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THE TREATMENT OF HYPOTHYROIDISM IN PREGNANCY

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Abstract

Hypothyroidism is a pathologic condition generated by the thyroid hormone deficiency. The American Thyroid Association advises for the screening of hypothyroidism beginning at 35 years and thereafter every 5 years in people at high risk for this condition: females older than 60 years, pregnant women, patients with other autoimmune disease or patients with a history of neck irradiation. In pregnant women, hypothyroidism can been associated with adverse effect for both mother and child. The „Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum" recommends the treatment of maternal overt hypothyroidism: females with a thyrotropin (TSH) level higher than the trimester-specific reference interval and decreased free thyroxine (FT_4), and females for which TSH level is higher than 10.0 mIU/L, irrespective of the FT_4 value, with administration of oral levothyroxine. The goal of treatment of maternal overt hypothyroidism is to bring back the serum TSH values to the reference range specific for the pregnancy trimester. The Guidelines of the „European Thyroid Association for the Management of Subclinical Hypothyroidism in Pregnancy and in Children" recommends treatment of pregnancy associated subclinical hypothyroidism with the following levothyroxine doses: „1.20 µg/kg/day for TSH≤4.2 mU/l, 1.42 µg/kg/day for TSH >4.2-10 and 2.33 µg/kg/day for overt hypothyroidism". The „Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum" and the „European Thyroid Association for the Management of Subclinical Hypothyroidism in Pregnancy and in Children" do not recommend the treatment of isolated hypothyroxinemia in pregnancy.

key words: *screening of thyroid dysfunction, hypothyroidism, pregnant women*

Introduction

Hypothyroidism is a pathologic condition generated by the thyroid hormone deficiency. The American Thyroid Association (ATA) advises for the screening of hypothyroidism beginning at 35 years and thereafter every 5 years in people at high risk for this condition: females older than 60 years, pregnant women, patients with other autoimmune disease or patients with a history of neck irradiation [1].

Hypothyroidism in pregnant women can been associated with adverse effect in mother (anemia, congestive heart failure, pre-eclampsia,

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placental abnormalities, gestational diabetes), and child (low birth weight and disorders of neuropsychological development). These complications occur in women in most cases in situations with severe hypothyroidism. Women with mild hypothyroidism or subclinical hypothyroidism may have no symptoms. Studies on the prevalence of hypothyroidism in pregnancy provided quite different results. Thus, in a study including 500.000 pregnant women from the United States of America, Blatt AJ *et al.* report that the prevalence of hypothyroidism in pregnancy was 15.5% [2]. In an issue of the Journal of Obstetrics and Gynecology of India, published in 2014, Ajmani SN *et al.* analyzed the prevalence of overt and subclinical thyroid dysfunction in pregnancy in India. Overall 400 pregnant women with a gestational age between 13 and 26 weeks were included in the study. The prevalence of hypothyroidism was 12% [3]. The authors state that *"The prevalence of thyroid disorders was high in our study with associated adverse maternal and fetal outcomes. Routine screening of thyroid dysfunction is recommended to prevent adverse fetal and maternal outcomes"* [3]. In another article, Sahu *et al* reported a prevalence of overt and subclinical hypothyroidism of 6.47 %. The study was conducted over a period of three years and included 633 pregnant women [4]. Finally, in a prospective study conducted by Saraladevi R *et al.* that included 1000 pregnant women from the first trimester till delivery, the prevalence of subclinical hypothyroidism was 6.4% and of overt hypothyroidism was 2.8% [5].

General considerations

Previous studies have shown that pregnancy generates increases in size of the thyroid gland and thyroid function changes [1,6]. Thus, in an issue of the Indian Journal of Endocrinology and Metabolism published in 2016 entitled "*Prevalence of hypothyroidism in pregnancy: An epidemiological study from 11 cities in 9 states of India*" Dhanwal DK *et al.* report that "*Pregnancy has a profound physiological impact on the thyroid gland and thyroid function. During pregnancy, the thyroid gland increases in size by 10% in iodine sufficient countries and to a greater extent in iodine deficiency countries. Production of thyroid hormones and iodine requirement both increases by approximately 50% during pregnancy as part of physiology. In addition, pregnancy is a stressful condition for the thyroid gland resulting in hypothyroidism in women with limited thyroid reserve or iodine deficiency."* [6].

Changes in thyroid volume in regions with a sufficient iodine intake, is evaluated at 10%. The authors state that most of the modifications are represented by vascular thyroid swelling [7]. In regions with a lower iodine intake, changes in thyroid volume range between 20-35% [8,9]. The World Health Organization (WHO), recommend a iodine intake for pregnant and lactating women of 250 µg per day [10].

Dietary requirements of iodine in pregnant women are increased in comparison with non pregnant women. Iodine is involved in the following mechanisms:

- Production of thyroid hormone increases by about 50% during pregnancy, starting during the first trimester, due to high human chorionic gonadotropin (HCG) and estrogen levels. HCG exhibits an action of thyroid stimulation and directly promotes the growth of the thyroid. In the same time, estrogens generate an increase "*in the sialylation of thyroxine binding globulin (TBG), leading to reduced hepatic TBG clearance and increased concentrations of circulating TBG"* [11-13].
- In the second half of pregnancy, the peripheral metabolism of thyroid hormones

may be increased as a result of placental deiodination of thyroxine (T_4) to reverse triiodothyronine (rT_3) [14].

- Iodide transport from the maternal to the fetal circulation. Feto-maternal transfer of iodide is mediated by two transporters: the sodium-iodide symporter and Pendrin [15,16].
- Early in the pregnancy there is an increase in the glomerular filtration which leads to an increase in iodide clearance from plasma [17].

Management of hypothyroidism during pregnancy

The "*Guidelines of the ATA for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum"* published in 2011, recommends trimester-specific intervals for thyrotropin (TSH). Thus, reference ranges for TSH are the following: "*first trimester, 0.1–2.5 mIU/L, second trimester, 0.2–3.0 mIU/L, third trimester, 0.3–3.0 mIU/L"* [1]. Regarding the determination of free thyroxine (FT_4), the authors of the guideline assert that "*The optimal method to assess serum FT_4 during pregnancy is measurement of T_4 in the dialysate or ultrafiltrate of serum samples employing on-line extraction/liquid chromatography/tandem mass spectrometry (LC/MS/MS). If FT_4 measurement by LC/MS/MS is not available, clinicians should use whichever measure or estimate of FT_4 is available in their laboratory, being aware of the limitations of each method. Serum TSH is a more accurate indication of thyroid status in pregnancy than any of these alternative methods*" [1].

Several studies recommend measurement of TSH during the first trimester of pregnancy in women with high risk for overt hypothyroidism: "*age>30 years, history of thyroid dysfunction or prior thyroid surgery, the presence of goiter, autoimmune disorders, history of neck radiation or spontaneous pregnancy loss, morbid obesity, use of amiodarone, lithium, thyroid auto-antibodies positivity"* [1]. International guidelines do not recommend FT_4 screening in pregnant women but FT_4 should be determined if TSH is elevated [1,18].

Primary hypothyroidism during pregnancy is defined by the presence of increased levels of TSH. The overt hypothyroidism is defined as high serum TSH level with FT_4 less than normal range, subclinical hypothyroidism (SCH) by high serum TSH level with normal FT_4 level [18]. Isolated hypothyroxinemia during pregnancy is defined as a low maternal FT_4 (value below the 2.5th percentile) with a normal TSH concentration [19].

The "*Guidelines of the ATA for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum"* recommend the treatment of maternal overt hypothyroidism: "*women with a TSH concentration above the trimester-specific reference interval and with a decreased FT_4, and all women with a TSH concentration above 10.0 mIU/L irrespective of the level of FT_4*". The goal of treatment of maternal overt hypothyroidism is to bring back the serum TSH values to the reference range specific for the pregnancy trimester [1]. The same guide recommends treatment of maternal hypothyroidism with oral levothyroxine, also known as LT_4 and states that *"It is strongly recommended not to use other thyroid preparations such as T_3 or desiccated thyroid. The goal of LT_4 treatment is to normalize maternal serum TSH values within the trimester-specific pregnancy reference range (first trimester, 0.1–2.5 mIU/L, second trimester, 0.2–3.0 mIU/L, third trimester, 0.3–3.0 mIU/L)."* [1]. In an issue of the *Drug Design, Development and Therapy* published in 2012 entitled "*Treatment for primary hypothyroidism: current approaches and future possibilities*" Chakera AJ

et al. recommend: "*Maternal hypothyroidism diagnosed in pregnancy should be corrected as soon as possible by initiating a full replacement dose of levothyroxine (100–150 μg/day or 2.0–2.4 μg/kg body weight/day). Most women with known hypothyroidism need a 30%–50% increase in the dose of levothyroxine during pregnancy and this increased dose requirement occurs as early as the first 4–6 weeks of gestation. Thyroid function should be monitored at regular intervals (every 4–6 weeks) to adjust the dose of levothyroxine to keep TSH under 2.5 mIU/L in the first trimester and under 3.0 mIU/L in the second and third trimesters*" [20]. Optimal treatment of maternal overt hypothyroidism decreases the rate of undesired obstetrical events.

Some studies highlight the association between subclinical hypothyroidism during pregnancy and increased risk for gestational diabetes, preterm delivery or pregnancy loss, hypertension or pre-eclampsia [21-24]. The relationship between SCH and gestational diabetes mellitus (GDM) is not fully elucidated. There are studies that highlight the association between elevated TSH and risk of occurrence of GDM. Tudela CM *et al.*, in an issue of the Obstetrics & Gynecology published in 2012 entitled "*Relationship of subclinical thyroid disease to the incidence of gestational diabetes*" report that "*the likelihood of gestational diabetes increased with thyrotropin level*". In this study were included 24.883 women, of which 95.5% were euthyroid, 2.3% had subclinical hyperthyroidism and 2% had subclinical hypothyroidism. In another study, Karakosta P *et al.* found that the high TSH in early pregnancy was associated with a 4-fold increased risk for GDM [25,26].

Several studies, but not all found an association between SCH in pregnancy and altered neuropsychological development of the child [27-29]. The Guidelines of the *"European Thyroid Association (ETA) for the Management of Subclinical Hypothyroidism in Pregnancy and in Children"* published in 2014 recommends "*treatment with the following levothyroxine doses: 1.20 μg/kg/day for SCH with TSH ≤ 4.2 mU/l, 1.42 μg/kg/day with TSH > 4.2-10 and 2.33 μg/kg/day for overt hypothyroidism. TSH values should be checked every 4-6 weeks at least during the first trimester and once during the second and third trimesters*" [18]. The *"Guidelines of the ATA for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum"* recommend: "*Women with SCH in pregnancy who are not initially treated should be monitored for progression to overt hypothyroidism with a serum TSH and FT_4 approximately every 4 weeks until 16—20 weeks gestation and at least once between 26 and 32 weeks gestation"* [1].

The committee of the "*Guidelines of the ATA for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum"* and the "*Guidelines of the ETA for the Management of Subclinical Hypothyroidism in Pregnancy and in Children*" do not recommend treatment of isolated hypothyroxinemia in pregnancy, due to the lack of randomized controlled trials [1,18]. Recent advances in the field recommends considering LT_4 replacement in isolated maternal hypothyroxinaemia in the first trimester [18].

LT_4 treatment in euthyroid pregnant women with autoimmune thyroid disease has been investigated in some studies. Negro R *et al.*, in a prospective study published in 2006 in the Journal of Clinical Endocrinology and Metabolism, found: "*... benefits of LT_4 administration, not only to correct maternal thyroid function but also to decrease the rate of undesired obstetrical events and bring their prevalence down to those of the control*

population" In this study were included 1029 pregnant women, with 984 women completing the study. Thyroid peroxidase antibodies titers and thyroid function tests were performed at the first gynecological visit, at 20 and 30 weeks gestation and after delivery. Overall 57 pregnant women with high titers of thyroid peroxidase antibodies received a dose of 0.5 μg/kg daily if they had TSH less than 1.0 mIU/L, 0.75 μg/kg daily for TSH between 1.0 and 2.0 mIU/L, and 1 μg/kg daily for TSH higher than 2.0 mIU/L. The LT_4 treatment appeared to reduce miscarriages whether given before or after the first trimester of pregnancy [30]. Nazarpour S *et al.* in a prospective study published in 2017 in the European Journal of Endocrinology entitled "*Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease*" report that treatment with LT_4 decreases the risk of preterm delivery in women who are positive for thyroid peroxidase antibodies [31]. The reduction of miscarriages through treatment of thyroid autoimmune diseases has been reported also by Lepoutre T *et al.* in a study published in 2012 in Gynecologic and Obstetric Investigation [32].

Conclusions

Hypothyroidism in pregnant women can been associated with adverse effect in mother and child. International guidelines recommend the treatment of maternal overt and subclinical hypothyroidism. Currently the international guidelines recommend that isolated hypothyroxinemia in pregnancy should not be treated, but recent advances in the field recommends considering LT_4 replacement in isolated maternal hypothyroxinaemia in the first trimester.

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