

Thyroid Disease during Pregnancy: What Changed with the Recent Guidelines?

Luiza V Fonseca¹, Marcus J A Vasconcellos¹ and Erika C O Naliato^{2*}

¹Serra dos Órgãos University Center (UNIFESO) - Brazil

²Ricardo A T Castilho Center of Studies - Teresopolis Medical Association; Brazil

***Corresponding Author:** Erika C O Naliato, Ricardo A T Castilho Center of Studies - Teresopolis Medical Association; Brazil.

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Abstract

Introduction: Despite the low prevalence, thyroid diseases present a considerable degree of severity during gestation, and therefore should be adequately investigated during pregnancy. Pre-eclampsia, abortion, and prematurity are important outcomes related to hypo- and hyperthyroidism. In Brazil, this subject remains neglected during prenatal care. This work seeks to rescue its importance.

Aims: To seek among recent clinical trials the possibility of new protocols and/or therapeutic schemes that may have a positive impact on the obstetric routine.

Method: This review was accomplished based on a search at MedLine, PubMed, LILACS, Cochrane library, and CAPES databases, using “hypothyroidism”, “hyperthyroidism”, “high risk gestation”, and “thyroid and pregnancy” as descriptors. Accepted articles were in English, Portuguese and Spanish, and published in the last 15 years.

Results: A few new supplements were added to the protocols and accepted by the American consensus published this year.

Conclusion: The addition of iodine to salt is still a better preventive way of hypothyroidism; levothyroxine and propylthiouracil are the best from the treatment choices, respectively, for hypo- and hyperthyroidism; TSH is the best way to follow up these patients.

Keywords: Hyperthyroidism; Hypothyroidism; Pregnancy Complications

Introduction

During pregnancy, physiological changes may interfere with thyroid function. Moreover, maternal thyroid disease may have relevant adverse effects on fetal development. Evaluating and treating women with these diseases during pregnancy requires careful observation to ensure favorable outcomes during this time [1].

During pregnancy, increased maternal estrogen production results in increased levels of Thyroid Binding Globulin (TBG) which consequently leads to an increase in total Thyroxine (T4) levels by 50%. With this increase, more T4 will be linked to TBG, with lower free levels of this circulating hormone (FT4) [1].

Changes in thyroid hormone levels during this period are also related to increased circulating levels of human chorionic gonadotropin (hCG). At high concentrations, hCG binds to the thyroid stimulating hormone (TSH) receptor, increasing thyroid hormone production [1,2].

Thus, in early pregnancy, the increased amount of hCG is related to a reciprocal reduction in the amount of thyroid stimulating hormone (TSH). Therefore, when hCG peaks in approximately 10 weeks, TSH levels have their concomitant nadir [1].

From 10 to 20 weeks of gestation, hCG levels progressively decrease, corresponding to reciprocal increases in circulating TSH concentrations. Considering changes in circulating thyroid hormone levels during this period, the specific levels of each gestational stage for T4, estimated free T4, and TSH should be used in interpreting thyroid hormone levels during pregnancy [1,2].

Prematurity and diseases such as hypertension, diabetes and, less frequently, heart disease, nephropathy and lupus, are the main concerns of obstetricians regarding high risk pregnancies. Thyroid pathologies, in turn, are often overlooked and are no longer traced even in prenatal care. However, thyroid disorders are common in adult women in reproductive phase and are mainly due to iodine deficiency, which still occurs in large areas of the planet, or to immunological changes in areas of iodine sufficiency. Given the profound hormonal and immunological changes that occur in this period, as well as the fetal dependence of maternal thyroid hormones and iodine, the repercussions of thyroid dysfunction are even greater during pregnancy [3].

Pregnancy is associated with the increased need for thyroid hormone secretion from the first weeks after conception. In order to fulfill this higher demand, pregnancy induces a series of physiological changes that affect the function of this organ [3].

In pregnant women with normal thyroid function living in areas of iodine sufficiency, the challenge of adjusting the hormonal release to a new steady state by the end of pregnancy usually occurs without difficulty. However, in women with thyroid functional capacity impaired by underlying disease or iodine insufficiency, this balance does not occur [3].

The management of thyroid dysfunction during pregnancy requires special considerations, as both hypothyroidism and hyperthyroidism can lead to maternal and fetal complications. Another important point is that with certain frequency, thyroid nodules are detected in pregnant women, which may lead to the need for differential diagnosis between benign and malignant even during pregnancy [3].

In healthy pregnant women, the thyroid gland increases by 10% in countries where iodine replacement is performed, and by 20% to 40% in areas of iodine deficiency. The production of thyroid hormones, T4 and triiodothyronine (T3), increases by almost 50% [2]. In addition, up to 18% of all pregnant women have positive thyroid peroxidase antibody (TPOAb) or thyroglobulin antibody (TgAb). Data suggest that TPOAb positivity negatively modulates the impact of maternal thyroid status (especially hypothyroidism) on pregnancy and fetal development. Therefore, thyroid function should be evaluated in pregnancy, but studies differ with respect to parameters for determining function abnormality [2].

Thyroid disorders in pregnancy have obstetric and fetal effects. Complications in the obstetric field include abortion, preeclampsia, placental detachment, and premature birth, while fetal complications include prematurity, low birth weight, and perinatal death. There is an increased incidence of hospitalizations and respiratory distress syndrome. Maternal hypothyroidism in the first trimester can be detrimental to fetal brain development and lead to retardation and cretinism with cognitive impairment, weight and height development, and development of most systems and organs [4].

The knowledge about the pathophysiology of thyroid disease in pregnancy has been advancing, and in the article by Korevaar, *et al.* [5] thyroid autoimmunity is shown to be an important risk factor for gestational thyroid disease. Since hCG is an important determinant of the function of this gland in pregnancy, positivity to TPOAb impairs thyroid response to hCG, the suggested mechanism by which thyroid autoimmunity acts as a risk factor.

To support this hypothesis, the authors performed a prospective cohort in which 5,435 pregnant women were evaluated. Results showed that higher hCG concentrations were associated with a higher risk of subclinical hyperthyroidism (SCH), while lower hCG

concentrations were associated with a higher risk of hypothyroidism. In contrast, hCG concentrations were not associated with subclinical hypothyroidism (HSC). Further analysis showed that, in women with low T4 levels, high hCG concentrations still suppressed TSH. However, in women with HSC, high hCG concentrations were not associated with higher FT4. In addition, higher body mass index, male fetal gender, and maternal parity above 2 were associated with lower thyroid response to hCG stimulation [5].

Lepez., *et al.* [6] explored the hypothesis of the role of fetal micro-chimerism in autoimmune thyroid disease (AIT), whereby it would trigger a Graft versus Host reaction or be the target of a Host versus Graft reaction, resulting in higher rates of prematurity, and concluded that the hypothesis was well founded. However, we will not address these thyroid disorders in this review, as we understand that they deserve a separate work.

Rodriguez and Zeron [7] stated that AIT is a multifactorial disease with genetic predisposition. They compared messenger RNA (mRNA) expression between healthy people and patients with hypothyroidism and their affected relatives in a cross-sectional, prospective and descriptive study. They concluded that there is no clear difference in mRNA expression, and that the ideal genes for systematic screening for AIT family members are yet to be found.

Just to illustrate the autoimmune issue, we report the work of Ayyagari [8], who presents a 27-year-old case with three-year hypothyroidism associated with the development of postpartum Graves Disease and a newborn with transient congenital hypothyroidism. Newborn thyroid function tests showed transient congenital hypothyroidism with remission at three months of age. Transient congenital hypothyroidism probably resulted from TSH receptor blockade. The mother was being treated with levothyroxine (100 mcg, daily). Seven months after delivery, she had ptosis, left eye proptosis, thyroid function tests compatible with thyrotoxicosis and positive TRAB (TSH receptor antibody). With levothyroxine withdrawal, orbitopathy resolved within six weeks and the mother remained euthyroid without levothyroxine at a follow-up period of eight months. From this case, we conclude that monitoring of AIT in pregnancy and postpartum is necessary due to the possible need for therapy. In addition, the suspicion of transient congenital hypothyroidism due to TRAB should be high in neonates born to mothers with AIT [8].

Over the past 15 years, knowledge of gestational thyroid physiology, definitions, risk stratification, and clinical consequences of gestational thyroid disease has expanded rapidly. This is illustrated, for example, by the number of articles in PubMed that have nearly doubled in the last 15 years (from 166 hits in 2001 to 316 in 2016) and includes 1700 new hits since the American Thyroid Association (ATA) published its 2011 Guidelines (303 - 356 hits per year). This demonstrates a constant search for update on the obstetric and endocrinological theme [9].

Thus, this paper attempts to rescue the importance of such changes, and to caution health professionals about how to conduct and deal with thyroid disorders during pregnancy.

Primary Objectives

To review possible new diagnostic and therapeutic schemes for thyroid diseases during pregnancy.

Methods

A literature review was performed using MedLine, PubMed, LILACS, Cochrane Library, and CAPES databases with articles published in English, Spanish or Portuguese, in the last 15 years, using the following descriptors: "hypothyroidism", "Hyperthyroidism", "High risk pregnancy", and "Thyroid and pregnancy".

Causes of thyroid function changes and pregnancy repercussions

For a long time, the literature has been presenting abundant material related to the diagnosis of SCH in pregnancy. Andrade., *et al.* [10] studied 75 pregnant women, living in the city of Itabuna, Bahia. The protocol contained the following inclusion criteria: pregnant woman

with no previous history of thyroid disease or diabetes mellitus, under 40 y.o., at any gestational age. These patients were evaluated through TSH, FT4, TPOAb, lipid profile and thyroid ultrasound. Results showed elevated TSH with normal free T4 (SCH) in three pregnant women (4.0%). TPOAb positivity was found in 8.0%, and 5.4% had thyroid ultrasound alterations. Based on these results, the authors considered the inclusion of thyroid evaluation in the prenatal examination routine of great importance. In 2005, laboratory evaluation of thyroid function was already indicated in the prenatal routine, in Brazil [10].

A very interesting study was published by Saraladevi, *et al* [4]. Based on the idea that thyroid disease is one of the most common endocrine disorders in pregnancy, they conducted a prospective clinical study in pregnant women during the first trimester. The results showed the prevalence of thyroid disorder of 11.6% (95% CI - 9.64 to 13.54) and corroborated those obtained in other parts of Asia. The prevalence of SCH and clinical hypothyroidism was 6.4% and 2.8%, respectively, while that of subclinical and clinical hyperthyroidism was 1.8% and 0.6%, respectively.

In this study, the main perinatal complications observed in SCH were: preeclampsia (9.3%), premature placental detachment (1.56%), premature delivery (7.81%), abortion (4.68%), restricted growth (6.25%), low birth weight (4.68%), and perinatal death (1.56%). When the authors analyzed the clinical hypothyroidism group, these numbers increased to 14.2%, 3.57%, 10.71%, 7.14%, 10.71%, 10.71% and 3.57%, respectively. Therefore, early diagnosis certainly helps to protect pregnancy [4].

Regarding hyperthyroidism, we can refer to an article by Parkers., *et al*. [11] which indicates that manifest, uncontrolled or poorly controlled maternal disease is associated with higher rates of preeclampsia and, less commonly, maternal heart failure. Thyroid “storm”, an acute and potentially fatal but uncommon function increase, can be precipitated by the stress of labor, caesarean section, or infection. As fetal complications, hyperthyroidism causes miscarriage, premature birth, restricted intrauterine growth, and stillbirth. Such complications can be reduced with the early control of overt hyperthyroidism.

The presence of thyroid antibodies in euthyroid pregnant women has been associated with several complications, such as miscarriage and premature delivery. The link between thyroid antibodies and infertility and assisted reproductive technology remains unclear [12]. In addition, further studies are necessary to clarify the mechanisms by which TPOAb increase adverse pregnancy outcomes [13].

Complications of thyroid control over pregnancy are ratified in the article by Stagnaro-Stein., *et al*. [14] which addresses the issue of diffuse lupus erythematosus (DLE). The study hypothesis is that pregnant women with DLE would have a high prevalence of undiagnosed hypothyroidism. The study shows a high prevalence of premature labor in DLE with hypothyroidism, much higher than in women with DLE without thyroid function changes. This was a retrospective study of the Hopkins Lupus Cohort and 63 pregnant women with DLE were tested for antibodies. About 13% of women had been treated with thyroid hormone before becoming pregnant, 11% were diagnosed with hypothyroidism during pregnancy, and 14% developed preterm labor. The prevalence of preterm birth was 67% in DLE women with thyroid disease and 18% in women free of thyroid disease ($p = 0.002$). Therefore, this is another concern in pregnancy in patients with collagen diseases.

An important intervening factor in thyroid diseases in pregnancy is the environment. An emblematic example for this fact is an article by Orvat., *et al*. [15] who studied this variable in Serbia at the time of war and aimed to clarify the tendency of pharmacological treatment of thyroid dysfunction during pregnancy. Depleted uranium radiation and pollution with polychlorinated biphenyls resulting from bombings in the Serbian territories, as well as additional long-term stress may have affected thyroid function. Women who gave birth at the Gynecology Department in 1989, 1999, 2007 and 2011 were interviewed for a month about thyroid disease in pregnancy, and also about the drugs they used. The results showed that no pregnant women were reported with thyroid disease in 1989 and 1999, while in 2007, four women were diagnosed with dysfunction in this gland. In 2011, fourteen of 18 women with thyroid dysfunction were

taking levothyroxine, and in most cases hypothyroidism was diagnosed as autoimmune. The authors indicated the need for more detailed analyzes of the correlation between the frequency of thyroid gland dysfunction and the effects of environmental pollution in Serbia.

Another very important repercussion of hypothyroidism on the fetus is explained in the work of Hu., *et al.* [16], which is based on the hypothesis that both perinatal hypothyroxinemia and iron deficiency are associated with fetal neurodevelopment. Iron is an important component of TPO, a key enzyme in thyroid hormone synthesis. The authors created two groups of guinea pigs and showed that maternal anemia led to maternal hypothyroidism and alterations in fetal brain development. Even mild pre-gestational iron deficiency decreased the total T3 level in the neonatal brain in some guinea pigs and led to reduced mRNA expression of thyroid hormones. In addition, there was a delay in sensorimotor skills. The study demonstrated that hypothyroxinemia associated with perinatal iron deficiency is enough to impair early brain development, even though this element is at normal levels in the neonatal brain. Thus, it is important to monitor the thyroid hormone level in women with perinatal iron deficiency.

Management of thyroid disease in pregnancy

In order to show that management of thyroid disease during pregnancy is still controversial, Koren., *et al.* [17] conducted a survey between Health professionals. The study involved obstetricians and endocrinologists from Israel, and the topic was how to diagnose and treat SCH and thyroid nodules during pregnancy. An electronic questionnaire was emailed to all members of the Israeli Societies of Endocrinology and Obstetrics and Gynecology and included demographic data and clinical scenarios with questions about screening and management of pregnant women with SCH, hypothyroxinemia, and a palpable thyroid nodule. Ninety responses were received from endocrinologists and 42 responses from obstetricians. Among endocrinologists, 39% would repeat TSH evaluation when a prior result was equivalent to 2.9 mU/L and accompanied of normal FT4 levels and would treat with levothyroxine if the second result was above 2.5 mU/L. Among obstetricians, 73% would follow the SCH patient in early pregnancy and only 22% would start thyroxine after a first TSH result above 2.5 mU/L [17]. Regarding screening, 57% endocrinologists and 71% obstetricians would recommend screening for thyroid dysfunction for all women in early pregnancy. Among endocrinologists, 54% would order an ultrasound for a palpable thyroid nodule and perform a fine needle aspiration only for suspicious lesions. The authors concluded that this approach requires well-defined and large-scale executable protocols [17].

Yamamoto and Donovan [18] investigated preconception issues in patients with thyroid disease. We can systematize their findings as follows: (1) Women in preconception and TSH less than 1.2 mIU/L should maintain the preconception levothyroxine dose, with adjustment indicated by TSH monitoring; (2) avoid ingesting levothyroxine along with iron or calcium-containing supplements as they interfere with thyroid hormone absorption (four-hour interval); (3) conception and birth rates are not influenced by mild thyroid dysfunction such as SCH, for example; (4) randomized clinical trial of levothyroxine therapy in women with TPOAb showed no difference in spontaneous abortion or preterm delivery rates; (5) women with active severe disease or toxic adenoma should delay pregnancy until thyroid function is restored. The maternal-fetal risk and benefits of available therapy (antithyroid drugs, radioactive iodine, thyroidectomy) should be discussed if pregnancy is planned. Women receiving radioactive iodine should be released from radiation six months before conception; Propylthiouracil (PTU) is the preferred drug for preconception treatment in patients with hyperthyroidism. Although there are studies that associate it with a small increase in the risk of congenital malformations, this drug is recommended for women who need treatment for hyperthyroidism and refuse radioactive iodine or thyroidectomy. Embryopathy secondary to the use of methimazole (MMI) in the first trimester is well established in several studies.

A Chinese study revealed that treatment of hypothyroid pregnant women with levothyroxine decreased the odds of gestational hypertension (odds ratio = 0.209), premature birth (OR = 0.253), and low (or very low) birth weight (OR = 0.327) when compared to the non-treatment group [19].

This section ends with the latest American consensus on thyroid disorders during pregnancy published by Korevaar [9], in 2017. Due to pregnancy-specific changes in thyroid physiology and maternal-placental-fetal interaction, thyroid care during pregnancy is complicated. The 2017 ATA Guidelines for Diagnosis and Treatment of Thyroid Disease during Pregnancy and Postpartum includes 97 recommendations based on 621 references [9]. The 2017 version has been considered strongly dependable and helpful to aid clinical decisions for medical providers and achieved high Guideline ratings [13,20].

The incorporation of new evidence into the old guidelines has led to several new and/or different recommendations that will impact clinical care. When evidence was strong, the recommendations allowed for the incorporation of risk stratification. On the other hand, upon weak impact evidence, treatment recommendations are made with caution (e.g. low initial dose of levothyroxine for mild thyroid disease) [9]. One of the most important changes in the current guidelines is the new recommendation on the definition of the reference range for TSH. In the previous edition, the TSH limit of 2.5 or 3.0 mIU/L was recommended for the first and second/third trimesters, respectively. Although many centers began to use these fixed cutoffs, studies have reported that their use led to a very high proportion of hyperthyrotropinemia (7.4 to 27.8%), and, in most cases, the upper limits of population based TSH thresholds were well above 2.5 and 3.0 mIU/L [9,19]. In addition to a population base or fixed TSH cutoff, the availability of recent reference interval studies facilitates a new approach, which is to adopt pregnancy specific TSH reference ranges, which were obtained using similar TSH assays and population. If adoption of a specific range assay reference is not possible, an upper TSH limit of 4.0 mIU/L is recommended [9].

This is in line with the TSH limits of large population studies on iodine insufficiency. Moreover, it is also consistent with the results of a recent US study demonstrating that levothyroxine may reduce the risk of miscarriage in women with TSH between 4.1 and 10.0 mIU/L and may increase the risk of adverse outcomes if the TSH is 2.5 to 4.0 mIU/L [9].

Another new aspect of current guidelines is the recommendation that levothyroxine therapy should be considered in women with TSH concentrations greater than 2.5 mIU/L and positive TPOAb due to increased risk of gestational complications. Such consideration is marked as a weak recommendation, as studies are still scarce and need to be replicated. However, there is circumstantial evidence supporting this recommendation, since women with positive TPOAb had an abnormal response to hCG stimulation, and two randomized controlled trials have shown that levothyroxine treatment in these pregnant women is beneficial [9]. Moreover, because thyroid antibodies may be falsely negative during gestation and serum negative chronic autoimmune thyroiditis is an important clinical entity to be considered in pregnancy, the Italian Thyroid Association emphasized their position favorable to the recommendation of treatment with levothyroxine in pregnant women with TSH levels ranging between the upper limit of the reference range and 10.0 mIU/L independently of their thyroid Ab status [21].

Future interventional trials may help to determine if early levothyroxine administration is needed in subclinical hypothyroidism and isolated hypothyroxinemia if their results suggest that treatment at 4 to 8 weeks' gestation, i.e. before organogenesis, is effective in establishing higher offspring IQ [13].

There are also important studies demonstrating that there is an association between MMI or PTU and adverse teratogenic effects. The 2011 recommendation was PTU treatment during the first trimester for hyperthyroidism due to Graves' Disease. However, new studies have identified an association of PTU with a higher risk of fetal anomalies. Since the association is with minor malformations, its prescription is still the preferred approach, and its use is now extended to the first 16 weeks [9]. Bartholo., *et al.* [22] suggest that PTU should be used in the first trimester of pregnancy due to embryonic effects of MMI. However, the former should be replaced by MMI after this period due to maternal and fetal hepatotoxicity.

From the new guidelines, it becomes clear that there is still insufficient evidence to recommend universal screening. The lack of adequate evidence on how to optimally identify at-risk women (i.e. using fixed cut-offs, population or risk profile) and the lack of data

on the benefits and/or harm of levothyroxine treatment are the two most important missing elements. For these two knowledge gaps, recent evidence suggests that some of the recommendations, standards of practice, and study designs that preceded these new guidelines may have been premature and very progressive. In retrospect, it seems likely that many physicians who strictly followed the diagnostic criteria established by the previous guidelines have diagnosed SCH early and excessively, leading to precocious and exaggerated treatment. Similarly, randomized controlled trials have been set up in the past without adequate knowledge of the expected effect size on the outcome of interest or dosage of treatment. The combined prevalence of SCH and hypothyroxinemia would exceed the prevalence of hypothyroidism manifested by a factor greater than 20. This index, combined with current cracks in knowledge in the field, makes universal screening prone to harm rather than benefit the population as a whole. Results from solid studies are expected to provide the tools needed to refine recommendations in the future [9].

New guidelines, published by Alexander, *et al.* [2], addresses several questions and answers that we summarize in the following paragraphs.

Thyroid function tests change during pregnancy due to increased iodine excretion, thyroxine-binding proteins and thyroid hormone production. Thus, the use of quarterly specific references based on the population studied remains the best way to deal with this problem [2].

According to studies with pregnant women in the United States and Europe, reference values for serum TSH concentrations in each trimester of pregnancy include an upper TSH limit of 2.5 mU/L in the first trimester and 3.0 mU/L in the second and third trimesters. When possible, we should create benchmarks for each trimester based on the local population. Reference range determination should include only pregnant women with no known thyroid disease, optimal iodine intake and negative TPOAb [2].

Regarding the ideal method for assessing serum T4 concentrations, the guideline indicates that the accuracy of serum FT4 measurement by the indirect analog radioimmunoassay method is influenced by pregnancy and also varies significantly according to manufacturer. If measured in pregnant women, the specific test method and pregnancy trimester specific reference ranges should be applied [2].

Iodine deficiency in the maternal diet results in impaired synthesis of maternal and fetal thyroid hormones. Low thyroid hormone values stimulate increased pituitary TSH production, resulting in maternal and fetal goiter. In areas of severe iodine deficiency, thyroid nodules may be present in up to 30% of pregnant women. Severe iodine deficiency in pregnant women has been associated with increasing rates of pregnancy loss, stillbirth, and infant mortality. Normal thyroid hormone levels are essential for migration, myelination, and other structural changes in the fetal brain. This fact is also demonstrated in the work of Hu., *et al* [16]. Universal salt iodization is the most cost-effective way of correcting this deficiency [2].

Thyroid dysfunction is associated with infertility in women so that, despite imperfect data, most evidence seems to support an association between thyroid dysfunction and increased risk of infertility. Treatment of the dysfunction is generally safe and can have a positive effect on fertility. So, it is prudent to treat thyroid disorders in infertile women focusing on normalizing gland function [2].

About SCH and its association with infertility in women, the guidelines stress that different definitions of SCH have been used in different studies making the results inconsistent. However, treatment with levothyroxine seemed to have positive results [2].

The authors had also pointed out that there is no evidence to support the idea that treating hypothyroidism leads to higher abortion rates [2]. Recommendations for the treatment of clinical hypothyroidism in pregnancy are definitive [2]. Therefore, women with hypothyroidism or risk of hypothyroidism should be monitored during pregnancy through monthly TSH [2]. In women who started levothyroxine treatment due to thyroid autoimmunity in the absence of TSH elevation, the medication may be discontinued at birth, with serum TSH assessed 6 weeks later [2].

Conclusion

The best way to prevent hypothyroidism is to add iodine to ingested salt.

Universal screening for thyroid function should be encouraged using TSH.

Levothyroxine is the drug of choice for the treatment of clinical and SCH in pregnancy. It should be adjusted according to the TSH levels.

For hyperthyroidism, PTU is the preferable option the first three months and, after this period, should be replaced by MMI.

The most prevalent complications arising from thyroid disease in pregnancy are preeclampsia, miscarriage, premature birth, and restricted growth. In hypothyroidism, impaired intellectual development and spontaneous abortion are more common, while in hyperthyroidism, RIUG and stillbirth are more frequent.

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