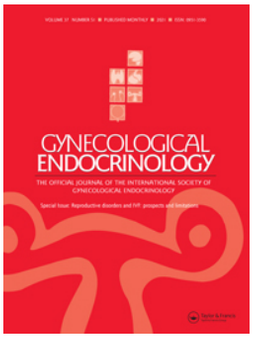

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ORIGINAL ARTICLE

Thyroid disorders and pathospermia in the ART clinic patients

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ABSTRACT

Objective: Over the past decade, a decrease in the semen quality in men of reproductive age, along with an increase in the incidence of thyroid diseases among young patients have been clearly noticed. The study was designed to determine various forms of pathospermia in the ART clinic patients with thyroid disorders.

Materials and methods: 168 men of reproductive age in infertile marriage were examined. Men with male infertility factor associated with erectile dysfunction and normospermia (9 patients, 5.3%) were excluded. The study included 159 men and the patients were divided into three groups: the 1st study group consisted of men with non-obstructive azoospermia – 11 men (6.9%); the 2nd study group included men with other forms of pathospermia – 38 men (23.9%) and the control group consisted of men in infertile marriage with normospermia – 110 men (69.2%). All patients had anthropometric measurements, laboratory tests, thyroid and testicular ultrasonography. Spermogram was analyzed in accordance with the WHO classification, 5th revision, 2010.

Results: Among all examined men with pathospermia ($n = 49$ patients), 51.02% had various thyroid disorders, while it was firstly verified in 34.7% men. In 45.5% patients with non-obstructive azoospermia, previously undiagnosed nodular goiter with normal values of thyroid-stimulating hormone and free thyroxine were found, and a significant correlation between nodular goiter and the presence of azoospermia was revealed: $r = 0.610$, $p = .01$.

Conclusion.: Men with various forms of pathospermia and patients of the ART clinic had higher risks of thyroid disorders than in general population that could possibly affect fertility. Patients of the ART clinic with non-obstructive azoospermia are at risk for nodular thyroid disorders, even with normal values of thyroid function tests, and require thyroid ultrasonography.

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Thyroid disorders; pathospermia; male infertility factor

Introduction

Over the past decades a significant decrease in the semen quality among European, Asian and American population is considered to be a negative tendency affecting male fertility and reproduction primarily in the industrialized countries [1]. To identify the reasons of decreased male fertility, studying endocrine regulation of male reproductive function was one of the main goals of carrying out the research [1].

The genomic effect of thyroid hormones on spermatogenesis is well known due to stimulation of Sertoli cell proliferation during puberty contributing to an increase in the testicular volume and the sperm quantity. In the postpubertal period, there is a differentiation of both Sertoli and Leydig cells with suppression of estrogen receptors and increased expression of androgen receptors [2,3].

In recent years, non-genomic effects of thyroid hormones on spermatogenesis and sperm fertility have been increasingly discussed [2,4]. Previously, it was determined that non-genomic effect of thyroid hormones (TH) on target cells was mediated by stimulating intracellular transport of proteins from the cytoplasm to the nucleus, as well as changing ion pump activity in the plasma membranes and mitochondria [5].

Interestingly, that thyroxine added to sperm samples promoted sperm hypermobility after 20 min and was effective for improving sperm motility [6]. It was also demonstrated that both iodine deficit and excess resulted not only in thyroid diseases but decreased the sperm quality [7]. Pathospermia in hypothyroidism and hyperthyroidism was proved to be reversible in most cases after reaching euthyroidism [4]. However, some authors believed that subclinical hypothyroidism insignificantly affected the sperm quality including the quantity, morphology and motility of spermatozoa [8,9]. At the same time, other researchers have described the effect of hypothyroidism on spermatogenesis only in men over 35 years [10].

The data about the impact of thyroid disorders on the development of non-obstructive azoospermia are scanty and insufficient, although a number of observations indicated of defective spermatogenesis such as azoospermia in toxic thyroid damage even with normal testosterone levels [11]. Patients with azoospermia had significantly higher levels of thyroid-stimulating hormone (TSH) and follicle-stimulating hormone (FSH), and significantly lower levels of free testosterone compared with patients with oligoastenoteratozoospermia and the control group with normal spermogram. However, prolactin levels in

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azoospermia and oligoastenoteratozoospermia did not significantly differ and were within normal limits [12].

The trials demonstrated the presence of genes with mutations associated with both nodular thyroid disorders and defective spermatogenesis (RET, THRA/NCOR1) are of great interest.

It was assumed that men with non-obstructive azoospermia had the same pathogenetic stages of thyroid cancer associated with mutation in both TTH and FSH receptor genes [13,14]. The received data have clearly demonstrated that the ART clinic patients with azoospermia should be referred to an andrologist and endocrinologist, and require thyroid ultrasonography for early detection of nodular goiter and timely oncologist consultation.

However, there is insufficient clinical data on the distribution and thyroid function abnormalities in various forms of pathospermia in patients of ART clinics.

The current study was designed to identify various forms of pathospermiain the ART clinic patients with thyroid disorders.

Materials and methods

A total of 168 men of infertile marriage were examined in the ART clinic from November 2020 to April 2021. Men with male infertility factor associated with erectile dysfunction and normospermia (9 patients, 5.3%) were excluded. The study included 159 men and the patients were divided into three groups: the 1st study group consisted of men with non-obstructive azoospermia – 11 men (6.9%); the 2nd study group included men with other forms of pathospermia – 38 men (23.9%) and the control group consisted of men in infertile marriage with normospermia – 110 men (69.2%). The median age of men with various azoospermia was 31.5 (29.25 ÷ 41) and 35 (32.5 ÷ 38) years in the study groups of patients with non-obstructive azoospermia and oligoasthenoteratozoospermia, respectively, and did not differ from the control group – 35 (33 ÷ 39.25) years, p>.05. All patients had anthropometric measurements, laboratory tests, thyroid and testicular ultrasonography. Spermogram was analyzed in accordance with the WHO classification, 5th revision, 2010. Thyroid function tests included TSH, free thyroxine (FT4), thyroperoxidase antibodies (anti-TPO) and thyroid ultrasonography (US).

Statistical analysis was carried out with Microsoft Office 2012 and SPSS for Windows 12.0. Nonparametric analysis was used to compare the median values and interquartile range Me (25%÷75%). Chi-square test with Yates' correction and Fisher's exact test were used to compare qualitative variables. Student's test was done to determine significant differences between groups. The comparative analysis of quantitative variables was carried out with Mann-Whitney criterion. The correlation analysis was done with Spearman rank correlation.

Ethical approval

The research was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent was obtained from all the examined patients

Results and discussion

Among men of both study groups with various forms of pathospermia ($n = 49$ patients), 51.02% had thyroid disorders, while it was firstly verified in 34.7% men. In patients with pathospermia

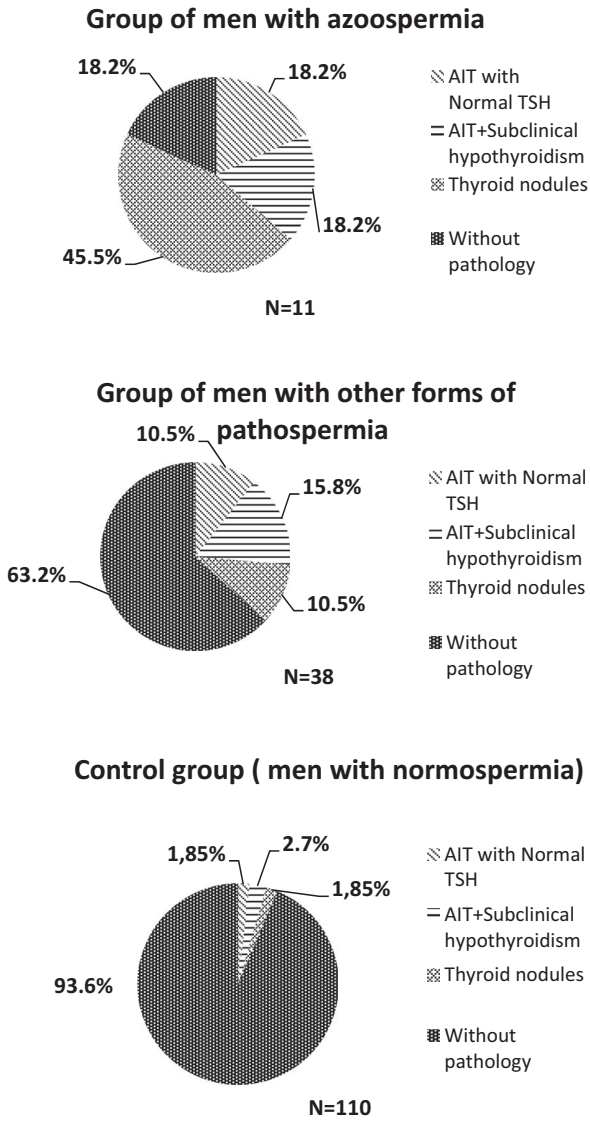

Figure 1. Distribution of thyroid disorders among men of the study groups.

and thyroid disorders, the prevailing signs of autoimmune thyroiditis (AIT) were anti-TPO or ultrasonic signs of AIT, that was also demonstrated by some researchers [15]. The incidence of AIT was significantly higher in the study groups compared with the control group, $p < .05$ (Figure 1) and exceeded the incidence of AIT in general population, accounting for 10-15% among healthy people with euthyroid status [16].

Some patients with non-obstructive azoospermia had significantly higher incidence of nodular goiter with normal values of TSH, FT4 and absence of anti-TPO (45.5%) compared with other forms of pathospermia and the control group (10.5% and 1.8%, respectively; $p < .05$). In one patient a diagnosis of papillary cancer was confirmed.

These findings corresponded to the idea that in non-obstructive azoospermia male infertility could serve as a biomarker of individual and family risk for thyroid cancer [13,17]. It could be explained by the presence of mutations in the same genes responsible for both spermatogenesis violation and thyroid cancer.

Unexpectedly, the analysis of hormonal and metabolic status of patients revealed significantly lower TSH levels in men with non-obstructive azoospermia (Me 1.9 [1.65–2.1] mU/l) compared

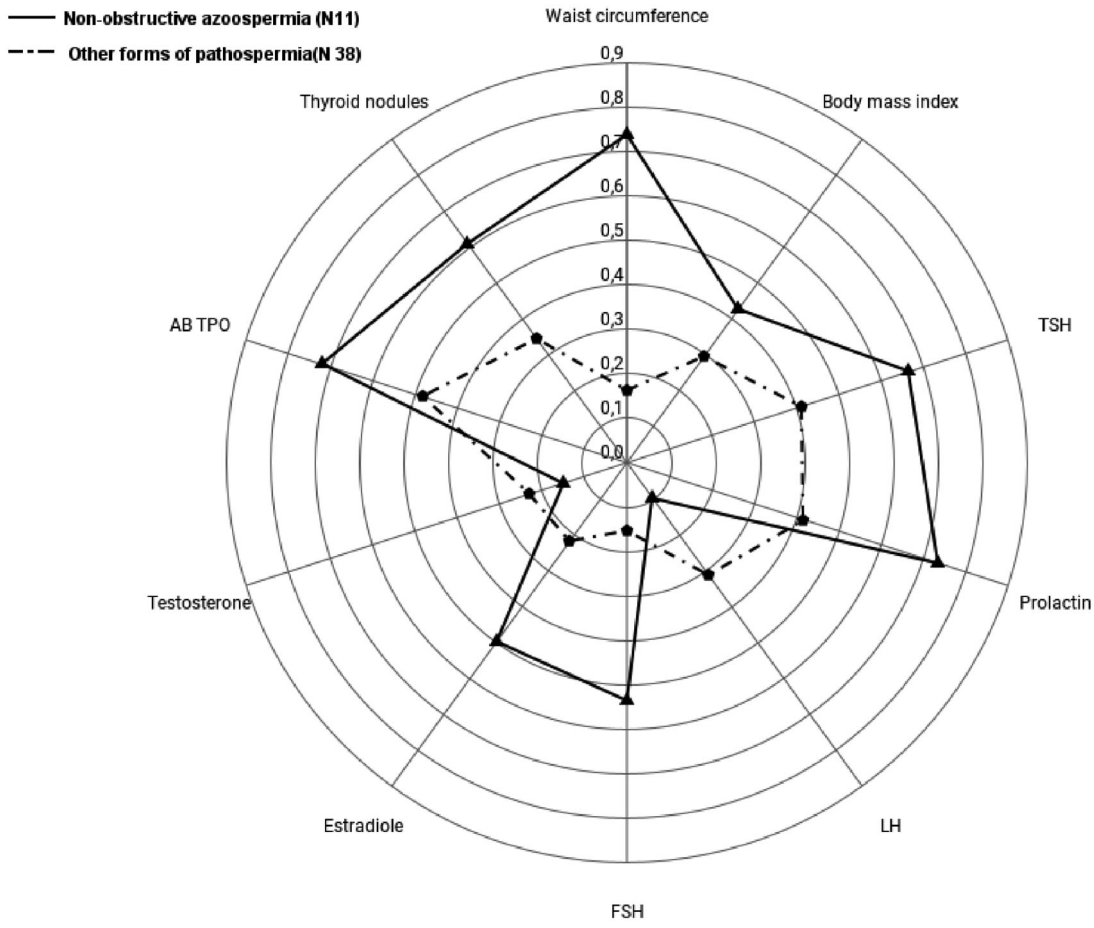

Figure 2. Correlation analysis of clinical and laboratory parameters with the presence of azoospermia and other forms of pathospermia.

Table 1. Baseline hormonal and metabolic parameters in the study and control groups, Me (25 ÷ 75).

Parameters	Study group 1 (NOA) $n = 11$ 1	Study group 2 (other forms of pathospermia) $n = 38$ 2	Control group 3 $n = 110$ 3	*p*-value $p_{1,2}$	$p_{1,3}$	$p_{2,3}$
WC, cm	111 (106.75–117.5)	100 (93.75–111.75)	100 (89–104.25)	.189	.022	.538
BMI, kg/cm^2	28 (24.0–31.0)	28 (24.5–30.05)	26.2 (23.8–30)	.928	.476	.173
TSH, mU/L	1.9 (1.65–2.1)	3.35 (1.64–5.7)	2.1 (1.7–3.05)	.041	.049	.036
Prolactin, mU/L	280 (203.4–344.5)	353.0 (211–473)	208 (150.00–288.00)	.228	.047	.002
LH, U/L	4.7 (3.35–6.97)	4.55 (2.325–7.675)	3.30 (2.525–4.75)	.596	.050	.109
FSH, U/L	13.7 (7.2–15.75)	5.08 (2.325–7.675)	4.9 (3.1–9.8)	.044	.001	.132
Estradiol, pmol/L	114 (87.5–130.75)	50 (32–72)	43.5 (19.1–112.75)	.210	.527	.043
Testosterone, pmol/L	15.7 (12.4–16.9)	17.5 (12.9–23.25)	17.35 (13.8–22.5)	.205	.316	.527
Glucose, mol/L	5.5 (5.45–5.9)	5.035 (4.8–5.425)	5.3 (4.875–5.547)	.093	.141	.194
Cholesterol,mmol/L	5.05 (4.4–5.15)	5.1 (4.5–5.5)	5.7 (4.65–9.96)	.650	.203	.255

with the control group (Me 2.1 [1.7 ÷ 3.05] mU/l), $p = .049$. That fact requires further research, since reduced TSH levels in the group of non-obstructive azoospermia compared with the group of other forms of pathospermia and the control group could be associated with a relatively small number of patients with azoospermia.

TSH levels in the group with other forms of pathospermia (oligoasthenoteratozoospermia) were significantly higher (Me 3.35 [1.64 ÷ 5.7] mU/L) in comparison with the control group (Me 2.1 [1.7 ÷ 3.05] mU/L), $p = .036$.

While there were no significant differences in BMI, in non-obstructive azoospermia group, visceral obesity was significantly more common: waist circumference (WC) was 111 [106.75–117.5] cm, $p_{1.3} = .022$. These results were also consistent with the literature data about obesity that could cause and worsen male infertility due to endocrine dysfunction, comorbidities and direct impact on spermatogenesis [18]. However, the fact that in non-obstructive azoospermia group, WC was significantly higher compared with oligoastenoteratozoospermia group, requires further research into a family history, with a view to recently published data on epigenetics, demonstrated the effect of paternal obesity on offsping's metabolic and reproductive phenotypes through epigenetic reprogramming of spermatogonial stem cells [19, 20].

A correlation analysis of clinical and laboratory parameters with the presense of non-obstructive azoospermia demonstrated significant relations with nodular thyroid disorders ($r = 0.610$, $p = .01$); AT TPO ($r = 0.722$, $p = .001$); blood prolactin levels

($r = 0.736$, $p = .01$); TSH levels ($r = 0.667$, $p = .035$) and WC ($r = 0.741$, $p = .036$), while no significant relations with BMI ($r = 0.428$, $p = .190$) (Figure 2). However, prolactin levels were within normal limits in both groups (Table 1).

Conclusion

Men with various forms of pathospermia and patients of the ART clinic had higher risks of thyroid disorders than in general population that could possibly affect fertility.

Patients of the ART clinic with non-obstructive azoospermia are at risk for nodular thyroid disorders, even with normal values of thyroid function tests, and require thyroid ultrasonography.

Disclosure statement

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