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Addressability issues: when is autoimmune thyroiditis a point in the evaluation of spontaneous recurrent abortion in fertile women?

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Abstract

Objective(s). *The present study aim to evaluate the impact of autoimmune thyroid disease on recurrent pregnancy loss.* ***Methods.*** *Prospective study, January 2010 - September 2011, screening of 395 cases that came for an endocrinological evaluation, with history of spontaneous abortion. The study group, 241 cases, was analysed by clinical, hormonal, immunological and imagistic means.* ***Results.*** *We identified 53 cases with thyroid disease, 48 with autoimmune thyroiditis. The presence of autoimmune thyroiditis increases the risk of miscarriage up to 3.75 times. Only 13.2% of thyroid ill women were diagnosed prior to our study, despite the 82.15% prevalence of infertility issues. The time span between the last abortion and the present evaluation was around 14.5 months, although 1 out of 5 cases had thyroid autoimmune disease. Presence of thyroid-stimulating hormone anomalies correlated with prevalent abortion.* ***Conclusions.*** *We believe that the best way to screen the patients is to measure all the antithyroid antibodies, ideally before any pregnancy, at least in the first 4-5 weeks of pregnancy.*

Keywords: *recurrent abortion, thyroid autoimmune disease screening*

Introduction

The etiology of recurrent miscarriage is relatively vast, comprising gynecological, hormonal, toxic, genetic, infectious, vascular or immunological factors[1,2,3]. Particularly, in Banat region, the incidence of autoimmune thyroid disease, is very high, and it seems it rises constantly[4]. Autoimmune thyroiditis is associated with subfertility, infertility, higher miscarriage rate[5] up to five times higher than in the general, apparently healthy population[2,6]. The connections between thyroid autoimmunity and miscarriage are multiple: some consider that the autoimmune thyroid disease is a marker of increased immune-reactivity, which can determine spontaneous abortion[5], other theories consider T lymphocytes activation[7]. Some authors consider that the same immunological imbalance in cluster of differentiation 5/20 activity induces both autoimmune thyroiditis and miscarriage[8]. A possible cross-reaction, with aberrant immunological recognition of anti maternal antibodies, can also be responsible for the initiation of miscarriage[9]. Despite the real mechanism of association between miscarriage and autoimmune thyroid disease, the task for the clinician is to identify the population at risk, which can be easily done by measurement of antithyroid antibodies, and also to assure a proper thyroid-stimulating hormone (TSH) value. There is a consensus between the major professional associations: American Thyroid Association, European Thyroid Association, American Association of Clinical Endocrinologist and the Endocrine Association, regarding TSH values in pregnancy optimum of 2.5 micro M/mL[10]. The monitoring of preconception in the first trimester of pregnancy should be always done after this recommendation. The present study aim to evaluate the impact of autoimmune thyroid disease on recurrent pregnancy loss.

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Methods

Study design

The present clinical retrospective study, comprising women patients with a positive history of spontaneous abortion, came in the endocrinology Clinique, Dr. D Center, affiliated with the Department of Obstetrics and Gynecology, University of Medicine and Pharmacy "Victor Babes" Timisoara, in January 2010 till September 2011 period. We included only sexually active women patients of childbearing age in our evaluation. Complete gynecological evaluation was conducted in the University Clinic of Obstetrics and Gynecology, County Hospital, Timisoara.

The inclusion criteria were: at least one prevalent spontaneous abortion, no known gynecological disease, no infections associated with recurrent abortion, self-referral/gynecological-referral and normal values in screening for thromboembolic diseases.

The exclusion criteria were: organic (tumoral) hyperprolactinemia, adrenal diseases, progesterone insufficiency due to follicular phase deficit, hyper-cortisolemia, known disease/

mutation associated increased clotting process, genetic mutation in one partner and gynecological diseases.

Definition used:

We considered the clinical hypothyroidism when TSH was >4 mUI/L, associated with decreased FT4 and/or FT3 values[10], bubclinical hypothyroidism when TSH was > 4 mUI/L associated with normal FT4 and/or FT3 values[10], progesterone deficiency when showed decreased progesterone values in the mid-luteal phase[11], organic hyperprolactinemia when MRI confirmed hypophisys tumor with repeated increased PRL levels[11], hypercortisolemia when the basal cortisol levels were increased, with no proper inhibition response (less decrease than 50%)[11] and autoimmune thyroid disease[12] (type 1, euthyroid with normal TSH values, type 2, persistent hypothyroidism and type 3, hyper/euthyroidism with suppressed TSH).

In all cases we performed the ultrasound evaluation of each patient on a Hitachi 7500 V device with a multiple frequency, 6-13 MHz variable, linear probe, with ultrasound and elastography software; Hitachi Medical System, Tokyo, Japan.

Evaluation

Clinical evaluation was considered in: hypothyroidism symptoms and signs, thyroid palpation with goiter diagnostic: Ia = goiter present only at clinical examination, Ib =visible goiter with neck in hyperextension, II = visible goiter in normal position, III = important visible goiter.

We also measured TSH, free thyroid hormones (FT4,FT3) regardless the menstrual period, prolactin (PRL), progesterone in the mid luteal phase (PRL in normal range = 127-637 mUI/L and progesterone in normal range = 5.3-86 nmol/L), and iodine homeostasis (iodine in serum, normal range= 46-70 μg/L).

The immunological evaluation constitutes in anti Tiroperoxidase antibodies (antiTPO Ab, normal range <34 UI/mL), anti Tireoglobulin antibodies (anti Tg Ab, normal range < 115 UI/mL), anti TSH receptor antibodies (Trab, normal range > 1.5 UI/mL), anti-ovarian antibodies including gynecological exam and transvaginal ultrasound.

Results

1. Characteristics of the study group

In the 21-month inclusion period, we screened 395 young women, between 19-44 years old. In cases with no sufficient data we referred the patients to complete all the investigations needed for inclusion in the evaluation. 264 females were referred by the obstetrician (66.83% of the group), the remaining 131 came without an obstetrician recommendation.

From this initial pool of cases we excluded the diagnosed prolactinoma (4 cases, 1.012%), presence of genetic anomalies in one of the partners (8 cases, 2.02%), anomalies of coagulation cascade (13 cases, 3.29%), progesterone insufficiency (88 cases, 22.27%), organic hypercortisolemia (1 case, 0.27%), gynecological pathology (28 cases, 7.08%). The resulting study group consisted of 241 cases. The dropout group comprised 154 cases, used as a control group.

Study group biases: gynecologists referred 45% of the cases, so we could consider that the real incidence of gynecological problems might be lower than in general abortion female population.

The study group was heterogeneous, spontaneous abortion being observed both in nulliparae and nulligravidae, but also in women with one or more prevalent pregnancies, with or without birth giving. As presented in Table 1, the most common feature of the study group was fertility problems, founded in 82.15% of the study group. There were no significant epidemiologic data differences between the study and the control group.

Very few cases had known thyroid pathology: 7 cases with 4 cases of hypothyroidism and 3 cases of nodular goiter. The prevalence of the thyroid disease is very low compared with the one described in other studies. In control group there was no previous known thyroid disease. Age, general appearance, body mass index, social background, rural or urban living place (see Table 1) were similar in both study and control group. The obstetrical history was sustained by the number of pregnancies, abortion and births, which was similar.

Table 1 General parameter characteristics in the study group versus control group

	Study group (241 cases)	Control group (145 cases)
Parameter	Mean value ± SD	Mean value ± SD
Mean age (years)	29,5 ± 1,2	28.7 ± 1,6
BMI (kg/m²sc)	26.4 ± 2.15	26.5 ± 2.5
Rural/urban	56/185	38/107
Spontaneous abortion (no)	2.2 ± 1.05	2.4 ± 1.25
Prevalent pregnancy (no)	2.8 ± 1.25	2.5 ± 1.7
Prevalent living birth (no)	1.28 ± 0.6	1.1 ± 0.5
Prevalent fertility issues (no)	198/241	113/145
Known thyroid diseases (no)	7/241	0

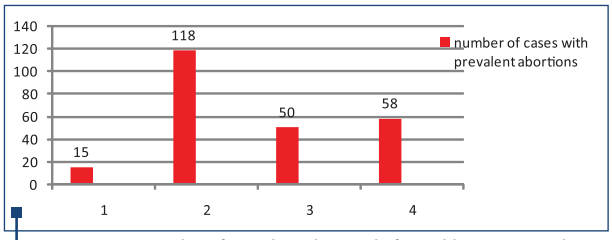


Figure 1. Mean number of prevalent abortion before addressing an endocrinological evaluation

2. History of spontaneous abortion in the study group

We analysed the characteristics of the abortive disease, before the timing of the endocrinological evaluation. As showed in Figure 1, when addressing to our Clinique, the patients had a number of prevalent abortions between one and four (mean = 2.2 ± 1.5 abortions).

Neither the number of previous abortions was very different, nor the mean time interval between the last abortive event and the endocrinological evaluation were different. The analysed women were in 1.5 up to 36 months after the last abortion (with a mean of 14.5 ± 2.4 months). Most of the patients came in our Clinique either in the first two months after the event (33.19% of cases), or 1 year after the event (34.85% of cases). The distribution in time is presented in Table 2.

3. Thyroid pathology in the study group

In the screened population (395 cases) we identified 65 cases with thyroid disease (16.45%): 12 cases in the dropout group (154 cases with other apparent causes for spontaneous abortion), and 46 new cases in the study group added to the 7 known diseases, the prevalence being 21.99% of the study group. The 'non-thyroid' disease from the study group was used as a control group for the evaluation (Table 3).

We observed the thyroid disease group (53 cases) which had a significant lower pregnancy rate (p=0.024), birth giving history (p =0.026) and subsequent a higher rate of pregnancy loss (p=0.011). The calculated odds ratio of having a miscarriage, in the presence of increased antithyroid antibodies was 3.75.

From the clinical point of view, we observed goiter in 40/53 patients: 17 cases Ia goiter, 14 cases: Ib cases, 7 goiter II and 3 goiter III cases. Hypothyroidism signs were observed in 20/53 cases, 15 cases having unspecific signs. Hypothyroidism was confirmed by the hormonal assays in 28 cases. The discussion in cases of future pregnancy is about the definition of hypothyroidism, respectively the optimum TSH value for no future abortive events[3,10].

The results of the thyroid ultrasound reflected a change in the volume or thyroid echogenicity which was not consistent with a thyroid disease diagnostic. Thyroid ultrasound has a definitive value only in cases with thyroid nodules[5].

Table 2 Time interval between spontaneous abortion and endocrinological evaluation

Time interval Spontaneous ab.	2 months	6 months	12 months	>12 months	Total
1	0	5	10	0	15
2	15	30	54	19	118
3	26	5	15	4	50
4	39	14	5	0	58
Total	**80**	**54**	**84**	**23**	**241**

Table 3 Clinical and obstetrical implications of association of the study group

	Thyroid disease study cases (53 cases)	Non-thyroid disease study cases (188 cases)
Parameter	Mean value ± SD	Mean value ± SD
Mean age (years)	29.9 ± 1.4	28.7 ± 1.6
BMI (kg/m^{2}sc)	27.9 ± 2.44	26.1 ± 1.7
Rural/urban	16/37	40/148
Spontaneous abortion (no)	3.0 ± 1.15	1.1 ± 0.75
Prevalent pregnancy (no)	1.1 ± 0.5	2.8 ± 1.2
Prevalent living birth (no)	0.5 ± 0.3	1.35 ± 0.65
Prevalent fertility issues (no)	51/53	147/188

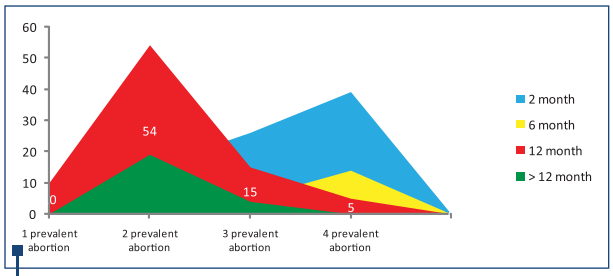
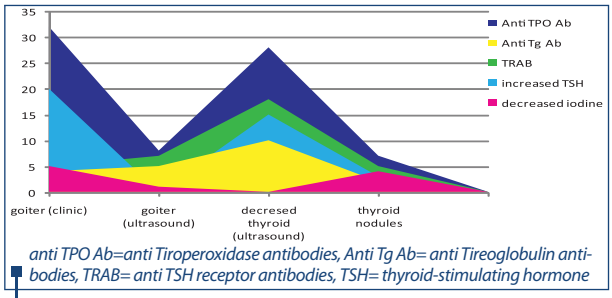


Figure 2. Distribution of cases regarding the moment of endocrinological evaluation-last abortion, in respect to the prevalent abortion number



anti TPO Ab=anti Tiroperoxidase antibodies, Anti Tg Ab= anti Tireoglobulin antibodies, TRAB= anti TSH receptor antibodies, TSH= thyroid-stimulating hormone

Figure 3. Etiopathogenetic forms of thyroid diseases in the study group

The most important diagnostic value[11] was the immunological assay. The presence of positive anti thyroid antibodies, completly changes the approach of the patient. Also the iodine level in blood adds significance of the thyroid pathology diagnostic (Figures 2 and 3).

Clinical goiter was confirmed by ultrasound only in 22 cases (11 diffuse goiter and 11 cases with nodular goiter). The types of autoimmune thyroid disease are presented in Tables 4 and 5.

The clinical presence of a goiter overestimates the real incidence of Hashimoto disease or of the nodular goiter, with a sensitivity of 90.9% and a low specificity, of 61.29%. Clinical signs of hypothyroidism were not at all reliable, showing a sensitivity of 50%, and a specificity of 38.4% in identifying cases with hypothyroidism. Thyroid ultrasound can suggest an autoimmune thyroid process, with a higher sensitivity of 75%, and a specificity of 80%. The golden diagnostic standard remains the evaluation of antithyroid antibodies.

4. Age of the patients and thyroid implications

We looked over the importance of age in respect to the incidence of autoimmune thyroid disease and prevalent spontaneous abortion. In the study group, in the absence of any apparent cause for recurrent abortion, we looked at the distribution of cases in different age decades (Figure 4).

Table 4 Thyroid ultrasound results in the study group, compared with controls

	Thyroid disease group	Remaining study group
Increased volume	11/53	0/188
Decreased volume	28/53	45/188
Hypo-ecogenicity	51/53	56/188
Thyroid nodules	11/53	0/188

Table 5 The spectrum of autoimmune thyroid disease (AIT)

AIT type	No of cases	Mean TSH* (mUI/L)	+ anti TPO Ab**	+ anti Tg Ab***	+ Trab****	Iodine (mcg/L)
1A[a]	4	1.88 ± 0.15	2	5	7	70.2 ± 11.3
1B[b]	13	1.76 ± 0.23	13	5	5	71.3 ± 10.4
2A[c]	13	5.45 ± 1,45	13	5	5	68.3 ± 11.4
2B[d]	15	5.24 ± 1.67	15	2	13	72.0 ± 10.4
3A[e]	1	0.003 ±0 .0	0	0	1	68.4± 12.4
3B[f]	0	-	0	0	0	-
3C[g]	0	-	0	0	0	-
Total	**48**		**43**	**17**	**30**	

*a1A = goitrous, b1B = non-goitrous, c2A = goitrous (classic Hashimoto disease), d2B = non-goitrous (atrophic thyroiditis), e3A = Graves disease, f3B = euthyroid Graves disease, g3C = orbitopathy with hypothyroidism, *TSH= thyroid-stimulating hormone, **anti TPO Ab=anti Tiroperoxidase antibodies, ***Anti Tg Ab= anti Tireoglobulin antibodies, ****Trab= anti TSH receptor antibodies.*

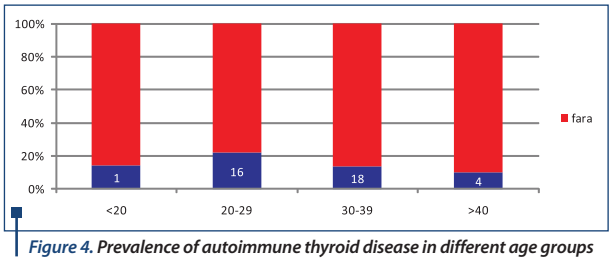


Figure 4. Prevalence of autoimmune thyroid disease in different age groups

There was a decreased correlation between the age and severity of autoimmune thyroid disease, appreciated by the values of TSH (r=0.245, p=0.015), and also between the age and the anti TPO antibodies (r=0.178, p=0.012). In contrary, there was an important correlation between the number of prevalent abortions and TSH values (r = 0.624, p= 0.012).

Discussion

The incidence of thyroid pathology from study group was much higher in comparison with other studies (21.99%)[3,11]. When we looked at the prevalence in the screened group, the incidence was similar, somewhat higher, secondary to the higher iodine intake in Banat region[4].

For the study accuracy we excluded all cases with other apparent causes for spontaneous abortion including gynecological diseases, altered clotting profile, chromosomal anomalies, and other endocrine diseases.

Despite the higher prevalence of autoimmune thyroiditis in Banat region[4], and the higher incidence of fertility issues in the screened (80.56%) and study population (82.15%), only a minority of cases had complete endocrinological evaluation, prior to the study. We identified an important number of thyroid diseases in the study group (21.99% of cases), the majority being autoimmune thyroiditis (90.56%). Only 13.2% of the patients were diagnosed prior the evaluation. These results are in contradiction with other studies[10-15].

Important to be mention is the long period of time between the endocrinological reference and the moment of spontaneous abortion (over 45% of cases came after 2 years post-abortion, with at least 2 to 3 recurrent events in the personal history). More than a half of the screened population (53.6% of cases) did not have any investigation regarding potential causes for recurrent abortion.

We believe that the diagnostic value can be improved by adding the ultrasound method that will identify autoimmune thyroid disease with a sensitivity of 75% and a proper specificity of 80%. The evaluation of thyroid antibodies remains the golden standard in the diagnostic of autoimmune thyroid disease[15,16]. These determinations should be included in the screening test recommended by the obstetrician in case of a spontaneous abortion.

Moreover, we observed an important association between the TSH values and the number of pregnancies stopped in evolution (r=0,624, p=0.012). It is described that suboptimal TSH levels are associated with infertility and higher rates of miscarriage[16,17].

Conclusions

Interestingly, from our results which came from a large population, we did not find any particular association between age groups, incidence of miscarriage or thyroid pathology.

The screening of autoimmune thyroid disease should be used at least in risk population, in the evaluation of spontaneous abortion. Prior history of autoimmune disease, positive familial thyroid history, personal thyroid disease history, signs and symptoms consistent with hypothyroidism, in particular, and all thyroid diseases in general, recurrent abortions and subfertility, with no apparent reason, should be considered as an indication for screening. We believe that the best way to screen the patients is to measure all the antithyroid antibodies, ideally before any pregnancy, at least in the first 4-5 weeks of pregnancy. ■

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