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IMPACT OF THYROID AUTOIMMUNITY ON PREGNANCY IN IODINE-SUFFICIENT AREAS

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ABSTRACT

Objectives: Pregnancy has a profound impact on maternal thyroid morpho-functionality; thus, thyroid dysfunction can cause multiple perinatal risks and complications. The aim of the study is to determine the incidence of maternal thyroid autoimmunity and dysfunction, their influence on some gestational and perinatal parameters of the newborn, and the impact of iodine status on thyroid autoimmunity in a region with sufficient iodine intake.

Material and method: Retrospective study conducted on a number of 74 full-term pregnancies with singletons, pregnant women originating from the perimarine area of Romania. The participants were divided into 2 groups: group 1 - pregnant with chronic autoimmune thyroiditis and subclinical/clinical manifest hypothyroidism; group 2 - pregnant without thyroid pathology considered as a control group. Maternal variables studied: dosage of thyroid hormone and antithyroid autoantibodies, median urinary iodine concentration; and for the newborns: birth weight, APGAR score, gestational age, incidence of perinatal events. The administration of iodine supplements during pregnancy was monitored.

Results: The incidence of chronic autoimmune thyroiditis was 36.4%. Maternal thyroid autoimmunity is associated with low birth weight and premature birth compared to the control group. The predominant perinatal pathology among pregnant women with thyroid autoimmunity was represented by spontaneous abortion, presenting a 2.8x higher risk compared to the control group. Median urinary iodine concentration was under 150 mcg/L in both studied groups of pregnant women. Iodine nutritional deficiency, but also excess iodine intake, were positively correlated with maternal thyroid autoimmunity. Consumption of iodine supplements and iodized salt was reduced in the category of pregnant women with thyroid autoimmunity.

Conclusions: Thyroid autoimmunity during pregnancy presents significant challenges even in iodine-sufficient geographical areas. Maternal autoimmune thyroiditis represents a risk factor with effects on fetal development and repercussions in the perinatal period. Evaluation of thyroid function parameters before conception or in the first weeks of pregnancy is recommended as a diagnostic and prophylactic measure.

Keywords: thyroid, iodine, autoimmunity, pregnancy, perinatal events.

Introduction

Undiagnosed or insufficiently treated thyroid dysfunction during pregnancy can have numerous repercussions on newborns(1, 2). Pregnancy – defines a complex functional unit – feto-placental unit – which has its own endocrine activity with a series of maternal adaptive changes necessary for embryo-fetal development. The factors involved in the genesis of morphological and functional changes in the thyroid during pregnancy are endogenous – autoimmunity, placental hormones and exogenous or environmental – iodine intake, contact with goitrogenic substances. Antithyroid antibodies (TPOAb – thyroid peroxidase antibody, TGAb – thyroglobulin antibody) are frequently detected above the upper limit during

pregnancy (incidence 2-17%), establishing the diagnosis of chronic autoimmune thyroiditis (CAT) or Hashimoto's disease (3). The risks of thyroid autoimmunity frequently associated with clinical or subclinical hypothyroidism are: sporadic/ spontaneous abortion (2x higher risk in pregnant women with positive TPOAb/TGAb), recurrent spontaneous abortion, premature birth, low APGAR score, placental abruption, postpartum depression, neonatal respiratory distress, gestational hypertension, attention deficit/hyperactivity disorder in children born to ATPO positive mothers (3).

Antithyroid antibodies as independent factors may increase the rate of spontaneous abortions or premature births with increased perinatal mortality (2-4) and maternal complications (1, 5). Although there is a consensus on the negative impact of thyroid dysfunction during pregnancy, differences between a number of studies regarding the availability of extensive data and ethnic differences in TSH concentrations determine the lack of firm conclusions. Also, large-scale population studies evaluating the effect of thyroid dysfunction and autoimmunity on pregnancy and the perinatal period in geographical regions with sufficient iodine intake are lacking (6).

Pregnant women with thyroid autoimmunity may remain euthyroid in the first trimester of pregnancy in approximately 10-20% of cases, according to the 2017 ATA (American Thyroid Association) guidelines on the diagnosis and management of thyroid disorders during pregnancy and postpartum (3). The lack of consensus on maternal-fetal complications in the perinatal period in euthyroid pregnant women with thyroid autoimmunity requires thyroid screening.

Iodine is an essential element for the synthesis of thyroid hormones, which are necessary for the growth process, neurocognitive development, maintenance of metabolic processes, and energy balance (7).

Although the south- eastern region of Romania, the Dobrogea area, is part of a geographic area with sufficient iodine intake and an apparently adequate iodine status of the general population, there may be differences in certain population categories, such as pregnancy, which is characterized by increased iodine requirements, but also by additional iodine excretion. It is known that maternal exposure to low or high iodine concentrations can have adverse effects during pregnancy, with a maternal-fetal impact in terms of initiating or aggravating thyroid autoimmunity (8, 9).

Materials and methods:

A study was conducted between 2020 and 2022 on 74 pregnancies with singletons born to mothers originating from the Dobrogea region. TPOAb/TGAb levels and trimester-specific TSH values were measured using the ECLIA method. The diagnosis of chronic autoimmune thyroiditis was established based on pathological values of TPOAb > 34 IU/ml/TGAb > 115 IU/ml and the thyroid functional status according to TSH-trimester specific values. The identification of the iodine status of pregnant women was assessed according to WHO (World Health Organisation) recommendations by determining the median of urinary iodine concentration (mUIC), which is adequate at values between 150 – 249 mcg/l, more than adequate: 250 - 499 mcg/l, insufficient < 150 mcg/l and excessive > 500 mcg/l (10).

Pregnant women were divided into 2 study groups: group 1 (n= 27) - pregnant with CAT and subclinical/clinically manifest hypothyroidism (increased TSH and normal/low FT4 – trimester specific), group 2 or control (n= 47) - pregnant without CAT and normal thyroid function. For newborns, the following data were evaluated: birth weight, APGAR score, gestational age at birth (premature birth being considered pregnancies with gestational age < 37 weeks), and perinatal events. Daily administration of iodine-containing supplements during pregnancy and daily consumption of iodized salt were also monitored.

Statistics

The research data were analyzed using the SPSS statistical software. The calculated data were reported as median and IQR or were expressed as numbers and percentages (%). Logistic regression analysis was used to evaluate the association between iodine status and thyroid autoimmunity during pregnancy. Non-parametric statistical tests were used for ordinal

data or numerical variables (Mann-Whitney U test, median test). Statistical significance was considered at $p < 0.05$.

Results

The incidence of chronic autoimmune thyroiditis among pregnant women was 36.4% (ATPOAb/TGAb positive = 27 cases; TPOAb/ TGAb negative = 47 cases) (Figure 1). The mean age of pregnant women at diagnosis of chronic autoimmune thyroiditis was higher compared to the control group (30.6 versus 29.6 years), but without statistical significance (Figure 2). Pregnant women with CAT presented subclinical or clinically manifest hypothyroidism, have a median TSH value of 3.7 mIU/ml and FT4 median value of 13,5 pmol/L (Table 1).

Tabel 1: UIC and thyroid hormones level in pregnant women with and without chronic autoimmune thyroiditis

Variables (median, IQR)	Group 1 (CAT +) subclinic/clinic hypothyroidism, n= 27 (36, 4 %)	Group 2 (CAT) euthyroidism, n=47, (63,5%) (control)	p
TSH (µUI/mL)	3.7 (2,2 -6,5)	1.6 (0,7 – 2,8)	< 0,05
FT4 (pmol/L)	13.5 (11,6 -16)	15,1 (13,5 – 17)	0,33
UIC, mcg/ml	141.4 (60- 203)	124.9 (77 - 217)	0,634

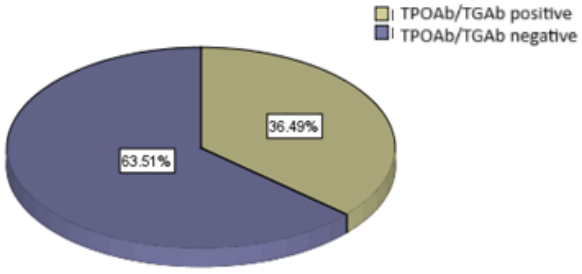

Figure nr. 1- Distribution of pregnant according to positive/negative antithyroid antibodies

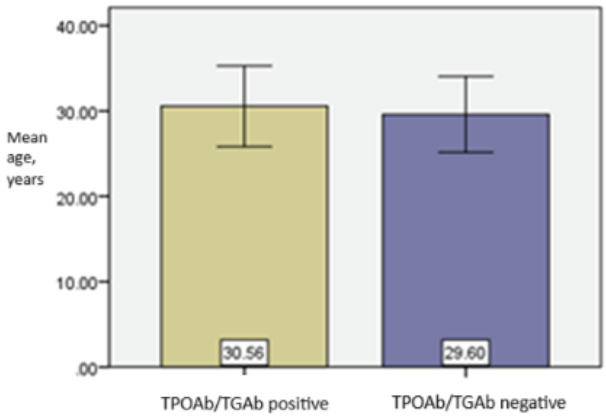

Figure nr. 2 – Distribution of pregnant with/without positive ATPOAb /ATGAb according to age

We identified an inadequate iodine status of pregnant women assessed by the UIC value, which fell within the insufficient range for both groups with a median of UIC <150 mcg/l (group1: mUIC = 141.4 mcg/L, group2: mUIC = 124.9mcg/L) although all pregnant women originated in iodine - sufficient geographical areas(Table 1).

The analysis of association between UIC distributed over value ranges (severe iodine deficiency < 50 mcg/L, moderate iodine deficiency: 50-150 mcg/L, adequate intake: 150 -250 mcg/L and excessive intake: 250 - 499 mcg/L) (according to WHO) (10) and the presence of positive TPOAb/ TGAb revealed a positive correlation in the group of pregnant women with UIC < 50 mcg/L ($r = 1.10$, $p < 0.045$) and in the group with excessively high UIC values between 250 - 499 mcg/L ($r = 0.90$, $p < 0.05$) (Table 2).

The group with maternal thyroid autoimmunity had lower birth weight compared to newborns from mothers with normal thyroid function, but without statistical significance. The APGAR score < 7 in the first minutes was described in 5.4% of pregnant women with CAT, showing a statistical difference compared to the control group.

Table 2. Distribution of pregnant women with positive/negative TPOAb/TGAb according to the range of UIC values mcg/L

UIC intervals	< 50 mcg/L	50-150 mcg/L	150-250 mcg/L	250- 499 mcg/L	p
TPOAb/TGAb pozitiv, n, %	8 (10,8 %)[1]	5 (6,8%)	5 (6,8%)	9 (12,2%) [2]	[1] 0,045 , [2] 0,050
TPOAb/TGAb negative, n, %	7 (9,5%)	24 (32,4%)	7 (9,5%)	9 (12,2%)	0,034

The incidence of premature births shows statistically significantly increased values in pregnant women with thyroid autoimmunity and thyroid dysfunction compared with the control group of pregnant women without thyroid autoimmune pathology (6,7 % versus 4,05 %).

The administration of iodine supplements recorded the highest incidence in group 2 (19% - pregnant women without autoimmunity with euthyroidism) compared with group 1 (14.8% - pregnant women with autoimmunity and thyroid dysfunction). Although the incidence of iodized salt intake is below the WHO recommended level (> 90% of households), only half of the pregnant control women used iodized salt (55.4%), and only a quarter of pregnant women with thyroid autoimmunity used iodized salt in their diet (27%).

Tabel 3: Neonatal and maternal variables

Variables	Group 1 CAT (+) subclinic/clinic hypothyroidism, n= 27	Group 2 CAT (-) euthyroidism, n= 47
Birth weight, gr. (mean)	3578	3620
APGAR score ≤ 7 (n, %)	4 (5,4 %) [1]	3 (4,05 %)
Premature birth (n, %)	5 (6,7 %) [1]	3 (4,05 %)
Iodine supplements, n, %	11 (14,8 %)	14 (19 %)
Iodized salt consumption, n, %	20 (27%)	41 (55,4%)
[1] p < 0,05 statistically significant by comparing with the control group		

We evaluated pregnant women according to perinatal events occurring during pregnancy, and the most frequent gestational pathology was spontaneous abortion among pregnant women with thyroid autoimmunity and thyroid dysfunction, with a relative risk of 2.8 times higher compared to pregnant women without thyroid autoimmunity. We did not identify a statistically significant difference between the threat of abortion and that of premature birth, pregnancies stopped in evolution in the case of pregnant women with and without thyroid autoimmunity (Table 4).

Table 4: Incidence of perinatal events

Nr. cases = 74	Group 1 (CAT +) subclinic/clinic hypothyroidism, n= 27	Group 2 (CAT) euthyroidism, n=47
Threatened Abortion	2 (2,7 %)	5 (6,7%)
Spontaneous abortion	2 (2,7 %) [1]	1 (1,3 %)
Pregnancy stopped in progress	1 (1,3%)	1 (1,3 %)
Threat of premature birth	2 (2,7%)	7 (9,4%)
Total	7 (9,4 %)	14 (18,9 %)
[1] RR = 2,8		

Discussions

Chronic autoimmune thyroiditis in pregnancy can be considered an element of immune imbalance with the risk of being the cause of rejection of the fetus by the maternal body. In iodine-sufficient regions, pregnant women with chronic autoimmune thyroiditis may present a series of pregnancy-related complications, possible causes proposed to be involved were: the presence of anti-thyroid antibodies as markers of a generalized autoimmune imbalance that may be responsible for the increased rate of spontaneous abortions; women with preconception CAT may develop subclinical or clinically manifest hypothyroidism in pregnancy; also chronic autoimmune thyroiditis is a risk factor for infertility and women with positive antithyroid antibodies have an older age which may explain the increased rate of abortions (11).

Perinatal complications related to thyroid autoimmunity, such as spontaneous abortion, premature birth, gestational hypertension, fetal dyspnea, and gestational diabetes, have been described in numerous studies (12).

Antithyroid antibodies (TPOAb, TGAb) are frequently positive in women of childbearing age with an incidence of 6-20%, and in pregnant women, they are found between 2-17% (3). The incidence of CAT in our study of 34% presents a higher value than the statistical values of the guidelines, possibly due to the small number of studied cases and/or excessive/low exogenous iodine intake, which can be considered a trigger of thyroid autoimmunity.

Women with thyroid autoimmunity remain pregnant. 3 - 4 years later and thus present a higher risk of miscarriage (13, 14). In our study, although there was no statistically significant difference in the age of the pregnant women between the groups, pregnant women with autoimmune thyroiditis presented an older age.

The correlation between iodine status and thyroid autoimmunity has been inconsistent, with studies identifying low urinary iodine concentration as an independent factor for positive TGAb values (9) and studies in iodine-sufficient geographical areas of China finding that iodine deficiency was associated with an increased risk of positive TPOAb and TGAb (15). However, there are also studies supporting the opposite, namely that exposure to excessive iodine intake causes or aggravates thyroid autoimmunity, according to Rayman et al., which means that maintaining an adequate iodine status is crucial for thyroid function (16). Low (< 50 mcg/L) and high (250–499 mcg/L) UIC values were positively correlated with the presence of antithyroid antibodies in the present study. It has been reported that iodine deficiency could influence thyroid autoimmunity through inflammatory responses induced by oxidative stress, and highly iodinated thyroglobulin caused by excessive iodine intake is more immunogenic, thus accelerating the thyroid autoimmune process (16, 17).

Lower birth weight was recorded in newborns of mothers with thyroid autoimmunity compared to newborns of mothers without autoimmunity in the present study. The same results were presented by the study of Karakosta et al., who claimed that the association between elevated TSH and thyroid autoimmunity presents a 3x higher risk for low birth weight, while the presence of autoantibodies alone was not associated with fetal growth restriction (12).

Pregnant women with positive TPOAb or TGAb have a higher risk of low APGAR score (< 7) in the first minutes, independent of thyroid dysfunction (11), the data being in agreement with the results of our study.

Thyroid antibodies may cause a subtle reduction in thyroid function or may reflect a generalized activation of the immune system, especially at the feto-maternal interface (12, 18). Pregnancy is associated with a change in the cytokine network at the placental-decidual level; an imbalance at this level may be associated with miscarriage and premature birth (18). Pregnant women with thyroid autoimmunity and subclinical/clinically manifest hypothyroidism (group 1) had a 2.5x higher risk compared to the control group regarding the incidence of premature births in our study. In support of the present study, we mention the results of a recent meta-analysis that claims that maternal autoimmunity increases the risk of premature birth by 2x in pregnant women with normal thyroid function (18). However, the rate of premature births decreases when combined with levothyroxine therapy (11). Increased perinatal mortality was associated with thyroid autoimmunity (2- 3x risk) and not with thyroid hormonal status, according to Mannisto et al. (1), results that may also be attributed to the increased incidence of preterm birth (1, 12, 18). The combined effect of thyroid autoimmunity and elevated TSH levels, however, was not associated with preterm birth (11).

There are numerous studies that support that iodine supplementation in patients with thyroid autoimmunity can worsen or accelerate the progression of the disease to clinically manifest hypothyroidism. This aspect is even more dangerous during pregnancy, associating a series of complications and adverse effects on fetal morpho-functional development (19, 20). It is considered necessary to evaluate maternal iodine status at a population level by urinary iodine, and then recommendations will be issued for iodine supplementation or not. The present study was conducted in a non-endemic area for IDD (iodine deficiency disease), so special attention will be paid to pregnant women with thyroid autoimmunity in terms of iodine supplements that can be considered triggers for morpho-functional thyroid dysfunction with a series of repercussions in the perinatal period (20). Thus, although iodine supplementation is necessary for the prevention and treatment of IDD, iodine supplementation must be maintained at a safe level. A number of other studies suggest that the negative effect of iodine supplementation in Hashimoto's thyroiditis may be related to selenium deficiency. Selenium supplementation reduces thyroid destruction by the autoimmune

process by eliminating free oxygen radicals and lowering antibody titers (5).

The most common gestational pathology associated with CAT is spontaneous or recurrent abortion. In the present study, we identified an increased incidence of spontaneous abortions in the group of pregnant women with thyroid autoimmunity compared to the control group. The relative risk of spontaneous abortion in the group with CAT is 2.8x higher than in the group without thyroid autoimmunity. The explanation may be due to pregnancy-related complications (diabetes or preeclampsia), fetal dyspnea, or intrauterine growth restriction present in pregnancies associated with thyroid dysfunction (2). Population studies in 1990 by Stagnaro-Green et al. were the first to demonstrate the association between spontaneous abortion and antithyroid antibodies, specifying a 2x higher risk for spontaneous abortion (21). Another recent meta-analysis on 14 cohort studies reveals a 2.3x higher relative risk of abortion in pregnant women with thyroid autoimmunity compared to those without autoimmunity (22). Possible mechanisms implicated are: the autoimmune process that causes increased fetal resorption, antibody-mediated hypothyroidism, cross-reactivity of antithyroid antibodies with hCG receptors in the zona pellucida, and the presence of a competing non-organ-specific autoimmunity and increased levels of endometrial cytokines in women with thyroid autoimmunity (3, 23).

Conclusions

Maternal and fetal health can be affected by thyroid dysfunction in pregnancy, making early screening, diagnosis, and therapeutic approach mandatory measures. Evaluation of thyroid autoimmunity during the first trimester of pregnancy can prevent a number of materno - fetal complications. Caution should also be exercised when administering iodine supplements to pregnant women with autoimmune thyroid disease.

Longitudinal studies are needed to understand particular aspects of thyroid physiology during pregnancy, along with specifying effective prevention measures in order to anticipate the adverse effects of autoimmune thyroid disease on the mother and child.

In conclusion, the relationship between thyroid autoimmunity and pregnancy in iodine-sufficient areas emphasizes the importance of monitoring and managing thyroid health in expectant mothers. Autoimmune thyroiditis carries risks that can affect perinatal outcomes, requiring careful evaluation and treatment. With appropriate management, women with thyroid autoimmunity can achieve healthy pregnancies, highlighting the importance of awareness and proactive care in this population.

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Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

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