levels). Thus, the interpretation of thyroid hormone levels is difficult during pregnancy and specific standards, depending on the term of the pregnancy, would be necessary;

- Iodine availability is decreased, due to the transplacental passage of part of the iodine (fetal needs) on the one hand, and the increased renal clearance of iodine on the other hand. In addition, the activity of the iodine transporter ("iodine-sodium symporter" or NIS) is reduced as a result of estrogen impregnation. As a result, there is a relative iodine deficiency during pregnancy. Epidemiological studies have shown that most pregnant women in France are deficient. Iodine deficiency favours hypothyroxinemia and contributes to the increase in maternal thyroid volume. In the foetus, the thyroid is functional from the second month of pregnancy and the decrease in iodine availability reduces its synthesis capacity. Thus, due to the consequences of iodine deficiency, a supplementation of 200 µg/day is recommended during pregnancy;
- Placental chorionic gonadotropin or HCG has a thyroid-stimulating effect, due to its structural homology with TSH. Thus, HCG binds to the TSH receptor, stimulates the growth of the thyroid gland and leads to an increase in T4. The elevation of HCG in the first trimester of pregnancy is accompanied by a mirror decrease in TSH. Classically, it is said that an increase in HCG of 10,000 units leads to an increase in T4 of 0.6 pmol/l, and a decrease in TSH of 0.1 mIU/l (by feedback). In certain circumstances (twin pregnancies, hydatidiform mole), high HCG levels can lead to transient gestational hyperthyroidism or "hyperemesis gravidarum" which resolves spontaneously between the third and fifth month of pregnancy. In the second half of pregnancy, TSH levels normalise and return to pre-pregnancy values;
- The placenta secretes type 3 deiodase, resulting in an increase in inactive T3. All these biological changes are responsible for an increase in the volume of the thyroid gland, by about 30%. The fetal thyroid is in place from the second trimester of gestation and hormone synthesis begins from the 18th week of gestation. Prior to this time, thyroid hormone levels detected in the amniotic fluid are the result of transplacental passage of maternal hormones. It should be noted that this transfer of maternal hormones continues throughout the pregnancy. In the fetus, the role of thyroid hormones is essential for proper neurological development. It is the type 2 deiodase of the fetus that transforms maternal T4 into the active hormone T3 in the brain. Thus, the maternal T4 level must be normal in order to maintain a normal brain T3 level in the fetus.

3 DIAGNOSIS

Approximately 2% of pregnant women have hypothyroidism, which is most often subclinical. The incidence of clinical hypothyroidism is estimated to be 0.5% [2]. The two main causes are iodine deficiency and autoimmune Hashimoto's disease, associated with the presence of antithyroperoxidase and antithyroglobulin antibodies. Patients with type 1 diabetes have a three- to five-fold increased risk of hypothyroidism [4,5]. Hypothyroidism may precede pregnancy or be discovered during pregnancy. The diagnosis of hypothyroidism is difficult during pregnancy. Indeed, most signs are often attributed to the pregnancy itself: weight gain, muscle cramps, asthenia, constipation. The presence of bradycardia, hair loss, and dry skin can guide the diagnosis. Very often, the diagnosis is made by chance during a biological assessment. The biological diagnosis is based on the elevation of plasma TSH. Due to the physiological decrease in TSH in early pregnancy, some authors consider that a TSH level above 2.5 mIU/l [1] is sufficient to suggest the diagnosis and treatment. Free T4 is normal or low.

4 MATERNAL CONSEQUENCES OF HYPOTHYROIDISM

The maternal consequences of hypothyroidism are multiple. Indeed, there is an increased incidence of gravid hypertension, pre-eclampsia and premature delivery. The incidence of postpartum haemorrhage is also higher in hypothyroid patients [1]. These complications appear to be more common in severe hypothyroidism, but are also described in subclinical hypothyroidism. Abalovich et al [6] studied 150 pregnancies in 114 hypothyroid women. Fifty-one pregnancies (34%) occurred in patients who were not well controlled, and 99 in patients who were well controlled on treatment. The rate of SCC was 60% in the frank clinical hypothyroidism group and 71% in the subclinical hypothyroidism group. The preterm delivery rate was 20% in the frank hypothyroidism group and 7% in the subclinical hypothyroidism group. Conversely, in the well-balanced patients, the complication rate was similar to that of the general population. This study therefore shows the value of perfect thyroid function adjustment, even in subclinical hypothyroidism.

5 FETAL IMPACT OF HYPOTHYROIDISM

Hypothyroidism may be permanent or transient, disappearing after birth. The transient form is usually the result of transplacental passage of blocking antibodies, iodinated drugs or immaturity of the hypothalamic-pituitary axis in the premature baby [7]. Congenital hypothyroidism may be manifest at birth (picture of growth retardation, hypothermia, myxedema, macroglossia, micrognathia, delayed closure of the posterior fontanel, dry skin, umbilical hernia, jaundice) [8]. In cases of maternal hypothyroidism, fetal development is usually normal with no birth sequelae. Thyroid hormone deficiency in

the fetus during the first trimester may also result in low birth weight, [8,9] moderate to severe intellectual deficits: cretinism (lower than average IQ, slower language development with occasional mutism, and poorer school performance), and spastic motor deficits of varying severity., [8,9] (J.-L. Wémeau et al.) Rovet et al [10] studied in 2004 the cognitive performance of 66 children born to mothers with hypothyroidism treated with L-thyroxine during pregnancy. The treatment was aimed at achieving a TSH between 5 and 7 mIU/l. The results show that certain cognitive performances are impaired (memory), which would therefore lead to a demand for a better balance of thyroid function during pregnancy. Iodine deficiency is one of the main causes of hypothyroidism during pregnancy. This deficiency leads to maternal and fetal thyroid morphological changes such as thyroid hyperplasia or goitre. In addition, this deficiency appears to impair the cognitive performance of the fetus, with an IQ 10 to 13 points lower than the average according to the studies [11,12].

However, the studies are difficult to interpret because they include patients with moderate to severe deficiency. A recent Sicilian study [13] showed that children born to mothers with moderate iodine deficiency had an IQ 10 points lower than children whose mothers were not deficient. Finally, the authors report an incidence of attention deficit hyperactivity disorder in 69% of children born to deficient mothers. Thus, these studies show that children born to mothers with hypothyroidism or hypothyroxinemia during pregnancy have (moderate) cognitive impairments. Substitution seems to improve the cognitive performance of the children. In addition, other studies have suggested the deleterious role of maternal antithyroid antibodies: a ten-point reduction in IQ in children born to mothers with increased antithyroperoxidase antibodies at 28 weeks has been reported [14]. But it cannot be excluded that this was related to a greater predisposition to maternal hypothyroxinemia. A few rare cases of fetal hyperthyroidism have been described in pregnant patients with Hashimoto's thyroiditis with the presence of anti-RTSH antibodies behaving as thyroid stimulating antibodies in the fetus [8].

Screening for hypothyroidism in some women considering pregnancy Since hypothyroidism is common in pregnancy and has neonatal and paediatric consequences, is easy, accessible and inexpensive to screen for, and can be effectively treated during pregnancy (in terms of maternal and foetal complications) with no side effects, screening for hypothyroidism can be suggested [15]. It is based on TSH measurement and it is only when TSH is increased that the assessment will include a T4l measurement (to be interpreted according to iodine deficiency prophylaxis) and possibly the search for anti-thyroperoxidase antibodies (TPO). 5] If possible, it should be carried out before the start of the pregnancy or during the first obstetric visit. It is recommended according to a recent consensus of endocrinologist experts in women with: [3,5]

-Personal or family history of thyroiditis, postpartum thyroiditis, thyroid surgery

-Family history of diabetes

-Goiter

-Anti-TPO+ antibodies

-Clinical signs of thyroiditis

-Type 1 diabetes

-History of autoimmunity

-History of cervical radiation

6 THERAPEUTIC MANAGEMENT AND PREVENTION

6.1 PREVENTION OF IODINE DEFICIENCY

Severe iodine deficiency is a major public health problem. The aim is to treat the deficiency preventively before or at the very beginning of pregnancy to allow the increase of thyroid production before the second trimester and prevent complications. 16] The WHO recommends 200 lg/d of iodine intake. Consumption of fortified sea salt, seafood and certain fish contributes to this, but not enough since it is recommended to reduce salt consumption during pregnancy. The measurement of ioduria (in lg/l or lg/24 h) is not very effective for individuals, as it represents an instantaneous reflection of iodine intake. Moreover, it is an out-of-nomenclature measurement, not covered by the health insurance. Hence the practical advisability of systematic iodine supplementation (100 lg/d, i.e. 1 tablet with 130 lg of potassium iodide) [1].

6.2 THYROID HORMONE REQUIREMENTS

If hypothyroidism is known prior to pregnancy, it is recommended in practice to increase thyroid hormone intake by approximately 30% once pregnancy has been confirmed, with subsequent dosage adjustment to achieve hormonal balance.

17] TSH should be monitored regularly and the replacement dosage increased to achieve a TSH level close to 1 mU/l throughout the pregnancy.

6.3 EARLY DIAGNOSIS

TSH and anti-TPO antibody testing should be recommended before 12 weeks of pregnancy if there is a family history of thyropathy, a history of postpartum thyroiditis or previous dysthyroidism, iodine medication, a geographical area of iodine deficiency, or if hypothyroidism is suspected. Because of the severity of complications and the often asymptomatic nature of hypothyroidism, routine testing of TSH, possibly anti-TPO antibodies before the 12th week of pregnancy in all pregnant women, is questioned. Treatment of hypothyroidism discovered in pregnancy If hypothyroidism is frank, immediate replacement therapy should be started at a dose of 1.8-2 lg/kg/d, which is higher than that used in the absence of pregnancy. 18] If hypothyroidism is discrete (<10 mU/l), a lower dose of around 100 lg/d is possible. Wiersinga recommends treatment if TSH is above 2 mU/l with positive anti-TPO antibodies, and if TSH is above 5 mU/l with negative anti-TPO antibodies in early pregnancy, reassessing TSH after 6 weeks, and adjusting therapy to achieve TSH close to 1 mU/l [19].

7 CONCLUSION

Thyroid function testing appears to have an important place in the preconception period and during pregnancy. It should be offered to all women with a history of thyroid disease, a family history of thyroid disease or other autoimmune diseases. There is no consensus in the scientific literature on routine screening of thyroid function in women of childbearing age. On the other hand, the most recent publications insist on the interest of systematic screening during pregnancy. In all cases, iodine substitution should be systematic during preconception (100µg/day), pregnancy and lactation (200 µg/day). The consumption of seafood, the choice of cooking method (in foil, in the microwave oven), and the use of iodine-enriched sea salt can contribute to this.

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