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Research article

Should we routinely assess ovarian reserve in girls and young women with autoimmune thyroid disease?

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ABSTRACT

Background and aims: Some studies report that reproductive aged women with autoimmune thyroid disease (ATD) have a significantly higher risk of diminished ovarian reserve (OR). What is the best time to assessed OR in females with ATD? To answer this question, we assessed OR in girls and young women with ATD and reviewed the current literature regarding on the topic.
Methods: The study included 70 patients with ATD, mean 14.4 ± 3.3 years, and 29 age-matched controls. Follicle-stimulating hormone (FSH), luteinizing hormone, estradiol, prolactin, thyroid stimulating hormone, free thyroxin, thyroid peroxidase antibody, thyroglobulin antibody and Anti-Mullerian Hormone (AMH), and Inhibin-B were measured in all participants, if possibly on day 3–5 of the menstrual cycle.
Results: Most ATD patients were euthyroid. All participants have normal OR. We found a significantly positive correlation between AMH and Inhibin-B in ATD patients and between Inhibin-B and FSH in both groups.
Conclusions: The results of our study and the literature review indicate that euthyroid adolescents with ATD do not have impaired OR. Routine evaluation of OR in adolescents with ATD does not seem necessary. But OR should be assessed in everyone with ATD and hypothyroidism, because not the presence of ATD but euthyroidism matters to OR.

1. Introduction

Autoimmune thyroid disease (ATD), which has recently been estimated to have an incidence of 3.5 per 1000 per year in women in the United States [1], may be associated with ovarian dysfunction [2,3]. However, the prevalence of thyroid peroxidase antibody (TPOAb), which is a major marker of ATD, is much higher at 8–14 % in women of reproductive age, as most TPOAb-positive women is euthyroid [2]. Women with ATD are often concerned about their fertility and ability to have healthy offspring. It has long been known that hypothyroidism is associated with irregular periods and infertility. Long-term reductions in thyroid hormone levels can affect reproductive processes, including abnormal folliculogenesis, ovulation and fertilization disorders, and ovarian failure. The effects of thyroid function on the ovaries can be explained by the presence of receptors for thyroid hormones in human oocytes [4]. Previous data showed that 30–50 % of patients diagnosed with chromosomally competent premature ovarian failure (POF) without previous POF

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risk factors, such as chemotherapy or radiation therapy, had an associated autoimmune disorder, most commonly autoimmune thyroiditis [5]. Routine endocrine testing in patients with normal spontaneous POF showed that 18.5 % (22/119) of POF patients were diagnosed with hypothyroidism [6]. Isolated autoimmune ovarian disease is rare in women, but often occurs in combination with other autoimmune diseases [7]. The isolated form of disease is rare probably due to the severity of this disease and the inability to transmit genetic information conferring the ovarian disease across generations. Its combination with other autoimmune diseases may be due to damage to the mechanisms that protect the ovary from autoimmune attack. One of these mechanisms is the surveillance of autoreactive T cells by thymus-derived regulatory T cells. The second is the important involvement of an autoimmune transcriptional regulator responsible for the induction of expression of tissue-restricted antigens in thymic medullary epithelial cells during T cell development [7]. In the etiopathogenesis of ATD and ovarian autoimmunity, similar complex environmental and genetic factors are important. There are disparate data on premature ovarian aging in adult patients with ATD [8–12] and scanty data on the subject in children [13–17]. Recent meta-analyses have shown that women of childbearing age with Hashimoto's thyroiditis had a significantly higher risk of decreased OR [18,19] and this is age-dependent. Therefore, what is the best time to evaluate OR in women with ATD?

There are several tests used to assess OR, and all of them involve certain inconveniences. Static tests (endocrine and ultrasound) should be performed in the early follicular phase. Serum levels of folliculotropic hormone (FSH), inhibin B and estradiol (E2) are interdependent. Inhibin B and E2 are produced by early antral follicles in response to FSH, and in a classic feedback loop of the pituitary-gonadal axis, both inhibit FSH secretion. While the follicle pool decreases, inhibin B and estradiol levels fall, and then serum FSH levels rise. Inhibin B is an important independent predictor of FSH [20]. Nevertheless, changes in serum FSH, inhibin B and estradiol levels occur relatively late. Assessment of the number of antral follicles by ultrasonography best predicts the quantitative aspect of OR [21]. However, again, measurement of antral follicle count (AFC) should be performed using transvaginal ultrasonography in the early follicular phase. Transvaginal ultrasonography is often not possible in adolescent girls. Dynamic endocrine tests that assess the ovarian response to an exogenous gonadotropic stimulus are invasive and inconvenient. Moreover, their prognostic value for ovarian reserve is similar to static tests [22]. Anti-Mullerian hormone (AMH) is another marker of ovarian function, and is considered the best for assessing OR [23,24]. AMH is a glycoprotein that belongs to the transforming growth factor-β family and plays an important role in male embryonic development. AMH is responsible for the regression of Muller's duct in fetal life. In women, AMH is produced in small amounts by ovarian granulosa cells after birth until menopause, and then becomes undetectable. Its concentration in circulating blood correlates with ovarian function and ovarian reserve [25]. It is a serum marker that reflects the number of follicles that have passed from the primary pool to the growing follicle pool and that are not controlled by gonadotropins [23]. A blood sample for AMH assessment is taken only once, regardless of the phase of the menstrual cycle and time of day.

The purpose of this study was to evaluate OR in young women with ATD using an assessment of the classic methods currently available in clinical practice, as well as to review the current literature on the subject to answer the question of whether all young women with ATD should have their OR routinely assessed and whether there are specific indications for OR assessment in this group of patients.

2. Materials and methods

2.1. Patients

Seventy girls and young women with ATD, aged 7.3–23.5 years, mean 15.4 ± 7.6 years, and 29 age-matched healthy girls and young women, aged 3.1–24.5 years, mean 15.1 ± 6.5 years, were included in a prospective cohort study between 2015 and 2021. Exclusion criteria were: prior oncological treatment, abnormal karyotype, other chronic diseases. All patients with ATD were positive for at least one of the following thyroid autoantibodies: thyroid peroxidase antibody (TPOAb) and/or thyroglobulin antibody (TgAb). Most of them (60/70, 85 %) also had ultrasound images of the thyroid gland typical of chronic autoimmune disease. Twelve patients with ATD were additionally diagnosed with type 1 diabetes, which led to the diagnosis of autoimmune polyendocrinopathy type 3 (APS 3). The local ethics committee approved the study (consent number: KBET/29/B/2014, dated February 27, 2014). All participants over 16 years of age and their parents gave written informed consent.

2.2. Methods

Fasting blood samples for measurement of FSH, luteinizing hormone (LH), E2, prolactin (PRL), thyrotropic hormone (TSH), free thyroxine (fT4), TPOAb, TgAb, AMH and Inhibin-B were collected from the elbow vein between 8:00 and 10:00 a.m. in patients with normal menstrual cycles on day 3–5 of the cycle.

FSH (Siemens Healthcare Diagnostics Inc., USA), LH (Siemens Healthcare Diagnostics Inc., USA), PRL (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. ATPO and aTG levels were measured using an immunochemical method with isotope label sets (Brahms, Germany)

2.3. Statistical analysis

Statistical analysis was performed using the Staf Soft Statistica 13.1 64-bit package (StatSoft, Poland, Krakow, Poland). Results are presented as mean ± SD. Student's t-test was used for analysis. To test whether the variance of hormone levels differed among the three groups (patients with ATD, patients with APS3 and the control group), analysis of variance was used. A p-value of less than 0.05 was

considered statistically significant.

3. Results

Between patients with ATD, 69/70 patients (99 %) were euthyroid (including 9 with subclinical hypothyroidism with normal fT4 and TSH over 4 uIU/ml) and one present with an overt hypothyroidism with TSH 32.8 uIU/ml and fT4 9,6 pmol/l (normal range 10–25 pmol/l). The time from ATD diagnosis to OR evaluation was 0.5–11 years, with a mean of 3.3 ± 2.2 years. SDS BMI was similar in both groups [Table 1]. Also, the levels of FSH, E2 and inhibin-B and AMH were not statistically different between patients with ATD and healthy controls [Table 2]. The mean age of menarche did not differ between the two groups. There were also no differences in parameters assessing ovarian function and ovarian reserve between patients with ATD alone and patients with APS 3. In addition, levels of LH, prolactin, TSH and fT4 were not different in patients with ATD, including APS 3, compared with controls. There was no correlation between AMH and FSH, LH, E2, SHBG and prolactin. AMH did not correlate with TSH, fT4, TPOAb, TgAb, AMH, or ATD duration or SDS BMI. However, we found a significantly positive correlation between AMH and inhibin-B ($r = 0.56$, $p = 0.01$) in patients with ATD and between inhibin-B and FSH ($r = 0.55$, $p = 0.01$) in both groups.

4. Discussion

A recent meta-analysis showed that women of childbearing age with Hashimoto's thyroiditis had statistically significant decreases in AMH, AFC and increases in basal FSH compared to age-matched controls. In addition, premature ovarian aging in this group of women was essential for the higher incidence of TPOAb positivity. These two-way associations suggested that women of childbearing age with Hashimoto's thyroiditis had a significantly higher risk of reduced OR [18]. The meta-analysis cited above ultimately selected 35 of 55 full-text articles comparing ovarian reserve in 1858 patients with ATD with a control group. Most of the patients (1056) had euthyroidism. Only five studies, including our pilot study, were conducted in adolescent girls with a mean age of 14.4–15.6 years [Table 3]. Four of them showed that adolescent girls diagnosed with ATD did not have a reduced OR based on measurements of AMH [13–17], inhibin B, FSH, LH/FSH ratio, estradiol [13,16,17] and AFC [16]. Only in one study by Metwalley et al. was the OR reduced in adolescent girls with ATD and hypothyroidism [17].

In the study by Ozalp et al. and in our pilot study, there was no statistically significant difference between ATD patients and healthy ones regarding serum AMH levels [15,16]. Authors of both studies observed a negative correlation between serum AMH levels and TSH levels, and did not find any correlation between serum AMH levels and TPOAbs or TgAbs. The authors concluded that Hashimoto's thyroiditis has no effect OR in teenagers. Autoimmune damage to the ovaries may take a long time for the disorder to manifest itself, so the age of puberty may not yet be captured. The authors concur in recommending further monitoring of ovarian function in young girls with ATD. In studies by Pirgon et al. and Erol et al. AMH levels were even higher in adolescent girls with ATD compared to healthy controls [13,14]. In studies by Pirgon et al. and Erol et al. AMH levels were even higher in adolescent girls with ATD compared to healthy controls [13,14]. The study by Pirgon et al. examined 30 adolescent girls (mean age 15.1 ± 1.4 years) recently diagnosed with Hashimoto's thyroiditis with high thyroid antibodies with glandular heterogeneity on ultrasound and 30 healthy age-matched females. There were no significant differences between girls with ATD and healthy controls in terms of LH/FSH ratio, estradiol and inhibin-B levels. Levels of ATOAb, AMH and total testosterone were higher in the group with ATD than in the control group. ATOAb levels were found to be positively correlated with LH/FSH ratio, AMH and inhibin-B in patients with Hashimoto's disease [13]. The surprising finding of higher AMH levels in the AID group is consistent with the results of a study in adult women with ATD by Tuten et al. These authors suggested that this observation may be due to polycystic ovary syndrome, which may share an etiological link with autoimmunity [26]. However, in the study by Pirgon et al. there were no data on the prevalence of polycystic ovary syndrome; on the contrary, their patients had no menstrual abnormalities. In the study, Erol et al. recruit 57 non-obese girls with newly diagnosed with Hashimoto's thyroiditis and 50 healthy subjects of the control group matched against age and BMI [14]. All participants were in a euthyroid state when their serum AMH levels, some hormonal and metabolic parameters, and antioxidant status as assessed by paraoxonase (PON) and arylesterase (ARE) activities were evaluated. Serum AMH levels were approximately higher, and serum PON and ARE activities were significantly lower in adolescents with Hashimoto's thyroiditis than in the control group. There were no significant associations between AMH levels and any of other parameters in the control group. But in the ATD group AMH levels were negatively correlated with PON and ARE activities [14]. Another 2021 meta-analysis on the evaluation of OR in women with ATD eventually identified nine studies, including two in adolescent girls, the same studies later analyzed in 2022 [13,14,19]. The authors of this meta-analysis suggest that the increase in serum AMH levels in adolescent girls with ATD may be the result of excessive activation of dormant primordial follicles leading to an increased pool of AMH-producing follicles. This may be compensatory mechanism against autoimmune damage that causes rapid maturation of follicles. Substantial recruitment of primary follicles after imperforation of

Table 1
Mean ± SD parameters assessing thyroid function and thyroid antibodies in girls with autoimmune thyroid disease (ATD) and in a healthy control group.

	Age [years]	SDS of BMI	Age for menarche [years]	TSH [uIU/ml]	fT4 [pmol/l]	TPOAb [mIU/ml]	TgAb [U/ml]
ATD (No 77)	14.4 ± 3.3	0.96 ± 2.20	11.8 ± 1.1	3.5 ± 4.8	15.5 ± 2.2	2543.8 ± 3552	753.5 ± 1782
Controls (No 29)	15.1 ± 6.5	0.83 ± 2.05	12.5 ± 1.3	3.6 ± 5.4	15.0 ± 2.2	16.7 ± 5.4	10.0 ± 4.0
P	0.32	0.95	0.8	0.94	0.33	<0.001	<0.001

Table 2
Mean ± SD parameters assessing ovarian reserve and function in girls with autoimmune thyroid disease (ATD) and in a healthy control group.

	AMH [ng/ml]	Inh-B [pg/ml]	FSH [mIU/ml]	LH [mIU/ml]	E2 [pg/ml]	Prolactin [pg/ml]
ATD (No 77)	5.8 ± 4.3	55.6 ± 36.5	5.6 ± 2.3	6.2 ± 5.4	52.6 ± 44.6	176.1 ± 88.9
Controls (No 29)	4.5 ± 2.8	66.3 ± 57.0	5.2 ± 3.0	4.8 ± 4.2	59.8 ± 43.2	204.3 ± 175
P	0.1	0.5	0.6	0.3	0.6	0.4
MD	1.29	−10.7	0.39	1.43	−7.19	−28.3
−95 % CI for MD	−0.46	−42.2	−0.93	−1.54	−31.8	−93.5
+95 % CI for MD	3.04	20.8	1.72	4.4	17.5	36.9

CI – confidence interval, MD – mean difference.

destructed growing follicles has been presented in cyclophosphamide-induced ovarian failure [27]. This theory is called the "burnout" theory, as continued activation of primary follicles eventually leads to follicle exhaustion. Present metanalysis suggests that slow "burn-out" may be involved in the loss of blisters caused by ATD.

The results of Metwalley et al. differ from the study cited above [17]. They reported decreased OR in adolescents with ATD compared to an age-matched control group. Therefore, it is worth taking a closer look at the results of this work. The majority of participants in this study, i.e. 78/96 patients (81 %) had hypothyroidism with TSH greater than 10 mIU/l, and their AMH was lower than 1.92 ± 1.07 ng/ml compared to 4.2 ± 1.27 ng/ml in the control group. Analyzing the results in detail, girls with overt hypothyroidism were older (16.21 ± 3.32 years) than healthy girls (14.9 ± 1.3 years). AMH levels in women are known to increase steadily until the age of 24 years. The authors of this study reported that in multivariate analysis AMH levels were significantly with age, BMI-SDS, TSH and TPOABs. Thus, the age differences between ATD patients and healthy girls may additionally affect the results of this study differently than in other studies [28]. Moreover, only in the study by Metwalley et al. were its female participants not euthyreotic. The pathophysiology of how ATD reduces OR is not well established. Some studies suggest that it is not thyroid autoimmunity, that thyroid malfunction that weakens OR [11,29–31]. The systemic review and meta-analysis by Shi et al. reported affected AMH concentration in adult females with subclinical hypothyroidism and overt hypothyroidism [31]. However basing on the previously mentioned studies by Pirgon et al. and Erol et al. it also concluded that euthyroid adolescent girls had higher AMH levels that healthy controls [13,14]. Thyroxine, which is found in human follicular fluid, is important for oocyte development, so a reduction in ATD thyroid function may interfere with the hypothalamic-pituitary-gonadal axis and consequently reduce OR [32]. Elevated TSH can have deleterious effects on ovarian function. It can directly inhibit the development of ovarian follicles or influence on the reproductive function via receptors of thyroid hormone on the surface of oocytes. But it can also indirectly affect gonadotropin-releasing hormone caused by increase prolactin secretion [33,34]. Indeed, some studies have shown significant negative correlations between TSH levels and OR [15,16]. On the other hand, TPOAb can initiate an immune response that damages ovarian tissue, as antithyroid antibodies are also detected in ovarian follicles [9,35]. TPOAb, which crosses the blood follicle barrier during follicle maturation, can begin antibody-dependent cytotoxicity in the growing follicle and destroy the maturing oocyte, result in destruction and damage to growing follicles and oocytes by thyroid receptors in these cells [36]. Autoimmune antibodies, directly and indirectly, affect folliculogenesis by altering follicular fluid composition and granulosa cell differentiation, as well as abnormal steroidogenesis via the hypothalamic-pituitary-gonadal axis [37,38]. However, our study did not show our study did not show any correlation between classic anti-tumor antibodies and OR. Patients with ATD may have concurrent ovarian autoimmunity, and the presence of antithyroid autoantibodies (ATA), anti-laminin-1 antibodies and pro-inflammatory cytokines (IL-17α) may affect oocyte immune homeostasis, which may impair OR, oocyte fertilization and embryogenesis [39]. In 2016, anti-LN-1 antibodies (aLN-1 Abs) were first demonstrated in the serum and follicular fluid of infertile women with Hashimoto's thyroiditis and suggested that aLN-1 Abs may worsen IVF outcomes [40]. Laminin-1 (LN-1) is a valuable component of the extracellular matrix and is involved in oocyte maturation, embryogenesis, implantation and placenta formation [39,41]. Meanwhile, the only effect that can be assessed in advance is OR.

Our data indicates that adolescent and young women with AITD and euthyroidism have normal OR, as their healthy peers using currently available diagnostic methods. The positive correlations found between AMH and FSH and AMH and Inhibin B confirm their usefulness in the diagnosis of OR. Although, based on the literature and our clinical experience, it should be emphasized that the determination of AMH has the highest diagnostic value, AMH is independent of the menstrual cycle or the medications used [23–25,42]. Notwithstanding, in interpreting its results, it is necessary to remember to relate the norm to the patient's age. Data from the literature indicate that diminished OR occurs and appears to be age-related in older women with ATD and euthyroidism [19]. An individually limited predictive power of the AMH concentration for the onset of natural menopause has been lately reported [43]. It would be desirable to find an early POF marker, perhaps aLN-1 Abs, or another that does not yet exist. In addition, further large clinical trials are needed to investigate the actual impact of autoimmunity on OR, as some patients may benefit from biologic therapy in the future. This would make it possible to identify selected groups of patients who are most likely to benefit from rapidly evolving biologic therapies that outweigh the benefits of conventional therapy.

5. Limitations

Our study has some limitations. We did not use AFC in our study because we could not use transvaginal ultrasonography in most of our patients. We recalled that all the ovarian reserve tests described so far examine the number of oocytes, and it was not possible to assess oocyte quality directly. We tried combinations of different markers (AFC, AMH and inhibin-B) and developed a common scoring

Table 3
Results of studies assessing the prevalence of premature ovarian failure (POF) in pediatric patients with autoimmune thyroid disease (ATD).

Study	N ATD/Control	Age median (range) or mean (±SD) of pts with ATD/ control [years]	Assessed parameters	Results of the study	Mean follow up of ATD Pts treated with L-tyroxin [%]	Prevalence of POF [%]
Pirgon et al. (2015)	30 (all euthyreotic, non-obese, PCOS was exluded)/30	(12–18) 15.1 (±1.4)	AMH, inhibin-B, LH, FSH, estradiol, TPOAb total testosterone, AFC, ovarian volumes and uterine length thyroid and pelvic ultrasonography	no significant differences between pts with ATD and controls in relation to LH/ FSH ratio, LH, FSH, estradiol, inhibin-B levels, and AFC AOAb ($p = 0.02$), AMH ($p = 0.007$), total testosterone levels and ovarian volumes were higher in ATD group than the control ($p = 0.03$). AOAb level was found to be positively correlated with LH/FSH ratio ($p = 0.03$), AMH ($p = 0.01$) and inhibin-B ($p < 0.001$) in ATD group. AOAb was positive in 33 % pts wih ATD, but they did not have any ovarian dysfunction such as menstrual irregularities.	newly diagnosed ATD (TSH <2.5 mIU/L) (0 %)	0 %
Erol et al. (2016)	57 non-obese with regular menses (all euthyreotic)/50 non-obese, with regular menses	(12–18) and 15.4 (±1.4)/ 15.1 (±1.6)	AMH TSH, fT4 prolactin, total testosterone, DHEAS TPOAb, TgAb Glucose, insulin, lipids Thyroid ultrasonography PON, ARE	AMH in ATD (median 4.65 ng/ml; (range 1.14–8.51)) higher than in controls (2.48 ng/ml, 1.12–6.74) ($P < 0.001$) negative correlations between AMH and PON ($r = -0.4$, $p = 0.001$) and ARE ($r = -0.4$, $p = 0.001$) in ATD no relationships between AMH and other parameters	No data	0
Ozalp et al. (2018)	30 (26 euthyreotic and 4 subclinical hypthyreosis/30	(10–18) and 14.4 (±1.85)/ age-matched	AMH TSH, fT4, TPOAb, TgAb thyroid ultrasonography	no differences regarding AMH levels between both groups ($P = 0.784$) AMH correlated negatively with TSH.	8.5 ± 4.5 months (86 %)	No data
Wędrychowicz et al. (2018)	21 (all euthyreotic)/ 17	15.6 (8.7–23.5) and 15.6 (±4.0)/age-matched 16.4 (8.8–24.6)	AMH, Inhibin-B FSH, LH, estradiol, SHBG prolactin TSH, fT4 TPOAb	no differences regarding examined parameters between groups in spite of TSH, $P = 0.02$)	88.8 ± 22 months (100 %)	0
Metwalley et al. (2023)	96 (79 overt hypthyreotic and 18 euthyreotic)/96	(16.21 ± 3.32, and 14.10 ± 2.53)/14.9 ± 1.3	AMH, FSH, LH TSH, fT4, fT3 TPOAb, TgAb	AMH of over hypothyreotic 1.92 ± 1.07 ng/ml euthyreotic 2.71 ± 1.2 ng/ml control 4.2 ± 1.27 ng/ml AMH levels correlated significantly with age, BMI SDS, TSH, and TPOAb.	No data	No data
Our study	70 (12 with T1DM also) (64 euthyreotic, 9 with subclinical hypothyreosis, one had overt hypothyreosis/29	7.6–23.5 15.4 ± 7.6/ 3.1–24.5 15.1 ± 6.5	AMH, inhibin-B, FSH, LH, estradiol, prolactin TSH, fT4 TPOAb, TgAb TRAb	any differences regarding parameters assessing ovarian function and reserve between patients with only ATD and those with APS 3 no correlations between AMH and TSH, fT4, anti-TPO, anti-TG, TRAB, neither with ATD duration nor SDS of BMI only significant positive correlation between AMH	3.2 ± 2.1 (90 %)	0

(*continued on next page*)

Table 3 (*continued*)

Study	N ATD/Control	Age median (range) or mean (±SD) of pts with ATD/ control [years]	Assessed parameters	Results of the study	Mean follow up of ATD Pts treated with L-tyroxin [%]	Prevalence of POF [%]
				and Inh-B ($r = 0.56$, $p = 0.01$) in ATD patients and between Inh-B and FSH ($r = 0.55$, $p = 0.01$) in both groups		

FSH – follicle stimulating hormone, LH – luteinizing hormone, TSH – thyroid stimulating hormone, fT4 – free thyroxine, DHEAS – dehydroepiandrostrone sulfate, TPOAb – anti-thyroid peroxidase antibodies, TgAb – anti-thyroglobulin antibodies, AMH – anti-Muellerian hormone, PON – paraoxonase, ARE arylesterase, AOAb – anti-ovarian antibodies, T1D – type 1 diabetes mellitus.

system that predicts a poor response to gonadotropin stimulation at best with a sensitivity of 87 % and specificity of 80 % and a positive likelihood ratio of 4.36 %. Nevertheless, they have not been tested for pregnancy prediction [44].

6. Conclusions

The results of our study do not indicate that young patients with ATD in euthyroidism, including those with APS 3, have impaired ovarian function and OR. It does not seen necessary to routinely assess OR in all adolescent and young women with ATD by assessing AMH, FSH or inhibin B. However, these tests are valuable in the diagnosis of OR and should be performed in patients with prolonged hypothyroidism. Based on the literature and our results, euthyroidism in ATD patients is most important for their OR. Therefore, novelty of our study is an indication that OR should be assessed in every young female with ATD and hypothyroidism. Maintaining euthyroidism in ATD therapy is crucial for normal OR in young patients.

CRediT authorship contribution statement

Anna Wędrychowicz: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Joanna Wojtyś:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Data curation. **Dominika Januś:** Writing – review & editing, Data curation. **Aleksandra Furtak:** Writing – review & editing, Software, Data curation. **Małgorzata Stelmach:** Writing – review & editing, Data curation. **Jerzy B. Starzyk:** Writing – review & editing, Formal analysis, Data curation, Conceptualization.

Availability of data and material

The presented data and material are available from the authors of the article in the institutions where they the study was conducted.

Ethics approval

KBET/29/B/2014.

Founding

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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