Assessment of ovarian reserve in young women with Hashimoto's thyroiditis

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Abstract

Background: Human ovary is commonly the target of an autoimmune attack in cases of organ- or non-organ-specific autoimmune disorders. Hashimoto's thyroiditis (HT) is likely to be associated with ovarian dysfunction and diminished ovarian reserve. The classical hormonal test assessing ovarian reserve as early follicular phase serum levels of *follicle-stimulating hormone* (FSH), inhibin B and estradiol (E2), which are interdependent, and the calculation of the number of antral follicles by transvaginal ultrasonography have some inconvenience in very young girls. Anti-Muellerian Hormone (AMH), a relatively new marker of the ovarian function is simultaneously the earliest marker of diminishing ovarian reserve. Serum AMH levels increase during the first decades of female live and then decrease gradually with age, and the levels become undetectable after menopause.

Objective: The aim of the study was to assess the ovarian reserve in young women with HT using the evaluation as well classical hormone methods (FSH, E2, Inibin B) as a measurement of AMH.

Methods: There were 21 patients treated due to Hashimoto disease, median age 15.6 yrs, and 17 healthy age-matched controls included to the study. In the group of patients with HT, 8 patients have additional T1DM diagnosed , so they presented with type 3 autoimmune poliendocrinopathy (APS 3). In all participants FSH, LH, estrogens, PRL, SHBG, TSH, fT4, anti-TPO, AMH, and Inhibin-B, if possibly in 3-5th day of the menstruation cycle were measured.

Results: As well FSH, E2, and Inhibin-B, as AMH levels did not differ statistically between group of patients with HT and healthy controls. Moreover we did not find any differences regarding parameters assessing ovarian function and reserve between patients with only HT and those with APS 3. Moreover levels of LH, SHBG, PRL, and fT4 did not differ in patients with HT, including APS 3 than in controls. Only TSH levels were significantly higher in HT group than in the control group (p = 0.02). BMI of HT patients did not differ statistically from healthy controls.

Conclusion: The results of our study did not indicate that young patients with HT, including those with APS 3 have impaired ovarian function and reserve.

The authors have NOTHING TO DISCLOSE.

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Background

HASHIMOTO DISEASE AND HYPOGONADISM

- Hashimoto's thyroiditis (HT) is likely to be associated with ovarian dysfunction and diminished ovarian reserve.
- 30-50% of patients with the diagnosis of chromosomally competent premature ovarian failure (POF) without previous risk factors of POF (chemo- and radiotherapy) had an associated autoimmune disorder, the most frequently autoimmune thyroiditis [1].
- In 18.5 % of patients (22/119) with POF had hypothyrodism [2].
- Isolated ovarian autoimmune disease is rare in women, but is often observed in association with other autoimmune diseases, as a result of the breakdown of at least two mechanisms that protect the ovary from autoimmune attack:
  - the control of autoreactive T cells by thymus-derived regulatory T cells,
  - a role for the autoimmune regulator (AIRE), a transcriptional regulator that induces expression of tissue-restricted antigens in medullary thymic epithelial cells during development of T cells [3].

There are contractory data on premature ovarian aging in HT adult patients [4, 5] and scare data on this subject in children [6].

ASSESSMENT OF OVARIAN RESERVE IN GIRLS AND WOMEN

❑ In females with normal menstrual cycles in 3rd - 5th day of the cycle
- ✓ FSH
- ✓ Estrogens
- ✓ Inhibin B
- In girls only after an age of about 7 years, elevated basal gonadotropins point to gonadal damage [7].

❑ Assessment of the number of antral follicles by ultrasonography best predicts the quantitative aspect of ovarian reserve. However, the measurement of the antral follicle should be performed using an transvaginal ultrasound during in the early follicular phase.

❑ **ANTY-MUELLERIAN HORMONE (AMH)**
- ➢ AMH is produced in females since prenatal time, but it's levels are 100-1000 lowers in compare to males.
- ➢ AMH is produced by the small growing (primary and preantral) follicles in the postnatal ovary and has two sites of action.
- ➢ It inhibits initial follicle recruitment (1) and inhibits FSH-dependent growth and selection of preantral and small antral follicles (2) [Fig. 1].

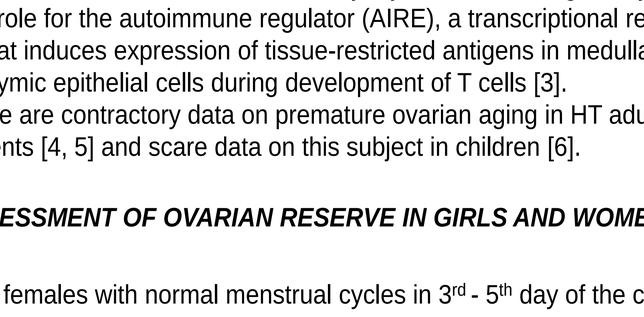

Figure 1. Model of AMH action in the ovary by Visser et al. [8].

Objective

to assess the ovarian reserve in young women with HT using the evaluation of:
- classical hormone methods (FSH, E2, Inibin B)
- and a measurement of AMH

Methods

PATIENTS

21 patients with Hashimoto's thyroiditis (HT),
age 8.7 – 23.5 lat (median 15.6 years)
13 patients with only HT
8 patients with HT and type 1 diabetes mellitus
(*autoimmune poliendocrinopathy 3*, APS 3)

Control group: 17 age-matched helathy girls

Fasting blood samples for measurement of FSH, luteinizing hormone (LH), E2, prolactin (PRL), sex hormone binding globulin (SHBG), thyroid-stimulating hormone (TSH), free thyroxin (fT4), anti-thyroid peroxidase (anti-TPO) antibodies, AMH, and Inhibin-B were taken from the antecubital vein, at 8.00-10.00 AM, in patients with normal menstrual cycles in 3rd - 5th day of the cycle.

Biochemical methods

Hormones: FSH (Siemens Healthcare Diagnostics Inc., USA), LH (Siemens Healthcare Diagnostics Inc., USA), PRL (Siemens Healthcare Diagnostics Inc., USA), SHBG (Siemens Healthcare Diagnostics Inc., USA), TSH (Siemens Healthcare Diagnostics Inc., USA), fT4 (Siemens Healthcare Diagnostics Inc., USA), AMH (Beckman Coulter Eurocenter S.A., Switzerland), and Inhibin B (Beckman Coulter Eurocenter S.A., Switzerland) were measured by immunochemistry.

The decreased ovarian reserve was defined as the occurrence of elevated gonadotropins (mainly FSH), decreased Inhibin B and decreased AMH levels.

Statistical analysis

Statistical analysis was performed using the Staf Soft Statistica 12 package. T-Student test and ANOVA were used for the analysis.

Results

There were no clinical signs and symptoms regarding ovarian function between examined and control groups.

As well FSH, E2, and Inhibin-B, as AMH levels did not differ statistically between group of patients with HT and healthy controls [Tab. 1]. BMI of HT patients did not differ statistically from healthy controls.

Table 1. Serum levels of AMH, Inhibin-B, FSH and estrogens in patients with HT and in controls

	Age [yrs]	AMH [ng/ml]	Inhibin B [pg/ml]	FSH [mIU/ml]	Estrogens
HD	**15.6**	**1.3-9.1**	**4-46.6**	**<0.07-123**	**8.7-144.8**
		4.5	**53**	**5.4**	**54.2**
Controls	**16.9**	**2.1-9.9**	**7.1-224.7**	**<0.07-28.01**	**8.3-152.9**
		4.2	**66**	**5.2**	**64.3**
P	**NS**	**NS**	**NS**	**NS**	**NS**

Moreover we did not find any differences regarding parameters assessing ovarian function and reserve between patients with only HT and those with APS 3. Moreover levels of LH, SHBG, PRL, and fT4 did not differ in patients with HT, including APS 3 than in controls [Tab. 2].

Table 2. Serum levels of SHBG, PRL, aTPO and LH in patients with HT and in controls

	Age [yrs]	SHBG [ng/ml]	PRL [pg/ml]	aTPO [mIU/ml]	LH [mIU/ml]
HD	**15.6**	**30.5-163.8**	**62-305.3**	**<0.07-123**	**<0.07-155**
		112.1	**139.9**	**1333**	**3.5**
Controls	**16.9**	**51-173.6**	**61.5-722.7**	**<0.07-28.01**	**<0.07-155**
		101.6	**177.4**	**33**	**4.0**
P	**NS**	**NS**	**NS**	**<0.0001**	**NS**

Only TSH levels were significantly higher in HT group than in the control group (p = 0.02), although fT4 levels were not different [Fig. 2].

Results

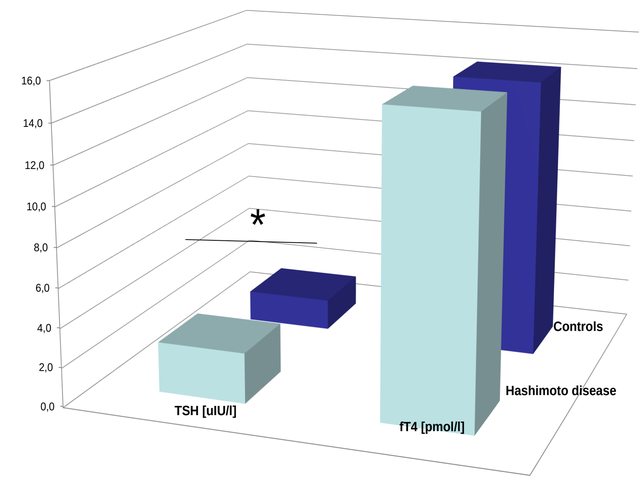

Figure 2. Serum levels of TSH and fT4 in the patients with HT and in the control group *(p = 0.02).

Conclusions

The results of our study did not indicate that young patients with HT, including those with APS 3 have impaired ovarian function and reserve.

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