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Influence of obstetric factors on the development of postpartum antithyroid antibodies

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ABSTRACT

Aim: To correlate obstetric data with the appearance of antithyroid antibodies. Methods: A 6 months follow up was performed on 135 healthy women with assessment of TSH, T3, T4 and antithyroid antibodies (anti thyroglobulin and anti peroxidase). Correlation of diverse obstetrical parameters with the appearance of antithyroid antibodies at 2 and 6 months postpartum was determined. Results: Only two parameters were significant during the complete follow up: the newborn weight, which correlated with both antibodies (anti-thyroglobulin and anti-peroxidase) positivity and the maternal height, which exclusively correlated with anti-thyroglobulin positivity. Conclusions: Correlation of maternal height and newborn weight with positive autoantibodies allows to consider a future clinical screening test for this disorder.

Keywords: Antithyroid Antibodies; Maternal Screening; Microchimerism; Postpartum Thyroiditis

1. INTRODUCTION

Postpartum thyroiditis is a rather frequent thyroid dysfunction affecting women during puerperium as a consequence of an autoimmune inflammation of the thyroid gland. It is the most frequent thyroid disorder at this period and normally develops with a brief hyperthyroid phase followed by a hypothyroid period, which may end in a permanent hypothyroidism or a spontaneous recovery of thyroid function [1-3].

Prevalence of postpartum thyroiditis widely varies between 1.1% in Thailand to 21.1% in the USA [2-21]. Its etiology is not known, although it is related with autoimmunity through the development of antithyroid antibodies: anti-thyroglobulin (anti-Tg) and anti-peroxidase (anti-TPO).

The thyroid dysfunction produced has a major importance for female health, as most women affected are not diagnosed and many years later present overweight, goiter and other anomalies due to long term hypothyroidism such as heart disease, cracked skin, susceptibility to infection, depression, mental confusion, fatigue, osteoporosis and anomalies of the blood lipid profile.

Currently, we do not have any screening for postpartum thyroiditis and no studies correlating obstetric data with appearance of antithyroid antibodies have been performed.

In order to find useful clinical parameters to design a screening test for postpartum thyroiditis, we considered the performance of a study with a 6 months follow up, correlating several thyroid analytical parameters with a variety of obstetric data in order to evaluate if any of these behaved as a significant factor for the appearance of antithyroid antibodies.

2. MATERIALS AND METHODS

We studied a sample of 135 healthy women attending a private clinic of whom we obtained an obstetrical and neonatal complete medical history including age, blood group, number of children and miscarriages, maternal height, maternal weight at the beginning and at the end of gestation, route of delivery and data related with the newborn (weight, sex, and blood group). All patients with past medical history of thyroiditis were discarded for the study.

We subsequently did a 6 months follow up of all the patients, performing a first blood test 2 months after delivery, which included assessment of TSH, T3, T4 and antithyroid antibodies (anti-TPO y anti-Tg). This blood test was repeated 6 months later with measurement of T3, T4 and antithyroid antibodies.

For a patient to be included in the study, levels of TSH in the first measurement had to be within the normal parameters in order to rule out subclinical anomalies of thyroid function.

To simplify the statistical analysis we divided patients into positive and negative for antithyroid antibodies; Positivity of antithyroid antibodies at 2 months postpartum included patients whose antibodies production started before labor and also patients whose antibodies produc-

tion was started early after labor When positivity was present only at 6 months, it included patients whose production started at any period between 2 and 6 months postpartum.

For comparative studies, the following groups were considered: 1) patients anti-Tg positive versus patients anti-Tg negative at 2 months, 2) patients anti-TPO positive versus patients anti-TPO negative at 2 months, 3) patients anti-Tg positive versus patients anti-Tg negative at 6 months and finally: 4) patients anti-TPO positive versus patients anti-TPO negative at 6 months. The characteristics of these groups were analysed and the relationship of the diverse obstetrical parameters with the appearance of antithyroid antibodies at 2 and 6 months postpartum was determined.

The following normality limits for thyroid hormones were considered: T3: 70 - 185 ng/dl, T4: 4.4 - 13 ng/dl. Antithyroid antibodies were considered normal below 50 U/ml [22]. Concerning TSH, although a controversy exists concerning its upper limit in euthyroid patients, we considered the TSH normal range between 0.1 and 5.6 mUI/l.

Physical measurements like height or weight were obtained with a Seca 220 scales. (Seca Weighing and measuring systems®. Hamburg. Germany). Fetal wellbeing control during pregnancy was done using a Toshiba Doppler color SSH 140A ultrasound machine. (Toshiba Corporation®, Japan) and a Toitu fetal monitor (Toitu CO LTD® (Tokio, Japan).

Finally, assessment of statistical significance was done with the software Statplus® version 2009 for Apple Macintosh, using the test of t-Student for numerical data and the test of Chi-square for frequency data.

3. RESULTS

Results are described in **Tables 1-4**.

Table 1. Comparison of patients anti-Tg (+) with patients anti-Tg (–) at 2 months of puerperium.

	Anti-Tg (+) at 2 months (n = 10)	Anti-Tg (–) at 2 months (n = 125)	
Numerical data	**Mean (SD)**	**Mean (SD)**	**SS**
TSH	1.09 (0.86)	2.02 (1.05)	$p < 0.05$
T3 at 2 m	119.00 (34.98)	104.97 (25.86)	$p > 0.05$
T4 at 2 m	9.41 (3.52)	10.20 (16.09)	$p > 0.05$
T3 at 6 m	87.14 (37.60)	113.50 (29.87)	$p < 0.05$
T4 at 2 m	7.35 (3.51)	9.73 (11.05)	$p > 0.05$
Maternal age	30.00 (2.40)	29.90 (2.93)	$p > 0.05$
Maternal height	167 (6.45)	162.31(5.61)	$p < 0.05$
IMW	68.00 (12.31)	60.18 (10.09)	$p > 0.05$
FMW	85.90 (16.26)	74.85(11.13)	$p > 0.05$
Weight increase	17.90 (7.34)	12.29 (13.92)	$p < 0.05$
Body mass index	24.22 (4.64)	22.83 (3.52)	$p > 0.05$
# Children	1.10 (0.57)	1.15 (0.55)	$p > 0.05$
# Miscarriages	0.10 (0.32)	0.27 (0.51)	$p > 0.05$
Neonatal weight	3493 (523)	3155 (431)	$p < 0.05$
Frequency data	**N (%)**	**N (%)**	**SS**
Maternal blood A	5 (50.00)	60 (48.00)	$p > 0.05$
Maternal blood O	2 (20.00)	50 (40.00)	
Maternal blood B	3 (30.00)	15 (12.00)	
Maternal Rh (–)	2 (20.00)	17 (13.60)	$p > 0.05$
Maternal Rh (+)	8 (80.00)	108 (86.40)	
Newborn blood A	5 (50.00)	55 (44.00)	$p > 0.05$
Newborn blood B	4 (40.00)	57 (45.60)	
Newborn blood O	1 (10.00)	13 (10.40)	
Newborn blood Rh (–)	2 (20.00)	21 (16.80)	$p > 0.05$
Newborn blood Rh (–)	8 (80.00)	104 (83.20)	
Different ABO M/N	5 (50.00)	49 (39.20)	$p > 0.05$
Identical ABO M/N	5 (50.00)	76 (60.80)	
Different Rh M/N	0 (0.00)	101 (80.80)	$p < 0.05$
Identical Rh M/N	10 (100.00)	24 (19.20)	
Newborn sex male	7 (70.00)	64 (51.20)	$p > 0.05$
Newborn sex female	3 (30.00)	61 (48.80)	

Notes: FMW: Final maternal weight; IMW: Initial maternal weight; M/N: Between the mother and newborn bloods; SS: Statistical Significance.

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At 2 months 10 patients (7.4%) showed positivity for anti-Tg antibodies and 13 patients showed positivity for anti-TPO antibodies. 6 patients (4.4%) showed positivity for both anti-TG and anti-TPO antibodies.

This relation was increased at 6 months: 20 patients (14.8%) and 17 patients (12.5%) respectively showed positivity for anti-Tg and anti-TPO antibodies. Also, 9 patients (6.7%) showed positivity for both anti-TG and anti-TPO antibodies.

At 2 months, and for the positivity of anti-Tg antibodies: TSH levels, T3 levels at 6 months, maternal height, maternal weight increase, newborn weight and difference between maternal and neonatal Rh were significant (**Table 1**). At 2 months and for the positivity of anti-TPO antibodies: T4 levels at 6 months, number of children and newborn weight were also significant (**Table 2**).

At 6 months, and for the positivity of anti-Tg antibodies: values of maternal height and newborn weight were significant (**Table 3**).

At six moths and for the positivity of anti-TPO antibodies: the number of miscarriages, the newborn weight and the newborn Rh were also significant (**Table 4**).

Interestingly only two obstetrical parameters were significant during the complete follow up: the newborn weight, which correlated with both antibodies (anti-Tg and anti-TPO) positivity and the maternal height, which exclusively correlated with anti-Tg antibody positivity. We considered that the persistence of correlation throughout the entire study (2 and 6 months) strengthened the association.

Table 2. Comparison between patients anti-TPO (+) and patients anti-TPO (–) at 2 months of puerperium.

	Anti-TPO (+) at 2 months (n = 13)	Anti-TPO (–) at 2 months (n = 122)	
Numerical data	**Mean (SD)**	**Mean (SD)**	**SS**
TSH	1.09 (0.86)	2.02 (1.04)	p > 0.05
T3 at 2 m	110.51 (28.40)	105.50 (26.64)	p > 0.05
T4 at 2 m	8.03 (2.48)	10.37 (16.28)	p > 0.05
T3 at 6 m	107.52 (30.83)	111.97 (31.25)	p > 0.05
T4 at 2 m	7.05 (3.02)	9.82 (11.17)	**p < 0.05**
Maternal age	29.62 (1.98)	29.93 (2.93)	p > 0.05
Maternal height	166.23 (8.67)	162.34 (5.36)	p > 0.05
IMW	65.46 (14.27)	60.26 (9.87)	p > 0.05
FMW	81.46 (18.25)	75.11 (11.00)	p > 0.05
Weight increase	16.54 (6.92)	13.03 (11.80)	p > 0.05
Body mass index	23.64 (4.84)	22.86 (3.48)	p > 0.05
# Children	1.42 (0.51)	1.12 (0.55)	**p < 0.05**
# Miscarriages	0.17 (0.39)	0.26 (0.51)	p > 0.05
Neonatal weight	3401 (289.53)	3157 (453.23)	**p < 0.05**
Frequency data	**N (%)**	**N (%)**	**SS**
Maternal blood A	8 (61.54)	54 (48.00)	p > 0.05
Maternal blood O	5 (38.46)	50 (40.00)	
Maternal blood B	0 (0.00)	18 (12.00)	
Maternal Rh (–)	1 (7.69)	18 (13.60)	p > 0.05
Maternal Rh (+)	12 (92.31)	104 (86.40)	
Newborn blood A	9 (69.23)	53 (44.00)	p > 0.05
Newborn blood B	4 (30.77)	59 (45.60)	
Newborn blood O	0 (0.00)	10 (10.40)	
Newborn blood Rh (–)	3 (23.08)	20 (16.80)	p > 0.05
Newborn blood Rh (–)	10 (76.92)	102 (83.20)	
Different ABO M/N	3 (23.08)	52 (39.20)	p > 0.05
Identical ABO M/N	10 (76.92)	70 (60.80)	
Different Rh M/N	2 (15.38)	21 (80.80)	p > 0.05
Identical Rh M/N	11 (84.62)	101 (19.20)	
Newborn sex male	6 (46.15)	65 (51.20)	p > 0.05
Newborn sex female	7 (53.85)	57 (48.80)	

Notes: FMW: Final maternal weight; IMW: Initial maternal weight; M/N: Between the mother and newborn bloods; SS: Statistical Significance.

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Table 3. Comparison of patients anti-Tg (+) with patients anti-Tg (–) at 6 months of puerperium.

	Anti-Tg (+) at 6 months (n = 20)	Anti-Tg (–) at 6 months (n = 115)	
Numerical data	**Mean (SD)**	**Mean (SD)**	**SS**
TSH	2.07 (1.10)	2.00 (1.03)	p > 0.05
T3 at 2 m	106.63 (27.17)	105.92 (26.78)	p > 0.05
T4 at 2 m	7.65 (2.33)	7.25 (1.87)	p > 0.05
T3 at 6 m	112.59 (32.84)	113.61 (27.55)	p > 0.05
T4 at 2 m	7.55 (2.64)	7.74 (1.98)	p > 0.05
Maternal age	30.00 (2.29)	29.89 (2.98)	p > 0.05
Maternal height	166.55 (6.39)	162.00 (5.49)	**p < 0.05**
IMW	63.88 (11.14)	60.22 (10.24)	p > 0.05
FMW	80.16 (13.65)	74.93 (11.46)	p > 0.05
Weight increase	12.27 (20.52)	14.60 (4.76)	p > 0.05
Body mass index	22.99 (3.69)	22.92 (3.62)	p > 0.05
# Children	1.17 (0.51)	1.14 (0.56)	p > 0.05
# Miscarriages	0.33 (0.59)	0.24 (0.49)	p > 0.05
Neonatal weight	3377 (326)	3146 (455)	**p < 0.05**
Frequency data	**N (%)**	**N (%)**	**SS**
Maternal blood A	8 (40.00)	54 (46.96)	p > 0.05
Maternal blood O	9 (45.00)	46 (40.00)	
Maternal blood B	3 (15.00)	15 (13.04)	
Maternal Rh (–)	2 (10.00)	17 (14.78)	p > 0.05
Maternal Rh (+)	18 (90.00)	98 (85.22)	
Newborn blood A	8 (40.00)	52 (45.22)	p > 0.05
Newborn blood B	10 (50.00)	51 (44.35)	
Newborn blood O	2 (10.00)	12 (10.43)	
Newborn blood Rh (–)	5 (25.00)	18 (15.65)	p > 0.05
Newborn blood Rh (–)	15 (75.00)	97 (84.35)	
Different ABO M/N	6 (30.00)	39 (33.91)	p > 0.05
Identical ABO M/N	14 (70.00)	76 (66.09)	
Different Rh M/N	5 (25.00)	19 (16.52)	p > 0.05
Identical Rh M/N	15 (75.00)	96 (83.48)	
Newborn sex male	12 (60.00)	59 (51.30)	p > 0.05
Newborn sex female	8 (40.00)	56 (48.70)	

Notes: FMW: Final maternal weight; IMW: Initial maternal weight; M/N: Between the mother and newborn bloods; SS: Statistical Significance.

Conversely, other parameters such as TSH, T3, T4, number of children, number of miscarriages, newborn Rh or discrepancy between mother and newborn Rh were only significant for only one antibody and only at one time of the study. We therefore did not consider them to be strongly associated with the postpartum presence of antithyroid antibodies.

4. DISCUSSION

Postpartum thyroiditis etiology is not well understood. It has been related with the appearance of antithyroid antibodies (anti-TG and anti-TPO) [2-11]. But experimental observation shows that the initiation and progression of postpartum thyroiditis in women with positive antibodies is not only a function of their blood level, but is also related with their capability to activate the immune system [23-27]. Th1 and Th2 lymphocytes are also crucial in the pathogenesis of autoimmune thyroiditis: B-lymphocytes need the help of Th2 in order to produce antithyroid antibodies and Th1 lymphocytes are directly involved in thyroid cells' survival. Also, there is a higher frequency of HLA-DR3, DR4 and DR5 in patients with postpartum thyroiditis [28-32] and leptin, which promotes the development of Th1 [33] presents a higher level in the blood of women with positive anti-TPO antibodies.

It has been suggested that the origin of postpartum thyroiditis could be related with fetal microchimerism (infiltration during pregnancy and puerperium of maternal tissues by fetal haematopoietic or trophoblastic cells). Immune suppression of maternal immunity by the feto placental unit (with production of progesterone and other

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Table 4. Comparison of patients anti-TPO (+) with patients anti-TPO (–) at 6 months of puerperium.

	Anti-TPO (+) at 6 months (n = 17)	Anti-TPO (–) at 6 months (n = 118)	
Numerical data	**Mean (SD)**	**Mean (SD)**	**SS**
TSH	1.74 (0.98)	2.05 (1.04)	p > 0.05
T3 at 2 m	112.39 (28.63)	105.00 (26.46)	p > 0.05
T4 at 2 m	8.34 (2.79)	7.16(1.76)	p > 0.05
T3 at 6 m	114.22 (31.27)	113.35 (27.95)	p > 0.05
T4 at 2 m	7.37 (2.85)	7.76 (1.95)	p > 0.05
Maternal age	30.12 (2.06)	29.87 (2.99)	p > 0.05
Maternal height	165.82 (7.92)	162.26 (5.36)	p > 0.05
IMW	64.62 (13.39)	60.19 (9.86)	p > 0.05
FMW	80.88 (17.78)	74.97 (10.74)	p > 0.05
Weight increase	16.66 (6.67)	14.67 (4.57)	p > 0.05
Body mass index	23.41 (4.14)	22.86 (3.55)	p > 0.05
# Children	1.13 (0.74)	1.14 (0.53)	p > 0.05
# Miscarriages	0.07 (0.26)	0.28 (0.52)	**p < 0.05**
Neonatal weight	3422 (412)	3146 (440)	**p < 0.05**
Frequency data	**N (%)**	**N (%)**	**SS**
Maternal blood A	8 (47.06)	57 (48.31)	p > 0.05
Maternal blood O	8 (47.06)	50 (42.37)	
Maternal blood B	1 (05.88)	11 (9.32)	
Maternal Rh (–)	2 (11.76)	16 (13.56)	p > 0.05
Maternal Rh (+)	15 (88.24)	102 (86.44)	
Newborn blood A	10 (58.82)	52 (44.07)	p > 0.05
Newborn blood B	6 (35.29)	57 (48.31)	
Newborn blood O	1 (05.88)	9 (07.63)	
Newborn blood Rh (–)	6 (35.29)	16 (13.56)	p > 0.05
Newborn blood Rh (–)	11 (64.71)	102 (86.44)	
Different ABO M/N	6 (35.29)	47 (39.83)	p > 0.05
Identical ABO M/N	11 (64.71)	71 (60.17)	
Different Rh M/N	5 (29.41)	18 (15.25)	p > 0.05
Identical Rh M/N	12 (70.59)	100 (84.75)	
Newborn sex male	10 (58.82)	61 (51.69)	p > 0.05
Newborn sex female	7 (41.18)	57 (48.31)	

Notes: FMW: Final maternal weight; IMW: Initial maternal weight; M/N: Between the mother and newborn bloods; SS: Statistical Significance.

immunosuppressive molecules) and the increase of T helper differentiation into Th2, allow a transitory maternal tolerance to such cells. Once fetal cells migrate to maternal tissues, they take advantage of this immune status and survive. However, after delivery, the favourable immunological status ends, and fetal cells start to trigger graft versus host reactions producing antithyroid antibodies.

Therefore, accumulation of fetal cells inside the thyroid gland during pregnancy induces a posterior immunologic disturbance with the development of autoimmune thyroid disease. As fetal cells in maternal tissue have been found even 27 years after delivery, the effect on the immunological system may last for decades [34,35].

Other factors classically associated with the appearance of postpartum thyroiditis have been the iodine intake [36,37], (with contradictory conclusions), smoking [6] and type I diabetes [18,38,39].

In our study, the distinct parameters which turned out to be significant were heterogeneous and with the exception of the newborn weight and the maternal height, in the remaining parameters, statistical significance was not permanent throughout the 6 months follow up, so the correlations were not conclusive.

The higher newborn weight in patients with positive anti-TPO and anti-Tg might be related to a significantly higher increase in maternal weight during pregnancy. However in our study, maternal weight increase showed correlation only with anti-Tg at 2 months, while newborn

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weight maintained correlation for both antibodies at 2 and six months, showing that its positivity could not be explained only according to the well known relationship between neonatal weight and maternal weight increase. Therefore, the persistence of significance for neonatal weight indicated a possible relationship between neonatal weight and the appearance of antithyroid antibodies.

The cause of postpartum thyroiditis has been related with the existence of microchimerism (appearance of fetal cells in maternal tissues) [34], as a higher newborn weight supposes a higher number of fetal cells, the bigger fetal size supposes a higher possibility of fetal cells transfer to the mother´s tissues and especially to the thyroid gland. In the same manner, the persistence of significance for maternal height during the 6 month follow up in relation with the positivity of the anti-Tg antibody, makes us consider a certain influence of this parameter in the initiation of this disorder. In fact, the bigger the mother is, the bigger the thyroid gland is supposed to be and a higher possibility of fetal cells transfer to the mother's thyroid gland occurs. Both mechanisms: increased number of fetal cells and increased volume of maternal thyroid gland, raise the probability of fetal cells appearance in thyroid tissue and support the theory which explains development of postpartum thyoriditis as a consequence of fetal microchimerism. The relation between presence of fetal cells in maternal thyroid tissue and development of antithyroid antibodies has become an attractive model for the explanation of postpartum thyroiditis. Interestingly, our study fits within this model as the clinical parameters involved with a higher possibility of fetal microchimerism obtain the strongest correlation with the appearance of postpartum antithyroid antibodies. Although the number of patients with positive antithyroid antibodies was small, the association of their positivity throughout the whole period of study increased the strength of this association.

We recognize these results are preliminary. In spite of that, they might be used as a basis in the search of a postpartum thyroiditis screening. However, in order to develop it, a more detailed analysis will be required, including assessment of a higher number of cases and amplification of the patients' follow up period.

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