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THE EFFICIENCY OF IVF/ICSI PROTOCOLS IN FEMALE SUBCLINICAL HYPOTHYROIDISM AND THYROID AUTOIMMUNITY

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▪ While overt hypothyroidism is a well-known risk factor for infertility, the association of subclinical hypothyroidism (SCH) or thyroid autoimmunity with reproductive failure has been still not cleared. This literature review focuses on the most current data linking SCH and/or thyroid autoimmunity with human reproduction, starting with the parameters of ovarian reserve and ending with generalized immunological alterations. The main ART outcome measures are as follows: number of oocytes retrieved, fertilization rate, embryo quality, implantation rate, clinical pregnancy rate per embryo transfer, miscarriage rate, and live birth rate. Summary of the information regarding the effect of levothyroxine supplementation on IVF outcome as well as workup and management of women with SCH and thyroid autoimmunity undergoing ART cycles is also presented in this review.

▪ **Keywords:** subclinical hypothyroidism; thyroid peroxidase antibodies; assisted reproductive technology; infertility; ovarian reserve; fertilization; embryo quality.

РЕЗУЛЬТАТИВНОСТЬ ПРОТОКОЛОВ ЭКО/ИКСИ У ЖЕНЩИН С СУБКЛИНИЧЕСКИМ ГИПОТИРЕОЗОМ И НОСИТЕЛЬСТВОМ АНТИТЕЛ К ЩИТОВИДНОЙ ЖЕЛЕЗЕ

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▪ В настоящее время хорошо известно, что клинически выраженный гипотиреоз является фактором риска развития бесплодия. Однако роль субклинического гипотиреоза и носительства антител к щитовидной железе в развитии репродуктивных неудач зачастую остается неясной. В данном обзоре приведены современные данные о взаимосвязи субклинического гипотиреоза и/или носительства антитиреоидных антител и процесса репродукции человека, начиная с параметров овариального резерва и заканчивая изменениями иммунологического статуса в организме в целом. В качестве основных показателей результатов лечения в программах вспомогательных репродуктивных технологий рассматривали число полученных ооцитов, частоту оплодотворения, качество эмбрионов, частоту имплантации эмбрионов, частоту наступления клинической беременности на перенос эмбриона, частоту развития ранних репродуктивных потерь и частоту живорождений. Представлены данные об эффектах заместительной терапии на исходы программ вспомогательных репродуктивных технологий, а также тактика обследования и ведения пациенток с субклиническим гипотиреозом и носительством антител в рамках подготовки к экстракорпоральному оплодотворению.

▪ **Ключевые слова:** субклинический гипотиреоз; антитела к тиреоидной пероксидазе; вспомогательные репродуктивные технологии; бесплодие; овариальный резерв; оплодотворение; качество эмбрионов.

Despite current advances in human reproduction, the prevalence of infertility in marriage remains consistently high (10%–15%) [1]. In recent years, the problem of the relationship between reproductive function disorders and autoimmune diseases, including the thyroid gland, has attracted increasing attention. In the structure of endocrine pathology, thyroid disorders rank first and are detected in 5% of the population in Western countries, and their incidence among women of reproductive age is 5–10 times higher than that in men [2]. In infertility in women, the most characteristic dysfunction of the thyroid gland is hypothyroidism, including overt and subclinical in autoimmune thyroiditis.

Autoimmune thyroiditis (AIT) is a chronic progredient disease in which an autoreactive process develops against the thyroid gland tissue with the involvement of all populations of lymphocytes. This disease is morphologically manifested by mononuclear infiltration, signs of inflammation, and gradual loss of thyroid function with a number of complications. It was first described in 1912 by the Japanese doctor Hakaru Hashimoto and was named "lymphomatous goiter." AIT is currently a socially significant and globally prevalent disease. In Russia, the AIT incidence reaches 45 cases per 1000 population; in the United States since 1997, AIT has been the third most common autoimmune disease. AIT is the most frequent endocrine disease among women and affects approximately 5 %–15 % of women of reproductive age [2, 3]. In 95 % of cases, diagnostically significant autoantibodies (ABs) against thyroperoxidase (TPO), thyroglobulin (TG), and other colloidal and cytosolic autoantigens are determined in the blood of patients. Hypothyroidism develops gradually with AIT and proceeds slowly over the years without vivid clinical symptoms and is classified as overt hypothyroidism. The laboratory signs of overt hypothyroidism are high levels of thyroid-stimulating hormone (TSH) and low levels of thyroid hormones and subclinical hypothyroidism. The latter occurs in populations much more often than clinically expressed one and is characterized by an increase in TSH concentration in the blood with normal levels of free thyroxine (T_4) and triiodothyronine (T_3) [3].

Among women with infertility of unknown origin, the prevalence of AIT constitutes approximately 10 % [4]. Most laboratories use 4–4.5 mU/L as the upper limit of the norm for TSH; however, the American Society for Reproductive Medicine (2015) recommended that the level of TSH should not exceed 2.5 mU/L before entering the in vitro fertilization (IVF) program [5]. The total prevalence of overt hypothyroidism in the population amounts to 0.2 %–2 %, whereas that of subclinical hypothyroidism is approximately 5 %–10 %, and carriage of antibodies without impaired gland function is 8%–14% among women of reproductive age [6].

Adequate secretion of thyroid hormones is extremely important for the normal functioning of a female reproductive system. This dependence is especially clearly observed with overt hypothyroidism, where suppression of the pulsating release of luteinizing hormone leads to the development of hyperprolactinemia, disruption of folliculogenesis regulation, and occurrence of anovulation and infertility. At the same time, these processes can be quickly corrected if the euthyroid state is restored [7]. Unlike severe hypothyroidism, subclinical hypothyroidism or isolated carriage of thyroid gland antibodies is often not diagnosed because of the absence of typical clinical symptoms of the disease in patients.

The effect of subclinical hypothyroidism or carriage of thyroid gland antibodies on female fertility was studied mainly in women with infertility, including those undergoing assisted reproductive technologies (ARTs). Poppe et al. [8] reported that the total relative risk (RR) for infertility and miscarriage among women with subclinical hypothyroidism is 2.1 (95 % CI 1.7–2.6; $p < 0.0001$). According to this indicator, the incidence of AIT women among those seeking help in infertility treatment clinics is significantly higher compared with the general population. This relationship is clearly observed in women with concomitant polycystic ovarian syndrome (approximately 25 %) and infertility of unknown origin (approximately 10 %) [4].

A relationship has been established between subclinical hypothyroidism and/or carriage of antithyroid antibodies with unfavorable obstetric outcomes in spontaneous and induced pregnancy, such as preeclampsia, premature detachment of a normally located placenta, early termination of pregnancy, premature birth, and neonatal mortality [9].

The available literature presents the possible mechanisms of the effect of subclinical hypothyroidism and isolated carriage of antibodies to autoantibodies against thyroid peroxidase (AB-TPO) and autoantibodies against thyroglobulin (AB-TG) on the state of the female reproductive system.

Effect on ovarian function

Clinically apparent hypothyroidism is a well-known risk factor for the development of infertility. However, the study of the potential role of subclinical hypothyroidism or isolated antibody carriage in the female reproductive system may be relevant when the cause of infertility is unknown. The direct importance of AIT in outcomes of ART cycles and ovulation induction has been widely studied, but the parameters of the ovarian reserve are rarely investigated.

A large amount of receptors for thyroid hormones are produced in tissues of the female reproductive system, including granulosa cells and oocytes [10, 11]. Preclinical studies indicated that thyroid hormones participate in the growth and development of follicles, which is synergistic with follicle-stimulating hormone, and in the suppression of apoptosis [12, 13]. A lack of thyroid hormones can considerably influence the ovarian reserve. It can decrease the number of antral follicles, which can partially be associated with exposure to nitric oxide synthase. Mice with hypothyroidism have a reduced number of primary, growing, and antral follicles [14, 15].

Scientists of the University of Massachusetts [7] evaluated the relationship of the functional condition of the thyroid gland and the carriage of antithyroid antibodies to the ovarian reserve among women with infertility of unknown origin. A total of 436 women were enrolled in the study, and the number of antral follicles was measured in 378 of them (women with more than 20 follicles were excluded).

Among women with infertility of unknown origin, a relationship was found between a reduced concentration of free triiodothyronine (fT_3) and a reduced number of antral follicles (continuous non-linear association, $p = 0.009$). No relationship was detected between the levels of TSH, T_4, and free thyroxine (fT_4) and the follicular pool. Regarding antibody carriage, among women with AB-TPO, a smaller number of antral follicles was noted, that is, less than 8 (average discrepancy is 2.3 follicles; 95% CI 3.8–0.5; $p = 0.01$). In the general population of the patients studied, isolated AB-TG carriage was associated with a higher value of the number of antral follicles (average discrepancy is 3.4; 95% CI 1.8–5.1; $p < 0.001$). However, in the group of women with infertility of unclear origin, this dependence was not revealed. The thyroid gland functional status and the presence of antibodies did not affect the level of follicle-stimulating hormone determined on day 3 of the menstrual cycle [7]. Thus, the authors pointed to a direct relationship of the concentration of fT_3 and the carriage of AB-TPO to the number of antral follicles. The lack of a similar ability in TSH and fT_4 suggests that the woman's ovary is more sensitive to T_3 because of the presence of type 8 monocarboxylate carrier (for T_3) and type II deiodinase, an intracellular enzyme that converts T_4 to a more active form of T_3 [16]. In addition, experimental studies proved that the ovary can accumulate iodine and locally produce T_3 by external deiodination of the ring, which exerts a dose- and time-dependent effect on the availability of local estrogen [17].

Theories have been developed regarding the effect of antithyroid antibodies on the number of antral follicles. First, carriage of AB-TPO may be accompanied by a decrease in thyroid function and the development of hypothyroidism (overt or subclinical), which can lead to disturbances in the early stages of follicular development. However, this potential mechanism seems unlikely because the relationship between antibody carriage and the number of follicles remains unchanged even after the drug correction of thyroid function (including fT_3). Second, autoimmune thyropathies can be part of autoimmune polyendocrine syndrome I and II with damage to other endocrine glands, including the structure of the reproductive system, affecting folliculogenesis [18]. Monteleone et al. (2011) hypothesized that infertility is caused by changes in the structures of follicles in female patients with AIT [19]. AB-TG and AB-TPO were found in all follicular fluid samples among 14 female patients with AIT. Moreover, they showed a clear correlation with the level of serum antibodies, indicating their ability to pass freely through the hematofollicular barrier. In the control group of 17 women, antibodies in the follicular fluid were not determined. The authors reported that autobodies to the thyroid gland can have a direct cytotoxic effect on the growing follicle and affect adversely the state of the embryo through direct interaction with *zona pellucida* antigens, disrupting its functional role. Thus, the frequency of fertilization, the number of embryos of optimal quality, and the frequency of pregnancy are significantly lower in the study group compared with the comparison group. Thus, we can assume that antibodies to the thyroid gland affect directly the ovarian tissue. After excluding women with established causes of reduced ovarian reserve from the study, the incidence of AB-TPO carriage varies significantly in groups with reduced (22.7 %), normal (14.0%), and high (10.3 %,

$p = 0.012$) ovarian reserves. In a group of female patients with idiopathic infertility, the AB-TPO value is significantly correlated with the ovarian reserve, which is reduced for an unknown reason (low is 28.6 %, normal is 15.7 %, high is 9.5 %, $p = 0.20$) [20].

Michalakis et al. (2011) attempted to identify a relationship between a subclinical increase in TSH concentration before the onset of stimulation cycles on ART outcomes and on ovarian reserve parameters. Ovarian reserve reduces with an increase in follicle-stimulating hormone levels of more than 14 mIU/mL on day 3 of the menstrual cycle in the presence of less than five antral follicles before stimulation or with a reduced ovarian response in previous stimulation cycles.

Subclinical hypothyroidism was diagnosed in 23 % of female patients in the test group (laboratory TSH values were 2.5–4.0 mU/L). Regression multivariate analysis revealed a statistically significant increase in the frequency of reduced ovarian reserve with TSH figures more than 2.5 mU/L ($p = 0.023$). None of the female patients with TSH values lower than 0.4 mU/L showed a decrease in ovarian reserve, whereas the ovarian reserve was reduced in 14% of female patients with subclinical hypothyroidism and 18% with overt hypothyroidism [21].

These data indicate an indisputable decrease in the main parameters of the ovarian reserve in female patients with AIT relative to a group of women without thyroid disease, which is probably due to the autoimmune genesis of this disease. This theory is further supported by a study by scientists from the University of Bari (Italy), who assessed the effect of antibodies against laminin-1 in the serum and follicular fluid of infertile female patients with AIT on oocyte maturation and IVF results. Laminin-1 is a significant component of the extracellular matrix and is necessary for the maturation of oocytes (it accelerates the formation of polar bodies, embryogenesis, implantation, and placentation). Therefore, antibodies to laminin-1 are assumed to have a negative effect on the earliest stages of reproduction, leading to infertility. The authors first obtained data on high titers of these ABs in the sera of female patients with AIT (19/44—43.2 %) compared with the control group (1/28—3.6 %). An inverse negative relationship was found between the number of mature oocytes in metaphase II of meiosis and the level of ABs to laminin-1 in follicular fluid (correlation coefficient–0.34; $p = 0.024$ and correlation coefficient–0.33; $p = 0.03$, respectively). The frequency of implantation and clinical pregnancy was much lower in the group of patients with AIT (7.9 % and 9.1 %, respectively) than in the control group (23 % and 31.1 %, respectively) ($p = 0.015$ and $p = 0.03$, respectively). Thus, the results of IVF cycles revealed the negative effect of ABs on laminin-1 with AB-TPO in autoimmune damage to the thyroid gland [22].

Embryo quality

The relationship of the thyroid gland functional status with the reproductive system is especially pronounced in induced pregnancy. Stimulation of superovulation conducted in IVF programs is accompanied by high levels of estrogen in the blood. Hyperestrogenism due to a number of compensatory mechanisms (increased synthesis of thyroxine binding globulin in the liver, binding of an additional amount of free thyroid hormones, and a decrease in the level of the latter) increases TSH level. Werghofer et al. (2015) suggested that this pattern may affect the results of IVF programs. Their case–control study aimed to determine the effect of AIT on the quality of embryos in women with reduced ovarian reserve who received ICSI treatment [23].

In 88.2 % of cases, the protocol was used with microdoses of preparations of gonadotropin-releasing hormone agonists (GnRH). In 11.2 % of cases, it was with GnRH antagonists. Embryos were described in accordance with D.K. Gardner criteria (2003).

Among female patients with TSH levels at the upper limit of normal, the quality of the embryos ($p = 0.013$) was more often affected, which was confirmed by multivariate regression analysis. A tendency toward a deterioration in the quality of embryos was also revealed in female carriers of AB-TPO regardless of TSH level ($p = 0.056$). These data are supported in the theory of Monteleone et al. (2011) and emphasize the key role of the influence of antibodies, rather than hypothyroidism, on the outcome of IVF/ICSI procedures. The trend toward a successful outcome of pregnancy resulting from ICSI was observed at a TSH level at the lower limit of normal.

Given the lower incidence of clinical pregnancy (only 15%) in a group of female patients with positive antithyroid antibodies and TSH more than 2.5 IU/mL, we can assume that AIT affects not only the quality of the embryos but also the formation of the immune tolerance of the mother's body, which causes a disorder of embryo implantation.

Endometrium

Transcription factors of TPS and TG are present in the endometrium, which possibly influences the local production of thyroxine. Their presence makes the endometrium susceptible to antithyroid antibodies. In addition, receptors for TSH and thyroid hormones are present under physiological conditions in the endometrium in women, and the severity of their expression directly depends on the phase of the menstrual cycle. As a result, studies suggested that endometrial proliferation, phase transformation, and embryo implantation may be impaired under low levels of thyroid hormones, leading to the early development of a blastocyst.

However, at present, very few studies assessed comprehensively the state of the endometrium in female patients with AIT. Thus, Kilic et al. (2008) [24] analyzed IVF outcomes in 69 female patients with infertility of unknown origin, among other parameters, and examined the thickness of the endometrium to assess its readiness for pregnancy. Women were divided into three groups: 31 female patients with no thyroid dysfunction and no antibodies to the thyroid gland, 23 female patients with antithyroid antibodies and subclinical hypothyroidism, and another 15 female patients with antibodies and compensated hypothyroidism. No difference in endometrial thickness was found between the groups. At the same time, the endometrium ultrastructure or the presence of immunocompetent molecules in it was not analyzed.

The antibodies to thyroid tissue may have a direct embryotoxic effect on trophoblast, limiting its invasion and preventing the normal development of the fetus. This finding is evidenced by the results of an experimental study involving mice immunized with human TG, where the pathological immune recognition of the latter and placental antigen AB-TG was registered, accompanied by a decrease in the weight of the fetus and placenta, which resulted in the arrested development of pregnancy [25].

Cell immunity

Considering that AIT is associated with an increased risk of infertility, unsuccessful outcomes of IVF cycles, and the development of early reproductive losses even with subclinical hypothyroidism, scientists are concerned whether this phenomenon is connected with changes in cellular immunity. Researchers from Hungary revealed an increase in the population of peripheral NK and NK-like cells in the blood of female patients with AIT (18 carriers of antibodies and 14 carriers of subclinical hypothyroidism) compared with the control group (20 women). Analyzing the threshold level of these cells in the development of reproductive failures, they received a figure of 12 %–18 %, which corresponds to the data of other authors. In the subgroup of female patients with subclinical hypothyroidism, the expression on the surface of NK-like cells of inhibitory CD158a-receptors significantly increased, and the expression of activating NKG2P receptors significantly reduced, which indicated an imbalance of phenotypic and functional properties. The cytotoxic properties of NK cells were more pronounced in the blood of female patients with AIT (in both subgroups) compared with healthy women, as evidenced by an increase in the expression of CD107a, which is responsible for cell degranulation. According to the authors, the immunological status of female patients with AIT is undoubtedly changed due to an increase in the number of NK- and NK-like cells, their cytotoxicity potential, and the predominance of pro-inflammatory reactions, which affect the reproductive potential. The authors emphasized that the above changes occur already at the very early stages of the disease, before the development of clinical symptoms, when the disease can be revealed only by the accidental detection of antithyroid antibodies [26].

Results of IVF/ICSI protocols in patients with subclinical hypothyroidism and antithyroid antibodies

Number of oocytes obtained, frequency of fertilization, frequency of implantation, and frequency of clinical pregnancy per one embryo transfer

Medenica et al. [27] evaluated the aspects of ART protocols among 52 women (26 with AIT, 26 without AIT). Preparations for stimulating ovulation were selected individually; either a long protocol with GnRH agonist drugs or a short protocol with GnRH antagonist drugs was used. Twenty female patients of the AIT group were using thyroxine replacement therapy (average dose was 67.49 ± 29.40 μg/day, average duration of treatment was 19.5 months). AIT showed no negative effect on the number of eggs obtained and on the frequency of fertilization, as evidenced by the lack of statistically significant difference between these parameters in the compared groups. However, the frequency of embryo implantation was significantly lower in the group of patients with AIT compared with the control group (21.01 % versus 31.94 %, $p = 0.092$).

Moreover, the frequency of clinical pregnancy per embryo transfer differed significantly in the AIT group relative to the control (30.8% and 61.5%, respectively, $p = 0.026$). Multivariate analysis confirmed again the delay in pregnancy among female patients with positive antithyroid antibodies, despite the compensated state of the thyroid gland (RR 0.036; 95% CI 0.004–0.347; $p = 0.004$).

A similar work was performed by Zhong et al. [28]. The group of subjects included 90 female patients with AIT (156 IVF/ICSI cycles). The control group included 1062 women without AIT (1062 IVF/ICSI cycles, transfer of 981 and cryopreservation of 81 embryos). In all cases, stimulation was performed with GnRH agonist drugs. The duration of stimulation, the total dose of stimulation preparations, and the number of eggs received did not differ significantly between the two groups. However, the frequency of fertilization (64.3 % versus 74.6 %, $p < 0.001$), implantation (17.8 % versus 27.1 %, $p < 0.001$), and the onset of clinical pregnancy (33.3% versus 46.7%, $p = 0.002$) was significantly lower in the group of patients with AIT compared with the control.

Based on a systematic review of nine articles on the outcome of IVF/ICSI cycles among 4396 female carriers of antithyroid antibodies, Busnelli et al. (2016) revealed no difference in the number of oocytes received (RR 0.10; 95 % CI 0.09–0.29; $p = 0.28$), fertilization rate (RR 1.11; 95 % CI 0.97–1.27; $p = 0.13$), implantation frequency (RR 0.98; 95 % CI 0.73–1.32, $p = 0.91$), and in the probability of pregnancy (RR 0.90; 95 % CI 0.77–1.06; $p = 0.22$) among carriers of AB-TPO within ART programs in relation to the comparison group [29]. The authors, based on the work of Monteleone et al. (2011), believe that a possible cause of the absence of a difference in the rates of fertilization and implantation between female patients with AIT and women of the control group is the fact that this indicator was analyzed only in ICSI protocols and not in classical IVF protocols. Thus, they introduced the theory that the negative effect of antibodies to the thyroid gland on *zona pellucida* can be avoided in this way when choosing the ICSI procedure.

In 2018, Poppe et al. conducted a meta-analysis of four works on the outcomes of ICSI procedures among women with subclinical hypothyroidism and antibody carriage [4]. In one study, subclinical hypothyroidism is defined as TSH concentrations ranging from 2.5 mIU/L to 4 mIU/L; in another, TSH values range from 3 mIU/L to 4 mIU/L. Three authors described the frequency of fertilization [30–32]. They did not reveal by meta-analysis the differences in the frequency of fertilization between the groups compared (odds ratio (OR) 1.02; 95 % CI 0.89–1.16; $p = 0.09$). Two studies evaluated implantation rates [31, 32]. The authors did not find a statistically significant difference in the parameters studied in the AIT groups compared with the control ones (OR 0.98; 95 % CI 0.73–1.32; $p = 0.92$). The frequency of clinical pregnancy per embryo transfer was described by all four authors [30–33]. Moreover, AIT showed no negative effect on this indicator (OR 0.91; 95 % CI 0.70–1.18; $p = 0.94$). When analyzing the selected four parameters in IVF protocols, an ambiguous conclusion can be drawn about the effect of antithyroid antibodies and the state of subclinical hypothyroidism on these parameters.

For example, Zhong et al. (2012) claimed that AIT affects adversely the rate of fertilization, implantation, and clinical pregnancy [28], whereas Medenica et al. (2018) did not find data confirming a decrease in the frequency of fertilization [27] possibly because some women also underwent ICSI in their group of subjects. The assumption of Busnelli et al. in 2016 [29] seems today quite reasonable, given the results of Poppe et al. in 2018 [4].

Incidence of early reproductive losses

The risk of abortion is increased among carriers of AB-TPO with compensated hypothyroidism in the case of naturally occurring pregnancy and in IVF cycles. Among women with recurrent miscarriage, carriage of antibodies occurs in 17 %–30 % of cases [34]. Benhadi et al. (2009) performed a cohort study of 2497 women with spontaneous pregnancy and revealed an increased risk of spontaneous abortion at a term of up to 13 weeks of pregnancy, death of the fetus, or a newborn with moderately increased TSH values [35].

The relationship between antithyroid antibodies and miscarriage is unclear, although various hypotheses have been suggested. According to one of them, circulating antibodies are markers of autoimmune generalized dysfunction, which affects adversely the embryo implantation and fetal development. At the same time, the presence of antithyroid antibodies is associated with the development of hypothyroidism, which leads to early pregnancy discontinuation due to an inadequate response of the gland to a physiological increase in estrogen levels. As a result, the concentration of thyroid hormones is insufficient for this gestation

period. Given the effect of ovarian stimulation on the thyroid gland affected by the autoimmune process, this effect is assumed to be further enhanced with ART [29]. In consideration of the increased risk of miscarriage in older women, the increasing incidence of antibodies to the thyroid gland due to age, reaching a maximum after the age of 40 years, cannot be ignored [29].

Zhong et al. (2012) showed that the risk of early spontaneous abortion after IVF is significantly higher in a group of patients with AIT relative to the control group (26.9 % and 11.8 %, respectively, $p = 0.002$). However, a serious drawback in their work was the lack of data on the average TSH values before the onset of stimulation cycles [28].

Thangaratinam et al. (2011) conducted a large meta-analysis that included 31 studies (19 cohort and 12 case–control type), with enrollment of 12,126 women in total. They found a three-fold (OR 3.90; 95% CI 2.48–6.12; $p < 0.001$) and a twofold (OR 1.80; 95% CI 1.25–2.60; $p = 0.002$) increased risk of early pregnancy loss for female carriers of antibodies to the thyroid gland without impaired thyroid function in the cohort studies and in case–control studies, respectively [36]. As a result of a systematic analysis, Busnelli et al. (2016) revealed a similar pattern (OR 1.44; 95% CI 1.06–1.95; $p = 0.02$), taking into account adjustments for age and TSH concentration [29].

Numerous works with similar results are presented in the world literature. In this case, the question of the existence of a similar pattern when conducting ICSI is of particular interest. In a meta-analysis, Porre et al. (2018) assessed the incidence rate of early spontaneous abortion based on the results of 765 ICSI cycles, and 114 pregnancies were achieved in carriers of antithyroid antibodies while 651 pregnancies in control groups. As a result, no difference was found in the frequency of abortion between groups (OR 0.95; 95% CI 0.48–1.87; $p = 0.31$) [4].

Frequency of live births per IVF/ICSI cycle

Busnelli et al. (2016) conducted a meta-analysis and found a statistically significant decrease in the rate of live births by AIT women compared with the control group (OR 0.73; 95% CI 0.54–0.99; $p = 0.04$). The total value was calculated by the random effect method (OR 0.64; 95% CI 0.42–0.99; $p = 0.05$) [29].

Due to the relatively small sample, Werghofer et al. (2015) considered performing a statistical analysis on the effect of basal TSH level on the frequency of live births inappropriate. However, they indicated a tendency to increase this indicator in the group of women with a TSH concentration of 2.5 IU/mL or lower (13.9 %) relative to the group with a TSH level more than 2.5 IU/mL (5 %) [23].

Thangaratinam et al. (2011) conducted a meta-analysis of five cohort studies. The authors evaluated the risk of preterm delivery (up to 37 weeks of gestation) and revealed that the risk of preterm delivery increases in the group of women with positive antithyroid antibodies (OR 2.07; 95 % CI 1.17–3.68; $p = 0.01$) [36].

However, opposing data were also obtained. In a meta-analysis, Porre et al. (2018) analyzed the frequency of live births after ICSI and found no tendency to decrease this indicator (OR 1.12; 95 % CI 0.62–2.03; $p = 0.26$) [4].

In a cohort study, Unuane et al. (2017) obtained similar results. The authors evaluated the frequency of live births after 25 weeks of pregnancy after six cycles of IVF/ICSI. The test group included 333 female patients with AIT, whereas the control group included 2019 women without antibodies (2406 patients in total). The TSH index in both groups ranged from 0.01 mU/L to 5 mU/L, the level of fT_4 was within the reference values, and AB-TPO was considered positive at a concentration of more than 34 kIU/L. In 84.5 % of cases, stimulation was performed with GnRH antagonist drugs. In 13.2 %, a long protocol with a GnRH agonist was used, and a short protocol with a GnRH agonist was used in 2.3 %.

A total of 802 IVF/ICSI cycles were performed in a group of female patients with AIT, 156 cycles of which ended in childbirth, abortion was recorded in 18% of cases, and the total frequency of deliveries with a live fetus was 47 %. In the comparison group, 3937 cycles were performed, the number of births was 948, spontaneous abortion was recorded in 13.4 % of cases, and the total frequency of births after six cycles was 47 %. Thus, no significant differences were found between the two groups. In the proportional risk model (Cox regression), no relationship was found between the frequency of live births after ICSI and the level of TSH in the group of female patients with AIT. However, this indicator decreased in proportion to the age of the patients, namely, 57 %, 48 %, and 33 % in the age subgroups of 20–29, 30–37, and 38–45 years, respectively. Similar results were also obtained in the comparison group. The authors concluded that age, rather than carriage of antithyroid antibodies, is the most important predictor of outcomes of ICSI cycles among patients with AIT [37].

Effect of L-thyroxine replacement therapy on ART program outcomes in women with subclinical hypothyroidism and antibodies

Scientists and practitioners have long been interested in the clinical effectiveness of replacement therapy for outcomes of ART cycles in female patients with AIT. Negro et al. (2005) conducted a randomized controlled study among carriers of AB-TPO [38] and found no difference in the frequency of pregnancy, the frequency of live births, and termination of pregnancy after IVF/ICSI between the subjects and the placebo groups. However, Rahman et al. (2010) showed that replacement therapy affects positively the rate of fertilization, the onset of clinical pregnancy, and live births and reduces the incidence of spontaneous abortions at early terms [39]. These data were confirmed in another study [40]. In 2013, Velkeniers et al. performed a meta-analysis of the above articles [38–40] to evaluate the effect of L-thyroxine on the outcomes of induced pregnancies in women with subclinical hypothyroidism and carriers of antithyroid antibodies [41]. Among 220 women, an increase in live births (total RR 2.76; 95 % CI 1.20–6.44; $p = 0.018$) and a decrease in abortion (total RR 0.45; 95 % CI 0.24–0.82; $p = 0.010$) were observed with replacement therapy. However, the positive effect of thyroxine on the frequency of pregnancy was not detected. All of the above studies [38–40] are based on an insufficient number of clinical cases. In China, a recent randomized population-based study has analyzed the effectiveness of L-thyroxine in outcomes of ART cycles. However, the authors did not reveal significant differences in the incidence of spontaneous abortion and the frequency of live births between the compared groups of women [42].

The most recent systematic review of this issue was conducted by Rao et al. [43] basing from the above articles [38–40, 42]. A meta-analysis of the outcomes of ART cycles in 787 infertile couples did not establish a positive effect of thyroxine on such indicators as the clinical pregnancy rate (RR 1.46; 95% CI 0.86–2.48; p = 0.16), live birth rate per IVF/ICSI cycle (RR 2.05; 95% CI 0.96–4.36; $p = 0.06$), and preterm delivery up to 37 weeks of pregnancy (RR 1.13; 95% CI 0.65–1.96; $p = 0.67$). The risk of early pregnancy loss significantly reduced in the test group compared with the placebo (RR 0.51; 95% CI 0.32–0.82; $p = 0.005$).

Some authors considered the effectiveness of alternative therapeutic options based on the theory of latent imbalance in autoimmune diseases. In a retrospective study, Revelli et al. (2009) analyzed the effect of various drug combinations on the results of IVF/ICSI cycles in 138 female patients with AIT. In 36 subjects who received a combination of L-thyroxine, acetylsalicylic acid, and prednisone, the pregnancy rate increased significantly compared with 38 women who did not receive treatment (OR 4.14; 95 % CI 1.47–11.66; $p < 0.007$). The authors found no difference in the incidence of early pregnancy loss between the groups compared (OR 2.27; 95 % CI 0.27–19.23; $p = 0.45$) [44].

Litwicka et al. [45] studied the efficacy of glucocorticoids in a sample including 60 female patients with AIT, 30 of whom received 5 mg of prednisone in a day of follicular puncture. A significantly higher incidence of clinical pregnancy and live birth was registered in the subgroup of women who received prednisone compared with the group of patients who did not receive prednisone (60 % versus 30 %, $p = 0.02$; 46.6 % versus 16.6%, $p = 0.03$, and 46.6% relative to 20 %, $p = 0.05$). However, these data alone are insufficient, and additional extensive studies with a larger sample are required to confirm the efficacy of alternative therapies. To date, L-thyroxine is the only recognized gold standard for treating patients with AIT entering IVF cycles.

Therapeutic approach and management of patients with autoimmune thyroiditis

In accordance with the clinical recommendations of the American Thyroid Society (2017), the level of TSH must be determined in all women planning treatment in ART cycles, especially those with AB-TPO, who, when joining the IVF program, require replacement therapy with levothyroxine drugs with a TSH level of more than 2.5 mU/L followed by monitoring of TSH and fT_4 levels every 8–10 weeks. [46]. In case of hypothyroidism, revealed at the stage of examination with regard to infertility, L-thyroxine is recommended (1.6–1.8 μg/kg per day). When pregnancy occurs in the IVF program in women with compensated hypothyroidism, the dose of the drug must be increased (by approximately 50 μg immediately after the onset of pregnancy) no later than the weeks 5–6 of pregnancy, and the levels of TSH and fT_4 should be monitored every 8–10 weeks. Adequate replacement therapy implies maintaining a TSH level of less than 2.5 mU/L [2].

In accordance with ASRM recommendations for 2015, a routine measurement of TSH level

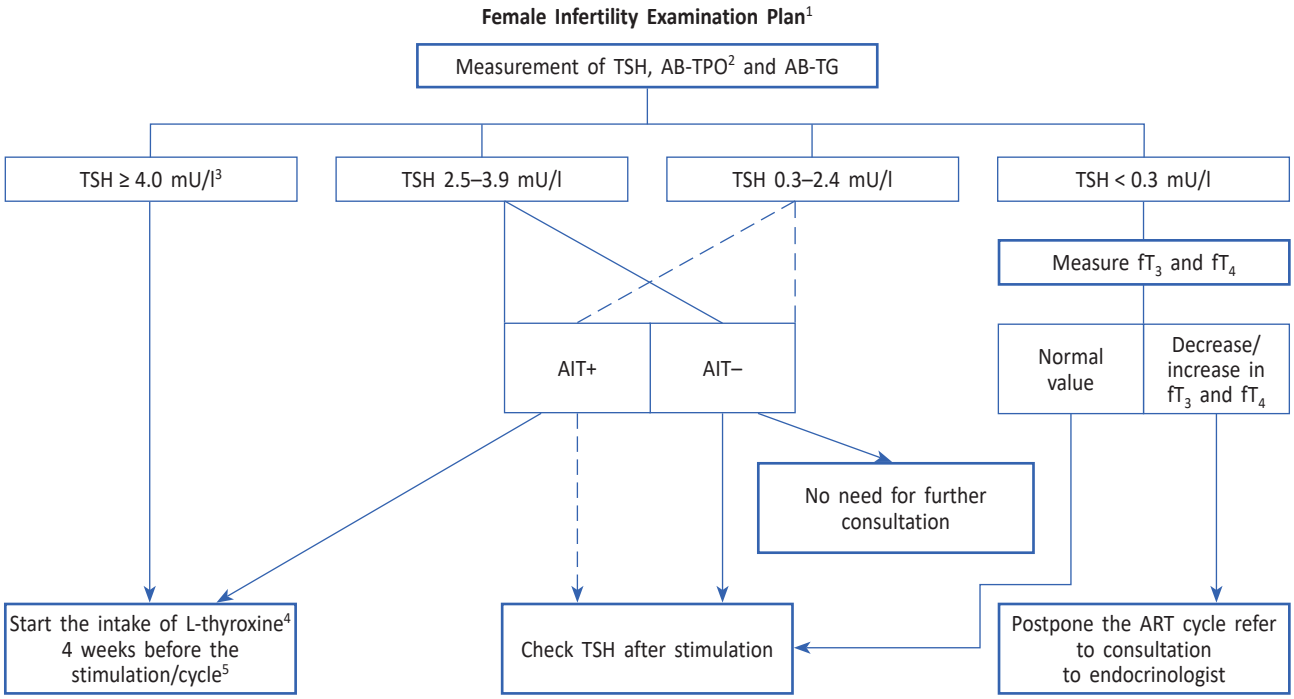

Fig. 1. Algorithm for the examination and management of women in preparation for IVF / ICSI. ТТГ, thyroid-stimulating hormone; АИТ, autoimmune thyroiditis; АТ-ТПО, autoantibodies against thyroid peroxidase; АТ-ТГ, antibodies against thyroglobulin; [1] measure only in case of ovarian causes or idiopathic infertility; [2] when a choice has to be made, measure autoantibodies against thyroid peroxidase; [3] or above institutional cut-off; [4] dose depending on baseline thyroid-stimulating hormone level; [5] thyroid-stimulating hormone target < 2,5 mIU/L

Рис. 1. Алгоритм обследования и ведения женщин в рамках подготовки к ЭКО/ИКСИ. ТТГ — тиреотропный гормон; АИТ — аутоиммунный тиреоидит; АТ-ТПО — аутоантитела против тиреопероксидазы; АТ-ТГ — антитела против тиреоглобулина; [1] в случае овариального или неясного генеза бесплодия; [2] если нужно выбрать один показатель, измеряйте АТ-ТПО; [3] или выше установленного учреждением уровня; [4] дозу рассчитывают на основании базального уровня ТТГ; [5] таргетное значение ТТГ < 2,5 мЕД/л

within the diagnostic search for the causes of infertility is necessary for all women suffering from infertility and planning ART. Determination of the level of AB-TPO is considered appropriate in case of repeated TSH values of 2.5 mU/L or greater or in the presence of other risk factors for the development of thyroid diseases [5].

Recently, Porre et al. (2018) have developed an algorithm for the examination and management of women in preparation for IVF/ICSI, which is presented in Fig. 1. However, the authors have yet to find out whether this strategy is effective in improving pregnancy outcomes after ART cycles [4].

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