ORIGINAL ARTICLE

Thyroid Function in Offspring of Mothers with Hashimoto's Thyroiditis

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ABSTRACT

Autoimmune thyroid disease (AITD) in mother may be a cause of thyroid dysfunction in child. The aim of this paper was to evaluate thyroid function and presence of antithyroid antibodies in children of mothers with Hashimoto's thyroiditis (HT) in the 1st year of life. **Materials and Methods:** Four hundred children were included into the study (195 boys, 205 girls, two twin pregnancies) of mothers with HT. The first visit in endocrinology out-patient clinic was done in 1st–2nd months of life and the follow-up visit at 6th–9th months of life. Anthropometrics were taken as well as blood samples for thyroid-stimulating hormone (TSH), fT3, fT4, ATPO, and ATG. Mothers had all proper thyroid function during the whole pregnancy. **Results:** 356 children (89.2%) were born on term (38–42 Hbd), 283 (70.1%) with normal vaginal delivery, 356 (89.0%) in good condition (Apgar 8–10), mean birth weight was 3394.28 ± 374.81 g, and mean birth body length was 56.09 ± 1.90 cm. In three patients, trisomy 21 was diagnosed. The neurological development of all children was not concerning. Thyroid function was proper (mean TSH 5.41 ± 0.90 μIU/ml, fT3 8.00 ± 1.24 pg/ml, fT4 16.89 ± 2.09 TSH 5.39 ± 0.90 μIU/ml, fT3 7.99 ± 1.22 pg/ml, and fT4 16.86 ± 2.12 pmol/l). None of the observed child had elevated titer of antithyroid antibodies. **Conclusions:** (1) Malfunction of the thyroid gland in children of mothers with HT is rare; therefore, no further diagnostic procedures except screening test is required. (2) In preterm babies as well as in children presenting characteristic signs and symptoms, more detailed evaluation (TSH and fT4 levels) is necessary.

Key words: Antithyroid antibodies, autoimmune thyroid disease, congenital hypothyroidism, hashimoto's thyroiditis

INTRODUCTION

Hypothyroidism in pregnancy occurs in approximately 3% of women, including subclinical hypothyroidism (thyroid-stimulating hormone [TSH] concentration above the upper limit of normal for pregnancy and normal free thyroxine (fT4) concentration) diagnosed in 2–2.5% of pregnant women, and overt hypothyroidism (fT4 below normal in combination with elevated TSH, or TSH concentration above 10 mIU/L regardless of fT4 concentration) in 0.2–0.5% (Lazarus *et al*. 2014). The main cause of mother's hypothyroidism is autoimmune Hashimoto's thyroiditis (HT) and iodine deficiency.[1-3]

Untreated thyroid disease in a pregnant woman increases the risk of obstetric complications, including anemia, hypertension, miscarriage or premature birth, as well as low-birth weight and low Apgar score in offspring.[1,4-6] It is believed that proper treatment of the mother with L-thyroxine (LT4) reduces the risk of above-mentioned complications.[7,8]

Thyroid hormones determine the correct growth and development of the child. In the first trimester, the fetus is completely dependent on maternal hormones, in the subsequent months of pregnancy, after fetal thyroid gland is formed - partially.[9,10] Abnormal maturation of nerve tissue and fetal brain, followed by worsening of the child's

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neuropsychological development, including attention deficit hyperactivity disorder (ADHD), is a possible consequence of untreated hypothyroidism in the mother during pregnancy.[11-14]

The detection of antibodies against thyroid antigens in serum is not only important in the differential diagnosis of thyroid diseases but also has prognostic significance. In 8–18% of women of childbearing age, positive titers of anti-thyroperoxidase (ATPO) and/or thyroglobulin (ATG) antibodies, characteristic of HT, are found. The prevalence of thyroglobulin and thyroperoxidase antibody positivity is increasing with the age of the women. Autoimmune thyroid disease (AITD) is diagnosed in 5–20% of pregnant women.[15,16] It is believed that even if a pregnant woman remains euthyroid, the presence of antithyroid antibodies may increase the risk of obstetric failure: Infertility, miscarriage or premature birth, and postpartum thyroiditis.[4,8] In addition, the risk of developing overt hypothyroidism in women who have been diagnosed with thyroid antibodies and who have remained euthyroid so far, is higher. Therefore, thyroid function in these women requires systematic monitoring.[1,2,8]

The mother's AITD may cause thyroid dysfunction in the child. Both in Graves' disease and in lymphocytic thyroiditis, thyrotropin receptor blocking antibodies (TRBAb) are present. These are IgG antibodies against the thyrotropin receptors located in cell membrane of thyroid follicular cells. Maternal TRBAb antibodies pass through the placenta and may block the TSH access to appropriate receptors in the fetal thyroid. In the first trimester of pregnancy, this results in dysgenesis of fetal thyroid gland, and in the next ones, due to insufficient production of thyroid hormones, it leads to primary hypothyroidism.[17]

Hypothyroidism caused by TRBAb occurs in 1–2% of children with congenital hypothyroidism.[17] It is usually detected in a neonatal screening test, because the child has a high concentration of TSH and low concentration of fT4.[11,17,18] The immediate administration of LT4 substitution in these children ensures their proper psychomotor development. Hypothyroidism caused by TRBAb usually recovers after elimination of maternal antibodies within 1–6 months. At the 12th month of the child's life, the diagnosis may be verified and the LT4 treatment is possibly terminated.[11,17]

The aim of the study was to assess the function of the thyroid gland and the presence of antithyroid antibodies in offspring of mothers suffering from chronic lymphocytic HT, in their 1st year of life.

PATIENTS AND METHODS

The retrospective study involved 400 children (195 boys and 205 girls, two twin pregnancies), offspring of mothers with HT, referred to our department in 2012–2017 from neonatal wards. Endocrine check-up in the 1st month of life is routinely recommended for those children. Children were examined twice in the department by the authors of the publication. Only children, in whom the control visit was performed, were included in the analysis. The first visit took place in 1–2 months of life (average 4.5 weeks), the second visit in 6–9 months (average 7.5 months). Anthropometric measurements were performed, and venous blood was collected for: TSH, fT3 (free triiodothyronine), fT4, ATPO, and ATG concentrations measurements.

Maternal history

All mothers were diagnosed and treated for HT from 6 months to 15 years before pregnancy. The diagnosis in all cases was confirmed by the presence of ATPO antibodies and/or (in 15%) by positive ATG antibodies titer. Furthermore, during pregnancy all women were treated with LT4 at a dose of 25–150 mcg/day. The TSH level during pregnancy was within normal ranges and did not exceed 2.5 μIU/ml (mean TSH concentration was 1.6 ± 0.8 μIU/ml).

The statistical analysis was conducted with the use of Statistica software (TIBCO Software Inc. (2017), Statistica (data analysis software system), version 13. http://statistica.io.). Means (standard deviations) and percentages for all included variables are presented.

The Shapiro–Wilk test was used to confirm the consistency of analyzed sample's age distribution with the normal distribution. As the distribution of analyzed samples was not significantly different from normal distribution of statistically identical variance, to assess eventual differences the t-test was used. The intergroup frequency assessment was performed with the use of Chi-squared test. Yate's correction was applied when the expected frequency was less than 5 or the total count was <50. Any difference with $P < 0.05$ was statistically significant.

RESULTS

Clinical characteristics of children are presented in Tables 1 and 2.

In all 400 children examined, the result of screening for hypothyroidism was negative. Three children were diagnosed with trisomy 21, while others did not have any genetic syndromes.

Condition of 356 (89.25%) children was good, no significant abnormalities were found in the physical examination. Six (1.5%) children (including all four from two twin pregnancies) had increased muscle tone, six (1.5%) children (including all three with Down's syndrome) had a heart defect, and one (0.25%) had vesicoureteral reflux; moreover, in two boys (1.03%) hypospadias was found.

Table 1: Clinical characteristics of studied children – perinatal history

	All children *n*=400 (%)	Boys *n*=195 (%)	Girls *n*=182 (%)	*P*
Parity				0.0461
1	235 (58.8)	114 (58.5)	121 (59.0)	
2	133 (33.3)	59 (30.3)	74 (36.1)	
3	32 (8.0)	22 (11.3)	10 (4.9)	
Labor				>0.05
Vaginal delivery	283 (70.8)	137 (70.3)	146 (71.2)	
Cesarean section	117 (29.2)	58 (29.7)	59 (28.8)	
Gestational age				>0.05
41–42 Hbd	8 (2.0)	5 (2.6)	3 (1.5)	
38–40 Hbd	349 (87.2)	169 (86.7)	180 (87.8)	
36–37 Hbd	27 (6.8)	15 (7.7)	12 (5.9)	
35 Hbd	16 (4.0)	6 (3.1)	10 (4.9)	
<35 Hbd	0	0	0	
Mean birth weight (g)	3394.3±374.8	3419.3±351.7	3370.5±395.0	>0.05
Mean birth length (cm)	56.1±1.9	56.0±2.0	56.2±1.8	>0.05
Apgar score in 5’				>0.05
8–10	356 (89.0)	179 (91.8)	177 (86.3)	
6–7	29 (7.2)	9 (4.6)	20 (9.8)	
5	15 (3.8)	7 (3.6)	8 (3.9)	
<5	0	0	0	

Table 2: Results of the follow-up examination

	All children *n*=400 (%)	Boys *n*=195 (%)	Girls *n*=205 (%)	*P*
Body mass (percentiles)				>0.05
90–97	2 (0.5)	2 (1.0)	0	
75–90	14 (3.5)	9 (4.6)	5 (2.4)	
50–75	50 (12.5)	21 (10.8)	29 (14.1)	
50	240 (60.0)	119 (61.0)	121 (59.0)	
25–50	58 (14.5)	26 (13.3)	32 (15.6)	
10–25	29 (7.2)	16 (8.2)	13 (6.3)	
3–10	7 (1.7)	2 (1.0)	5 (2.4)	
TSH (μIU/ml)	5.40±0.90	5.39±0.94	5.41±0.87	>0.05
fT3 (pg/ml)	8.00±1.22	8.06±1.29	7.94±1.16	>0.05
fT4 (pmol/l)	16.86±2.12	16.91±2.26	16.82±1.98	>0.05

In all examined children, thyroperoxidase and thyroglobulin antibodies titers were negative during both visits. Both intellectual and motor emotional development of patients did not raise any objections. None of them presented symptoms of thyroid dysfunction.

Birth weight, Apgar scores and gestational age were not significantly affected. Likewise, body weight at second visit was not influenced by thyroid function.

DISCUSSION

It is believed that the risk of thyroid dysfunction in a newborn of mother with autoimmune thyroiditis is higher than in the general population. This is because antithyroid antibodies freely cross the placenta: Both ATPO and ATG, as well as thyrotropin receptor blockers and cytotoxic antibodies. Therefore, some researcher’s advice to assess the anti-thyroid antibodies (especially thyrotropin receptor antibodies – TRAb) in a child’s mother in early pregnancy: If the titers of these antibodies are within the reference range, the risk of thyroid dysfunction in the newborn is small.[15,16] The screening test would then be the only diagnostic method for the child’s thyroid function. If, however, the determination of TRAb antibody titers would be impossible, the child is advised to evaluate the thyroid function (both TSH and fT4) on the 7–14 day of life to detect transient hypothyroidism or, rarely, hyperthyroidism.[17,19]

Data on the prevalence of antithyroid antibodies and thyroid function of infants from women with HT are scant. Brown *et al*. showed that in the United States the presence of TSH receptor

blocking antibodies is the cause of congenital hypothyroidism in 2% of patients with this disorder, occurring at a frequency of 1:180,000 births. All children positive for TRBAb antibodies were diagnosed with transient hypothyroidism and all mothers of these children had AITD.[20] The only hormonal disruption observed by Danish researchers in newborns of AITD mothers was transient hyperthyroxinemia for the first 7 days of age. The ATPO antibody titers in the blood of the studied children correlated with the titers of these antibodies in the mothers during pregnancy and normalized within few weeks concomitantly with a decrease in fT4 concentration. There was no need to substitute LT4 in this group. It was noteworthy that up to 21% of newborns had severe hyperbilirubinemia.[21] In Rovelli *et al*. study, in 28% (36/129 patients), the children of mothers with AITD, tested at 3, 15, and 30 days of age, elevated level of TSH in at least one examination was determined, which normalized in most cases without the need for pharmacotherapy. Only 2% (three children) of all subjects required substitution with levothyroxine due to persistent "mild" hyperthyroidism (TSH concentration around 10 mIU/L). ATPO antibodies were positive in 59% of children in the 15th day of life, however negative on 6 month of life check-up. Furthermore, ATPO was detected in 47% of patients with hyperthyroidism and in 2 of 3 patients who needed to be treated with LT4.[22]

Disorders of thyroid function in children of mothers with AITD seem to be rare. Furthermore, in our observation, both during the first and second examination, none of the children presented symptoms of thyroid dysfunction. Moreover, the concentrations of fT3, fT4, and TSH were within the reference range. In contrast to the cited authors, none of the infants, we examined were positive for thyroid antibodies. It should be underlined however that we tested for ATPO and ATG in the 4th week of life and after the child finished 6 months of life, so later than in mentioned studies. Therefore, even initially elevated thyroid antibodies titer might have normalized until the time of the visit.

Screening for congenital hypothyroidism in Poland includes assessment of TSH levels after the second up to 5th day of life. In case of an abnormal result, the newborn is referred for counseling by a pediatric endocrinologist: Both TSH and fT4 levels should be determined and appropriate substitution treatment initiated.[11] It is obvious that screening test involving only the assessment of TSH does not allow the diagnosis of secondary hypothyroidism; moreover, the measurement done usually on 3rd day of life excludes children in whom the level of TSH increases later. However, it should be emphasized that in our study, as well as in Danish and Italian observation, no child presented secondary hypothyroidism.[21,22] Italian researchers pointed out that in one newborn (out of 129 included in the trial), TSH levels increased between the 3rd and 15th day of life, and treatment with LT4 was required. In this patient, the only indication for the control of thyroid function afterward screening test was mother's HT. It is noteworthy that this patient did not show elevated ATPO titer. In the other two children receiving LT4, TSH was elevated already during screening – on the 3rd day of life.[22]

The presence of TRAb in Hashimoto's disease is relatively rare, with a probability of 10 to 20%.[23] In the observation of Rovelli *et al*., both ATPO and ATG antibody titers did not correlated with TSH concentration and there positive in two out of three children requiring LT4 treatment. This is another confirmation that both ATPO and ATG antibodies have no effect on fetal and neonatal thyroid function.[2,22-25] On the other hand, Weber *et al*. found that maternal antithyroid antibodies, including ATPO, are responsible for 27% of cases of transient congenital hypothyroidism.[26]

AITD are diagnosed in approximately 20% of pregnant women, while thyroid dysfunction in their offspring occurs sporadically and usually is possible to be detected by a screening test. It seems, therefore, that an additional assessment of the thyroid function in children of mothers with Hashimoto's disease is redundant and as so his procedure should be regarded as disproportionate diagnostics.[22,23] It should be emphasized that it results in the need to visit the reference center and collect blood in a healthy child, without any other indications, also involves unnecessary anxiety of parents. Deepening the diagnosis (evaluation of TSH, fT3, and fT4) should be reserved for patients presenting signs and symptoms of thyroid dysfunction.

It should also be remembered that in the preterm newborn, the activity of the hypothalamus-pituitary-thyroid axis may be immature and so results in secondary hypothyroidism in the child. In this situation, assessing the TSH and fT4 concentrations ensures proper and early diagnosis and, if needed, an appropriate treatment.[11]

CONCLUSIONS

1. Malfunction of the thyroid gland in children of mothers with HT is rare; therefore, no further diagnostic procedures except screening test is required.
2. In preterm babies as well as in children presenting characteristic signs and symptoms, more detailed evaluation (TSH and fT4 levels) is necessary.

DECLARATION OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

A statement of ethics approval and consent – not applicable.

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AUTHORS' CONTRIBUTIONS

AZK – concept of the study, methodology, investigation, data curation, formal analysis, drafting of the initial manuscript, review, and editing of the manuscript. JC – concept of the study, methodology, investigation, data curation, formal analysis, drafting of the initial manuscript, review, and editing of the manuscript. AN – concept of the study, methodology, investigation, data curation, formal analysis, review, and editing of the manuscript and supervision.

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