ORIGINAL PAPER

Submitted: 09.01.2022
Accepted: 22.04.2022
Early publication date: 19.07.2022

Endokrynologia Polska
DOI: 10.5603/EP.a2022.0061
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 73; Number/Numer 4/2022

The relationship between thyroid autoimmunity and poor response to ovarian stimulation in *in vitro* fertilization women with infertility

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Abstract

Introduction: Thyroid autoimmunity (TAI) is the most common autoimmune disorder. Patients with TAI are usually euthyroid, and the presence of anti-thyroid peroxidase (anti-TPO) in patients with or without thyroid dysfunction is associated with infertility, recurrent embryo implantation failure, and early pregnancy loss. We aimed to investigate the relationship between low ovarian reserve, pregnancy outcomes, and TAI.

Material and methods: This retrospective cohort study was conducted in *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) patients between 2010 and 2018. All patients (n = 1400) for whom thyroid autoantibody testing was requested were detected. A study group was formed from patients with anti-TPO positivity (n = 363). The control group (n = 555) comprised euthyroid anti-TPO negative patients matched to the study group regarding age and body mass index (BMI).

Results: Mean serum TSH value was 2.35 ± 1.70 mIU/mL in anti-TPO-positive patients and 1.81 ± 1.2 mIU/mL in controls, and the difference was significant ($p < 0.05$). Total dose of gonadotropins used in ovulation induction in anti-TPO-positive and control patients were 3000 IU and 2700 IU, respectively, and the difference was statistically significant ($p < 0.05$). The number of metaphase 2 oocytes was significantly lower in the anti-TPO-positive group ($p < 0.05$). Embryo transfer number and embryo grade were significantly lower in the anti-TPO-positive group ($p < 0.01$). Poor ovarian response was significantly higher in anti-TPO-positive patients (40%) as compared to anti-TPO-negative controls (30%) ($p < 0.01$). Clinical pregnancy rate was significantly lower in the anti-TPO-positive group (29.2%), as compared to the antibody-negative group (38.4%) ($p < 0.01$).

Conclusions: There are controversial data regarding the impact of antithyroid antibodies on ovarian reserve and pregnancy outcome after IVF treatment. The results of this study indicate that there was a relationship between TAI and poor ovarian response, and that TAI adversely affects IVF outcomes. Further investigations are required to explore the mechanism behind these effects. **(Endokrynol Pol 2022; 73 (4): 699–705)**

Key words: *IVF; poor ovarian response; thyroid autoimmunity*

Introduction

Thyroid autoimmunity (TAI) is the most common autoimmune disorder, with a prevalence 8–14%, and the first cause of hypothyroidism in women of reproductive age [1, 2]. A wide range of data suggest that TAI is a prevalent problem amongst infertile patients [35].

In TAI, thyroid autoantibodies (TA), mainly thyroid peroxidase (TPO) and thyroglobulin (Tg), are formed against the thyroid, causing chronic lymphocytic thyroiditis, which generally results in the destruction and loss of thyroid function. The presence of anti-thyroid peroxidase (anti-TPO) in patients with or without thyroid dysfunction has been associated with infertility, recurrent embryo implantation failure, early pregnancy loss, and adverse pregnancy outcomes [6].

The relationship between subfertility and TAI remains unclear. Increased TA may play a role in premature ovarian insufficiency, unexplained infertility, and recurrent *in vitro* fertilization IVF failures [7–9]. It has been shown that dominant immune responses to pro-inflammatory Th1 are linked to recurrent spontaneous miscarriages and numerous implantation defects, and cytokines including interferon gamma (INFγ) are related to inflammation and cell-mediated immune responses that are secreted by Th1 cells and could result with thyroid autoimmunity [10, 11]. In infertile women with TA, a substantial increase in the endometrial T cell

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population correlated with hypersecretion of INFγ has been reported compared to controls without anti-thyroid antibodies. In women with TA, the cytokines that activate Th cells could negatively affect fertility and pregnancy success [12, 13].

T cells (CD3+/CD4+) that were expressing cytokines like serum tumour necrosis factor (TNF)/interleukin 10 (IL-10) were significantly higher in women with thyroid autoimmunity, which suggests that activated T cells in the uteri of women with TA that secrete cytokines could interfere with pregnancy outcome [14, 15]. These findings suggest that TA are not necessarily abnormal pathogenic antibodies but serve as peripheral markers of abnormal T-cell function, which are responsible for pregnancy loss [12].

TA were measurable in the follicular fluid in all women with TAI and may cause oocyte damage due to cytotoxicity in the follicle, negatively affecting fertilization and development. It has also been reported that oocyte fertilization, formation of grade A embryos, and pregnancy rates were lower and early miscarriage rate was higher, in women with TAI as compared to controls [16].

Cross-reactivity of TA with extra-thyroid sites might contribute to infertility. Binding of TA to extra-thyroid antigens was reported previously by Matalon et al., who [17] showed that anti-TG were localized in the placenta in the presence of intact thyroid histology, suggesting possible cross-reactivity with placental antigens.

Decreased ovarian reserve is an indicator of ovarian aging, and the infertility rate increases with age. The European Society of Human Reproduction and Embryology (ESHRE) has suggested screening for anti-TPO in women with unknown causes of premature ovarian failure (POF) [18]. It was previously shown that levels of anti-Mullerian hormone (AMH) were substantially lower than those of controls in women with TAI [19]. However, it was also reported that there was no significant difference between normal and low ovarian reserve with regard to TA status [20, 21]. For that reason, more evidence is needed to demonstrate the association between the ovarian reserve and TAI.

In this study, we aimed to investigate the relationship between low ovarian reserve as manifested by poor response to ovarian stimulation, as defined according to the Bologna Criteria and TAI. Our secondary aim was to evaluate pregnancy outcomes in *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycles with regard to TAI status.

Material and methods

Study design and population

This retrospective cohort study was conducted on IVF/ICSI patients between 2010 and 2018 at the IVF Centre Gazi University Faculty of Medicine. It was approved by the Ethics Committee of the Gazi University.

Archive files and the database of patients that applied to Gazi University IVF Centre were examined between 2010 and 2018. All patients (n = 1400) for whom thyroid autoantibody testing was requested were detected. A study group was formed from patients with anti-TPO positivity (n = 363). The control group (n = 555) comprised euthyroid anti-TPO negative patients matched to the study group regarding age and body mass index (BMI). None of the patients received levothyroxine (LT4) replacement. The study included both primary and secondary infertile patients with at least one year of infertility, aged between 20 and 44 years. Patients with other endocrine disorders and patients who did not have sperm after testicular sperm extraction were excluded from the study. The first cycles of patients in our clinic were evaluated. Archive files and the database of patient records were examined for age, basal antral follicle counts (AFC), and basal hormone values on the 2nd–3rd day of menses, thyroid function tests, anti-TPO, and BMI. The cycle data of the patients including ovarian stimulation protocol, hormone levels during ovarian stimulation, total dose of ovulation induction, duration of ovulation induction, progesterone and luteinizing hormone (LH) value on the day of human chorionic gonadotropin (hCG), endometrial thickness on the day of hCG, oocyte numbers after ovum pickup, number of metaphase II oocytes, grade of embryos, number of embryos transferred, and day of embryo transfer were collected from the database.

Treatment protocol

Standardized ovarian stimulation regimens, including long gonadotropin-releasing hormone (GnRH) agonist, microdose flare-up, and GnRH antagonist protocols, were applied to patients with regard to age and ovarian reserve status. Ovarian response was monitored by hormonal and ultrasonographic measurements to adjust gonadotropin doses. All follicle measurements were performed using an Aloka SSD-1000 (Japan) with a 5 MHz transvaginal probe by one of the two authors for each case (M.E., A.E.). When at least two follicles reached a mean diameter of 18 mm, recombinant hCG (Ovitrelle; Serono, Italy) was injected to induce ovulation and oocyte retrieval was performed after 36 hours, under general anaesthesia. Oocytes were routinely retrieved from the affected ovary under general anaesthesia. The ICSI procedure was performed for all retrieved metaphase II oocytes. Embryo transfer (ET) was performed 2–3 days after oocyte retrieval for high- or good-quality embryos (grade I [high quality]: embryos with equal blastomere and no observed cytoplasmic fragmentation; grade II [good quality]: embryos with equal blastomere and < 20% fragmentation of the cytoplasm) under transabdominal ultrasound guidance by using a flexible catheter (Wallace; Irvine Scientific, Santa Ana, CA). The number of transferred embryos were determined depending on patients' age and embryo quality. ET were performed on the 3rd–5th day after ovum pick-up under ultrasonographic guidance. Patients received transvaginal micronized progesterone (Progestan-Koçak, Turkey) 200 mg three times daily until a pregnancy test was performed 12 days after ET. A clinical pregnancy was confirmed by increasing β-hCG concentrations and sonographic evidence of intrauterine gestational sac after ET. Clinical pregnancy was identified when a gestational sac or a foetus was observed by ultrasonography. Live birth was defined as the delivery of a viable foetus of ≥ 23 weeks' gestation. Miscarriage was defined as pregnancy loss before the 20th week of pregnancy or 500 g of the foetus. Poor ovarian responder patients were defined as women having at least two of the following three criteria: (i) advanced maternal age ≥ 40 years or any other risk factor for the poor ovarian response; (ii) a previous poor ovarian response (cycles cancelled or ≤ 3 oocytes retrieved with a conventional protocol); and (iii) an abnormal ovarian reserve test (AFC < 5–7 follicles or AMH< 0.5–1.1 ng/mL) according to the ESHRE Bologna Criteria [18].

Serum measurements

All biochemical assays were performed in the biochemistry laboratory of Gazi University Medical Hospital, and the chemiluminescence method was used by an autoanalyzer (Roche Analytics E170 Immunology Analyzer, Roche Diagnostics, Switzerland). Cut-off limits for normal levels were defined as 0–5.61 IU/mL for anti-TPO and 0.38–5.33 mIU/L for thyroid-stimulating hormone (TSH). Follicle-stimulating hormone (FSH) levels were measured by chemiluminescent immunometric assay with intra-assay and inter-assay coefficients of variation of 2.6% and 3.3%, respectively, and oestradiol (E2) levels were measured by competitive immunoassay with intra-assay and inter-assay coefficients of variation of 2.3% and 2.4%, respectively (Abbot Laboratories, Illinois, USA). Serum AMH measurement was not available in our hospital before 2019, so AMH was not used for the assessment of ovarian reserve.

Outcome measures

The primary outcome measure was comparison of AFC and total number of oocytes collected as measures of poor ovarian reserve with TAI. The secondary outcome measure was a comparison of clinical pregnancy rates (CPR), miscarriage rates, and live birth rates (LBR) with regard to thyroid autoantibody status.

Statistical analysis

SPSS version 22 was used for statistical analysis. Data were assessed with descriptive statistical methods [mean ± standard deviation (SD)]. The variables were evaluated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine whether they were normally distributed. Normally distributed parametric data was compared with Student's t-test. The Mann-Whitney U test was performed for comparison of non-normally distributed metric data. The chi-square test or Fischer's exact test was used to analyse the difference between categorical data. Multivariate logistic regression analysis was used to determine the effect of variables to predict poor ovarian response and ongoing pregnancy. P-value was considered significant at < 0.05.

Results

Of the 1400 patients admitted to our centre for *in vitro* fertilization treatment, 363 were anti-TPO positive and 555 were anti-TPO negative patients (Fig. 1). In total 482 patients were excluded. Comparison of demographic features and cycle characteristics of the anti-TPO-positive and -negative patients are shown in Table 1. There was no significant difference in mean age, mean BMI, and mean basal AFC between groups. Mean serum TSH value was 2.35 ± 1.70 mIU/mL in anti-TPO-positive patients and 1.81 ± 1.2 mIU/mL in controls, and the difference was significant ($p < 0.05$). Total dose of gonadotropins used in ovulation induction in anti-TPO-positive and control patients were 3000 IU and 2700 IU, respectively, and the difference was statistically significant ($p < 0.05$). Cycle characteristics such as duration of ovulation induction, maximum E2 level, LH, and progesterone levels were not statistically different between groups ($p > 0.05$).

The number of oocytes collected and the number of metaphase 2 oocytes were significantly lower in the anti-TPO-positive group ($p < 0.05$). Embryo transfer number and embryo grade were significantly lower in the anti-TPO-positive group ($p < 0.01$). There was no statistically significant difference between the groups in terms of embryo transfer day ($p > 0.05$).

Poor ovarian reserve was observed in 33.7% of the cycles. The difference between age and AFC data of groups with and without poor ovarian response is shown in Table 2. Poor ovarian response was significantly higher in the anti-TPO-positive patients (40%) as compared to controls (30%) ($p < 0.01$).

Clinical pregnancy rate was significantly lower in the anti-TPO-positive group (29.2%) as compared to control group (38.4%) ($p < 0.01$). Sixty-eight per cent of pregnancies seen in the first evaluation were singleton pregnancies. The ongoing pregnancy rate was also significantly lower in the anti-TPO positive group (20.4%) as compared to controls (26.5%) ($p < 0.05$). The miscar-

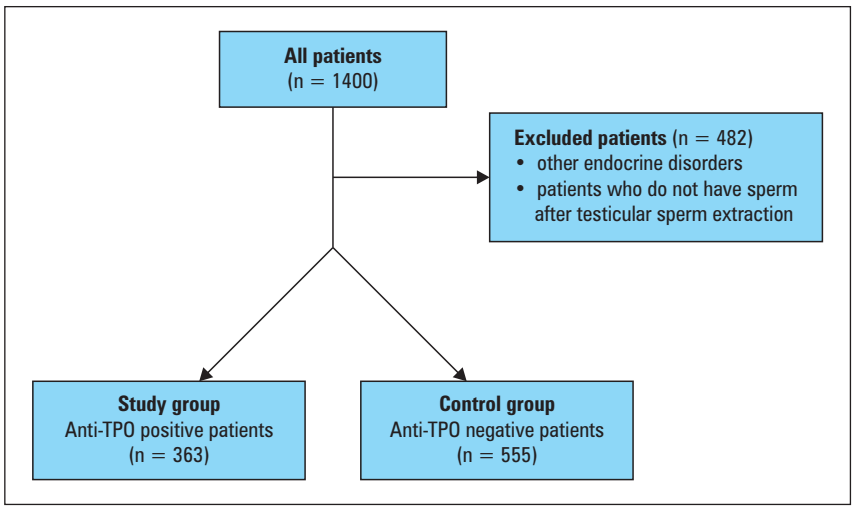

Figure 1. *Flow-chart of the study. anti-TPO — anti-thyroid peroxidase*

Table 1. *Comparison of demographic features and cycle characteristics of the anti-thyroid peroxidase (anti-TPO)-positive patients with control patients*

	anti-TPO (–) (n = 555)	anti-TPO (+) (n = 363)	p-value
Age*	32.1 ± 5.6	32.5 ±5.1	0.26
BMI*	24.9 ± 4.5	25.1 ± 4.68	0.14
TSH* [mIU/L]	1.81 ± 1.2	2.35 ± 1.70	< 0.05
AFC	9.23 ± 5.2	8.6 ± 4.76	0.06
Number of total oocytes retrieved*	10.9 ± 8.5	9.3 ± 8.1	< 0.05
Basal FSH* [IU/L]	7.62 ± 4.6	7.61 ± 6.8	0.82
Total dose of ovulation induction [median (minimum–maximum)]#	3000 (2100–4350)	2700 (2050–3525)	< 0.05
Duration of ovulation induction [day]*	10.8 ± 2.6	10.5 ± 2.7	0.16
Maximum E2* [pg/mL]	1726 ± 1196	1863 ± 1383	0.12
LH value on the day of hCG*	2.03 ± 1.55	2.29 ± 2.11	0.07
Progesterone value on the day of hCG*	0.71 ± 0.49	0.74 ± 0.49	0.43
Endometrium thickness on the day of hCG*	10.7 ± 2.7	10.4 ± 2.4	< 0.05

*Data are given as mean ± standard deviation (SD). #Data are given as median (minimum–maximum); BMI — body mass index; TSH — thyrotropin; FSH — follicle-stimulating hormone; AFC — antral follicle counts; E2 — oestradiol; LH — luteinizing hormone; hCG — human chorionic gonadotropin ($p < 0.05$ was considered significant)

Table 2. *The difference of age and antral follicle counts (AFC) between poor and non-poor groups*

	Poor ovarian response group	Non-poor ovarian response group	p-value
Age*	35.2 ± 5.5	30.8 ± 4.7	< 0.05
AFC*	4.8 ± 2.1	10.7 ± 4.5	< 0.05

*Data are given as mean ± standard deviation (SD)

riage rate was comparable in patients with anti-TPO positivity at 10.4% and controls, at 13.5%.

Binary multivariate logistic regression analysis was done to assess the effects of variables in the prediction of poor response to ovarian stimulation and ongoing pregnancy. When female age, mean basal AFC, total gonadotropin dose, TSH levels, and anti-TPO positivity were analysed together in multivariate logistic regression, all parameters except total gonadotropin dose were independent and significant factors in predicting ovarian response (Tab. 3). When factors including female age, mean basal AFC, total gonadotropin dose, TSH levels, and anti-TPO positivity were analysed together in multivariate regression analysis to predict ongoing pregnancy, all parameters except the presence of TSH level were independent and significant factors to predict ongoing pregnancy (Tab. 4).

Discussion

In this study, the relationship between TAI and low ovarian reserve manifesting as poor response to ovarian stimulation and pregnancy outcome in IVF was assessed, and it was found that poor response to ovarian stimulation was frequent in anti-thyroid-positive IVF patients and that the ongoing pregnancy rate was especially low in anti-TPO-positive patients. This study indicates that TAI is associated with poor response to ovarian stimulation as a measure of poor ovarian reserve and poor IVF outcome.

There are controversial data with regard to the impact of TA on ovarian reserve and pregnancy outcome after IVF treatment. In a meta-analysis of studies up to 2015, Busnelli et al. [22] investigated the impact of TAI on IVF/ICSI outcome, and TAI was associated with lower live birth rate and higher miscarriage rate. The impact of TAI on ovarian reserve was not assessed in this meta-analysis, but the numbers of oocytes, a measure of ovarian response, were not different between patients with TAI and controls [22]. Association of TAI with measures of ovarian reserve including basal FSH, AFC, and AMH were assessed in several studies with different conclusions [5, 19, 23–29]. In our study, basal FSH and AFC were comparable between groups, and in concordance with these results, Korevaar and Tuten et al. found that basal AFC was not associated with TA positivity [5, 23]. Bahri et al. assessed anti-TPO status with AMH quartiles and found that women in the lowest AMH

Table 3. *The effects of variables in the prediction of poor response to ovarian stimulation on multivariate logistic regression analysis*

Variable	OR	95% CI	p-value
Age	1.14	1.1–1.2	< 0.001
Basal AFC	0.83	0.8–0.9	< 0.001
Total gonadotropin dose	0,10	1	NS
TSH level	1.1	1.01–1.2	< 0.05
Anti-TPO positivity	1.6	1.1–2.3	< 0.001

OR — odds ratio; CI — confidence interval; AFC — antral follicle counts; TSH — thyrotropin; anti-TPO — anti-thyroid peroxidase; NS — non significant

Table 4. *The effects of variables in the prediction of ongoing pregnancy on multivariate logistic regression analysis*

Variable	OR	95% CI	p-value
Age	0.96	0.9–1	< 0.05
Basal AFC	1.1	1.0–1.1	< 0.001
Total gonadotropin dose	1	1–1	< 0.05
TSH level	1.1	0.9–1.2	NS
Anti-TPO positivity	0.7	0.5–0.9	< 0.05

OR — odds ratio; CI — confidence interval; AFC — antral follicle counts; TSH — thyrotropin; anti-TPO — anti-thyroid peroxidase; NS — non significant

quartiles had higher levels of anti-TPO [25]. It was found that in a premenopausal population of women < 40 years of age, AMH levels were lower as compared to healthy controls, and according to the multiple regression analysis, even after age adjustment, TAI significantly and independently affected AMH levels [19].

The current study differed from others that assessed ovarian reserve in relation to TA status, by using ovarian response to ovarian stimulation rather than indirect measures of ovarian reserve, such as basal hormones. In our study, although basal FSH and AFC were comparable in patients with or without TAI, poor response to ovarian stimulation was frequent in TA-positive IVF patients, and TAI was independently associated with poor response to ovarian stimulation on logistic regression. The impact of TA status in the IVF population has been assessed in a few studies [21, 30, 31]. It was found that the response to recombinant FSH (r-FSH) was significantly poorer in anti-TPO-positive than in anti-TPO-negative women and in the anti-TPO-positive group [30]. In our study, measures of response to ovarian stimulation such as total dose of gonadotropins in ovulation induction were higher. In contrast to our findings, Ke et al. recently reported in an IVF population in which the prevalence of diminished ovarian reserve, which was defined as basal FSH levels >12 IU/L, in women with positive and negative TAI was not significantly different [21].

The relationship between TAI and IVF outcome has piqued researchers' interest. Anti-TPO antibodies are thought to represent a general immune response, resulting in infertility and complications during early pregnancy. There exists evidence between thyroid hormone disorders — either thyroid deficiency or the presence of TA — and early pregnancy complications. Vissenberg et al., in a review, concluded that the presence of anti-TPO negatively influences folliculogenesis, spermatogenesis, fertilization rates, embryo quality, and pregnancy rates [1]. We found that clinical and ongoing pregnancy rates were significantly lower in the anti-TPO-positive group (29.2%), as compared to controls. In concordance with our study, in a systematic review and meta-analysis of studies comparing the impact of TAI on IVF/ICSI outcome, it was found that women with positive TAI had a lower live birth rate (LBR), a higher miscarriage rate, and a similar clinical pregnancy rate, a similar number of oocytes, fertilization rate, and implantation rate [22]. However, the miscarriage rate was similar between groups in our study.

In contrast with previous meta-analyses showing increased miscarriage rates and/or decreased LBR in TAI-positive women overall, in a recent systematic review and meta-analysis of 14 studies, it was reported that clinical pregnancy and miscarriage rates were not different with regard to the presence of thyroid autoimmunity. There was no significant difference in LBR per cycle or LBR per clinical pregnancy in euthyroid women [32]. These results were consistent with studies by Ke et al. and Leiva et al., who found no relation with TAI and pregnancy outcome after IVF [21, 33]. As

described by Venables et al. [32], discrepancies between the meta-analyses could be explained by the inclusion of recent studies and the use of strict criteria including analysing outcomes, in studies that were strictly limited to euthyroid women and restricted analyses to papers that reported female age. However, after adjusting associated variables like age in multi-logistic regression analysis, the presence of TAI was still a significantly important factor that predicted ongoing pregnancy in the current study. Hypothyroidism rather than the presence of TAI could be the reason for poor pregnancy outcome. In a meta-analysis of clinical studies that assess the effect of LT4 supplementation on pregnancy outcomes in women with subclinical hypothyroidism and TAI undergoing IVF/ICSI, Rao et al. found no significant associations of LT4 treatment with the clinical pregnancy rate, LBR, or preterm birth rate. Patients receiving LT4 supplementation had a significantly decreased miscarriage rate with regard to those receiving a placebo or no treatment. A further subgroup analysis showed that LT4 supplementation did not improve the miscarriage rates among patients with subclinical hypothyroidism or TAI [34].

A major limitation of this study is the retrospective design, with difficulty in accessing data and a potential for bias in these records.

Conclusion

The results of this study indicate that there is a relationship between TAI and poor ovarian response, evaluated according to the Bologna Criteria. This study also indicates that TAI adversely affects IVF outcomes. These results might be useful in informing patients that, with the relation of thyroid autoantibodies, a relatively poor ovarian response and treatment outcome in IVF cycles could result. Randomized controlled studies are needed to investigate the mechanism behind these effects.

Acknowledgements
None declared.

Conflict of interests
No competing financial interests exist.

Funding
No funding was received for this article.

References

1. Vissenberg R, Manders VD, Mastenbroek S, et al. Pathophysiological aspects of thyroid hormone disorders/thyroid peroxidase autoantibodies and reproduction. Hum Reprod Update. 2015; 21(3): 378–387, doi: 10.1093/humupd/dmv004, indexed in Pubmed: 25634660.
2. Poppe K, Velkeniers B, Glinoer D. The role of thyroid autoimmunity in fertility and pregnancy. Nat Clin Pract Endocrinol Metab. 2008; 4(7): 394–405, doi: 10.1038/ncpendmet0846, indexed in Pubmed: 18506157.
3. Artini PG, Uccelli A, Papini F, et al. Infertility and pregnancy loss in euthyroid women with thyroid autoimmunity. Gynecol Endocrinol. 2013; 29(1): 36–41, doi: 10.3109/09513590.2012.705391, indexed in Pubmed: 22835333.
4. Poppe K, Glinoer D, Van Steirteghem A, et al. Thyroid dysfunction and autoimmunity in infertile women. Thyroid. 2002; 12(11): 997–1001, doi: 10.1089/105072502320908330, indexed in Pubmed: 12490077.
5. Tuten A, Hatipoglu E, Oncul M, et al. Evaluation of ovarian reserve in Hashimoto's thyroiditis. Gynecol Endocrinol. 2014; 30(10): 708–711, doi: 10.3109/09513590.2014.926324, indexed in Pubmed: 24905723.
6. van den Boogaard E, Vissenberg R, Land JA, et al. Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Hum Reprod Update. 2011; 17(5): 605–619, doi: 10.1093/humupd/dmr024, indexed in Pubmed: 21622978.
7. Geva E, Amit A, Lerner-Geva L, et al. Autoimmunity and reproduction. Fertility Steril. 1997; 67(4): 599–611, doi: 10.1016/s0015-0282(97)81351-9.
8. Fénichel P, Gobert B, Carré Y, et al. Polycystic ovary syndrome in autoimmune disease. Lancet. 1999; 353(9171): 2210, doi: 10.1016/S0140-6736(99)00256-1, indexed in Pubmed: 10392989.
9. Forges T, Monnier-Barbarino P, Faure GC, et al. Autoimmunity and antigenic targets in ovarian pathology. Hum Reprod Update. 2004; 10(2): 163–175, doi: 10.1093/humupd/dmh014, indexed in Pubmed: 15073145.
10. Kwak-Kim JYH, Chung-Bang HS, Ng SC, et al. Increased T helper 1 cytokine responses by circulating T cells are present in women with recurrent pregnancy losses and in infertile women with multiple implantation failures after IVF. Hum Reprod. 2003; 18(4): 767–773, doi: 10.1093/humrep/deg156, indexed in Pubmed: 12660269.
11. Raghupathy R, Makhseed M, Azizieh F, et al. Cytokine production by maternal lymphocytes during normal human pregnancy and in unexplained recurrent spontaneous abortion. Hum Reprod. 2000; 15(3): 713–718, doi: 10.1093/humrep/15.3.713, indexed in Pubmed: 10686225.
12. Twig G, Shina A, Amital H, et al. Pathogenesis of infertility and recurrent pregnancy loss in thyroid autoimmunity. J Autoimmun. 2012; 38(2-3): J275–J281, doi: 10.1016/j.jaut.2011.11.014, indexed in Pubmed: 22218218.
13. Stewart-Akers AM, Krasnow JS, Brekosky J, et al. Endometrial leukocytes are altered numerically and functionally in women with implantation defects. Am J Reprod Immunol. 1998; 39(1): 1–11, doi: 10.1111/j.1600-0897.1998.tb00326.x, indexed in Pubmed: 9458927.
14. Kaider AS, Kaider BD, Janowicz PB, et al. Immunodiagnostic evaluation in women with reproductive failure. Am J Reprod Immunol. 1999; 42(6): 335–346, doi: 10.1111/j.1600-0897.1999.tb00110.x, indexed in Pubmed: 10622463.
15. Kim NaY, Cho HJ, Kim HY, et al. Thyroid autoimmunity and its association with cellular and humoral immunity in women with reproductive failures. Am J Reprod Immunol. 2011; 65(1): 78–87, doi: 10.1111/j.1600-0897.2010.00911.x, indexed in Pubmed: 20712806.
16. Monteleone P, Parrini D, Faviana P, et al. Female infertility related to thyroid autoimmunity: the ovarian follicle hypothesis. Am J Reprod Immunol. 2011; 66(2): 108–114, doi: 10.1111/j.1600-0897.2010.00961.x, indexed in Pubmed: 21241400.
17. Matalon ST, Blank M, Levy Y, et al. The pathogenic role of anti-thyroglobulin antibody on pregnancy: evidence from an active immunization model in mice. Hum Reprod. 2003; 18(5): 1094–1099, doi: 10.1093/humrep/deg210, indexed in Pubmed: 12721190.
18. Webber L, Davies M, Anderson R, et al. European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI. ESHRE Guideline: management of women with premature ovarian insufficiency. Hum Reprod. 2016; 31(5): 926–937, doi: 10.1093/humrep/dew027, indexed in Pubmed: 27008889.
19. Saglam F, Onal ED, Ersoy R, et al. Anti-Müllerian hormone as a marker of premature ovarian aging in autoimmune thyroid disease. Gynecol Endocrinol. 2015; 31(2): 165–168, doi: 10.3109/09513590.2014.973391, indexed in Pubmed: 25319839.
20. Polyzos NP, Sakkas E, Vaiarelli A, et al. Thyroid autoimmunity, hypothyroidism and ovarian reserve: a cross-sectional study of 5000 women based on age-specific AMH values. Hum Reprod. 2015; 30(7): 1690–1696, doi: 10.1093/humrep/dev089, indexed in Pubmed: 25948573.
21. Ke H, Hu J, Zhao L, et al. Impact of Thyroid Autoimmunity on Ovarian Reserve, Pregnancy Outcomes, and Offspring Health in Euthyroid Women Following Fertilization/Intracytoplasmic Sperm Injection. Thyroid. 2020; 30(4): 588–597, doi: 10.1089/thy.2018.0657, indexed in Pubmed: 31928166.
22. Busnelli A, Paffoni A, Fedele L, et al. The impact of thyroid autoimmunity on IVF/ICSI outcome: a systematic review and meta-analysis. Hum Reprod Update. 2016; 22(6): 793–794, doi: 10.1093/humupd/dmw034, indexed in Pubmed: 27671830.
23. Korevaar TIM, Mínguez-Alarcón L, Messerlian C, et al. Association of Thyroid Function and Autoimmunity with Ovarian Reserve in Women Seeking Infertility Care. Thyroid. 2018; 28(10): 1349–1358, doi: 10.1089/thy.2017.0582, indexed in Pubmed: 29943679.
24. Chen D, Zhang Z, Chen B, et al. Altered microRNA and Piwi-interacting RNA profiles in cumulus cells from patients with diminished ovarian

reserve. Biol Reprod. 2017; 97(1): 91–103, doi: 10.1093/biolre/iox062, indexed in Pubmed: 28651359.
25. Bahri S, Tehrani FR, Amouzgar A, et al. Overtime trend of thyroid hormones and thyroid autoimmunity and ovarian reserve: a longitudinal population study with a 12-year follow up. BMC Endocr Disord. 2019; 19(1): 47, doi: 10.1186/s12902-019-0370-7, indexed in Pubmed: 31064360.
26. Unuane D, Velkeniers B, Bravenboer B, et al. Impact of thyroid autoimmunity in euthyroid women on live birth rate after IUI. Hum Reprod. 2017; 32(4): 915–922, doi: 10.1093/humrep/dex033, indexed in Pubmed: 28333271.
27. Osuka S, Iwase A, Goto M, et al. Bayasula. Thyroid Autoantibodies do not Impair the Ovarian Reserve in Euthyroid Infertile Women: A Cross-Sectional Study. Horm Metab Res. 2018; 50(7): 537–542, doi: 10.1055/a-0637-9430, indexed in Pubmed: 29991084.
28. Weghofer A, Himaya E, Kushnir VA, et al. The impact of thyroid function and thyroid autoimmunity on embryo quality in women with low functional ovarian reserve: a case-control study. Reprod Biol Endocrinol. 2015; 13: 43, doi: 10.1186/s12958-015-0041-0, indexed in Pubmed: 25975563.
29. Rao M, Wang H, Zhao S, et al. Subclinical Hypothyroidism Is Associated with Lower Ovarian Reserve in Women Aged 35 Years or Older. Thyroid. 2020; 30(1): 95–105, doi: 10.1089/thy.2019.0031, indexed in Pubmed: 31650898.
30. Magri F, Capelli V, Gaiti M, et al. Impaired outcome of controlled ovarian hyperstimulation in women with thyroid autoimmune disease. Thyroid. 2013; 23(10): 1312–1318, doi: 10.1089/thy.2013.0022, indexed in Pubmed: 23556516.
31. Magri F, Schena L, Capelli V, et al. Anti-Mullerian hormone as a predictor of ovarian reserve in ART protocols: the hidden role of thyroid autoimmunity. Reprod Biol Endocrinol. 2015; 13(1): 106, doi: 10.1186/s12958-015-0103-3, indexed in Pubmed: 26391773.
32. Venables A, Wong W, Way M, et al. Thyroid autoimmunity and IVF/ICSI outcomes in euthyroid women: a systematic review and meta-analysis. Reprod Biol Endocrinol. 2020; 18(1): 120, doi: 10.1186/s12958-020-00671-3, indexed in Pubmed: 33239046.
33. Leiva P, Schwarze JE, Vasquez P, et al. There is no association between the presence of anti-thyroid antibodies and increased reproductive loss in pregnant women after ART: a systematic review and meta-analysis. JBRA Assist Reprod. 2017; 21(4): 361–365, doi: 10.5935/1518-0557.20170057, indexed in Pubmed: 29043757.
34. Rao M, Zeng Z, Zhao S, et al. Effect of levothyroxine supplementation on pregnancy outcomes in women with subclinical hypothyroidism and thyroid autoimmuneity undergoing in vitro fertilization/intracytoplasmic sperm injection: an updated meta-analysis of randomized controlled trials. Reprod Biol Endocrinol. 2018; 16(1): 92, doi: 10.1186/s12958-018-0410-6, indexed in Pubmed: 30249251.