CLINICAL STUDY

Is systematic screening for thyroid disorders indicated in subfertile men?

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Abstract

Context: Data on the prevalence of thyroid disorders in male subfertility remain scarce.

Objective: To investigate the prevalence of thyroid dysfunction and thyroid autoimmunity in men with normal and abnormal semen characteristics.

Setting: Tertiary referral center for reproductive medicine of the University Hospital AZ-VUB, Brussels, Belgium.

Patients and design: Two hundred and ninety-two men were stratified according to the presence of normal (group 1; $n = 39$) or abnormal (group 2; $n = 253$) semen characteristics. Thyroid function was assessed by serum thyrotropin (TSH) and free thyroxine (FT4), and thyroid peroxidase antibodies (TPO-Ab) for thyroid autoimmunity (TAI or TPO-Ab > 34 kU/l); both were correlated with semen characteristics.

Main outcome measures: Semen characteristics were determined by World Health Organisation criteria (rapid + slow motility $\geq 50\%$ and concentration $\geq 20 \times 10^6$) and Kruger criteria (morphology $\geq 14\%$ normal cells).

Results: In group 1, the mean ($\pm$ s.d.) age was 33 ± 4 years; serum TSH was 1.6 (0.3–29.6) mU/l (median (range)) and FT4 was 12.2 (8.8–15.6) ng/l. In group 2, the mean age was 33 ± 5 years, serum TSH was 1.3 (0.3–5.2) mU/l and FT4 was 12.5 (8.4–17.5) ng/l; (compared with group 1 $P = 0.008$ for TSH and $P = 0.037$ for FT4). In both groups, one patient had increased TSH (2.6% and 0.4%; $P =$ not significant (ns)). In group 1, one patient had TAI and in group 2 twelve patients had TAI (2.6% compared with 4.7%; $P =$ ns). FT4 was an independent determinant for semen characteristics.

Conclusions: The prevalence of thyroid dysfunction and autoimmunity is comparable between men with normal and abnormal semen characteristics. On the basis of these data, we do not advise systematic screening for thyroid disorders in subfertile men consulting a tertiary referral center for reproductive medicine.

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Introduction

Infertility, defined as the absence of pregnancy within one year of regular unprotected intercourse, is present in 10–15% of couples in developed countries. The usual causes of infertility include a male factor (30%), a female factor (35%), a combination of both (20%), and finally unexplained or 'idiopathic' infertility (15%) (1). Although thyroid disorders (i.e. hyperthyroidism, hypothyroidism and thyroid autoimmunity or TAI) are less frequent in men than in women, they remain relatively common diseases. The prevalence of TAI in men of reproductive age (20–40 years) is 7% for thyroid peroxidase antibodies (TPO-Ab) and 5%

for thyroglobulin antibodies. Increased serum thyrotropin (TSH > 4.5 mU/l) is present in 3.4% of the men and decreased TSH (< 0.4 mU/l) in 1.8% of the men in the USA (2). However, in areas with a lower iodine intake (such as Belgium), the prevalence of TAI and supranormal serum TSH may be different (3, 4). Associations between thyroid disorders and female infertility have been more extensively studied than associations between thyroid disorders and male infertility (5, 6). Thyroid dysfunction can impair the quality of semen, and lower sperm motility and/or concentration. Furthermore, an association between TAI and asthenozoospermia has been described. Semen alterations were reversible after patients

achieved euthyroidism. The impact of thyroid (dys)function on the semen is mainly due to an effect on central (luteinizing hormone/follicle-stimulating hormone) and peripheral gonadal function and via sex hormone binding proteins (for review see Krassas & Pontikides (7)).

The aim of this study was to assess whether thyroid dysfunction and/or TAI were more frequently present in men of subfertile couples with normal semen compared with men with altered semen characteristics and whether systematic screening should be undertaken in a tertiary referral center for reproductive medicine.

Materials and methods

Subjects

A prospective study was undertaken in 292 men of subfertile couples consulting at the Centre for Reproductive Medicine between October 1999 and November 2000 (tertiary referral center). After informed consent, all men were systematically screened for thyroid function by means of serum TSH and free thyroxine (FT4), and for the presence of TAI with TPO-Ab, before assisted reproductive technology (ART). Men with active thyroid disorders (taking thyroxine, antithyroid (i.e. propylthiouracyl and/or methimazole) or having an obvious clinical goiter) were excluded from the study. Furthermore, semen analysis was performed and the presence of sperm antibodies was established.

Methods

Serum assay TSH and FT4 were measured using a third generation electro-chemiluminescence immunoassay (Roche, Mannheim, Germany). The reference values were 0.27 to 4.2 mU/l for TSH and 9.3 to 18.0 ng/l (12 to 23.2 pmol/l) for FT4 (conversion factor for FT4 (ng/l → pmol/l): 1.29). TPO-Ab were determined using an RIA kit (B.R.A.H.M.S. Diagnostica, Berlin, Germany). The reference range was 0–34 kU/l. TPO-Ab titers were considered positive when they exceeded 34 kU/l.

Semen analysis Semen was obtained after 3 to 5 days of abstinence, collected in a sterile cup by masturbation at home or in the laboratory and was always analyzed within one hour and at body temperature. If there was any doubt about the semen quality, a second sample was obtained. Liquefaction, appearance, viscosity and volume were evaluated according to World Health Organisation (WHO) guidelines (8). Also, motility and semen concentration were examined according to WHO criteria, but for morphology the Kruger criteria were used (9). Sperm antibodies were detected by a direct mixed antiglobulin reaction test (the MAR test; FertiPro, Ghent, Belgium). After fresh untreated sperm were mixed with latex particles coated with human IgG (or IgA), a mixture of monospecific anti-human IgG (or IgA) antiserum was added. The formation of agglutinates indicated the presence of antibodies and the test was considered positive when ≥ 50% of the spermatozoa had latex particles attached. Men with azoospermia were excluded from the study.

Statistical analysis

The classified variables (TPO-Ab) were analyzed by means of a Fisher's exact test; differences between mean values (age) were analyzed by a Student's *t*-test and median values (TSH and FT4) by the Mann-Whitney U-test. The effects of explanatory variables in men with abnormal semen were analyzed by multiple linear regression. All data analyses were performed using SPSS version 12.0 (SPSS, Inc., Chicago, IL, USA).

Results

Table 1 shows thyroid function tests (expressed as median (range)) and the number of patients with TAI (measured by TPO-Ab) in all men and in the subgroups. Group 1 (normal semen) comprised 39 men and group 2 (abnormal semen) comprised 253 men. In the entire study group ($n = 292$), the men's mean age (mean ± s.d.) was 33 ± 5 years (range: 20–50 years); mean ages were comparable between the groups.

None of the men in either study group had a suppressed serum TSH concentration. Median (range) serum TSH was slightly but significantly higher in

Table 1 Thyroid function and autoimmunity in all men, and according to the semen analysis.

	All men ($n = 292$)	Group 1 normal semen ($n = 39$)	Group 2 altered semen ($n = 253$)
Age (years)	33 ± 5	33 ± 4	33 ± 5
TSH (mU/l) Reference values: 0.27–4.2	1.6 (0.3–29.6)	1.6 (0.3–29.6)*	1.3 (0.3–5.2)
FT4 (ng/l) Reference values: 9.3–18.0	12.5 (8.4–17.5)	12.2 (8.8–15.6)*	12.5 (8.4–17.5)
TPO-Ab#	13 (4.5%)	1 (2.6%)	12 (4.7%)

Numbers in parentheses represent ranges.

Number (%) of men with TPO-Ab > 34 kU/l.

* $P < 0.05$ compared with group 2.

group 1 compared with group 2 (1.6 (0.3–29.6) compared with 1.3 (0.3–5.2); $P = 0.008$). In both groups one patient had an increased serum TSH level (respectively 2.6% in group 1 and 0.4% in group 2; $P =$ not significant (ns)). Median FT4 was significantly lower in group 1 compared with group 2 (12.2 (8.8–15.6) compared with 12.5 (8.4–17.5); $P = 0.037$). In group 1, one patient had an infranormal FT4 (with associated TAI) and in group 2 four patients had an infranormal FT4 (none with TAI); respectively 2.6% vs 1.6%; $P =$ ns. The percentage of TAI in group 1 was comparable to that in group 2 (2.6% vs 4.7%; $P =$ ns).

In Table 2 semen abnormalities are described. The majority of the men had teratozoospermia ($n = 108$ or 43%) and a combination of oligo-astheno-teratozoospermia ($n = 89$ or 35%).

In 255 men of the total cohort, the MAR test was performed. In group 1, no man had a positive test compared with 9 in group 2 (0% vs 3.7%; $P =$ ns). None of the men with a positive MAR test had positive TPO-Ab. Multiple linear regression revealed that FT4 was a significant predictor for abnormal semen ($P = 0.03$).

Discussion

The aim of the present study was to investigate whether thyroid dysfunction and/or thyroid autoimmunity were more frequently present in men of subfertile couples with normal semen, compared with those with altered semen characteristics. This could answer the question whether systematic screening for thyroid disorders is indicated in a tertiary referral infertility center. Previous studies mainly investigated the impact of thyroid disorders and/or TAI on semen characteristics.

In the present study, there was no single man with a suppressed serum TSH, highlighting the rarity of the association because of the low prevalence of hyperthyroidism in the male population (2–4). The association between hyperthyroidism and spermatogenesis is poorly covered in the literature, with only two articles published in the 1970s and three during the last decade (10–14). Low sperm densities, lower motility and decreased sperm counts have been reported, although these changes were not more frequently present compared with euthyroid controls (however, only a small number of patients were included). Semen parameters such as fructose, zinc and mercury remained comparable between hyper- and euthyroid men. These

changes were reversed soon after the patients were treated for their hyperthyroidism (14). Together, these observations suggest that hyperthyroidism may impair spermatogenesis.

The number of patients with overt hypothyroidism in the present study was comparable in both study groups, although the median serum FT4 was slightly but significantly higher in men with abnormal sperm. Moreover, the median levels of FT4 remained in the reference range and the differences seem too subtle to explain changes in sperm characteristics. The percentage of hypothyroidism in the present study is also comparable to that in the male population of reproductive age (2–4). Increased serum TSH was present in one man in both study groups. The significantly higher median serum TSH in group 1 was probably due to one outlier (TSH > 29 mU/l). The association between hypothyroidism and spermatogenesis has already been studied thirty years ago in two clinical studies showing decreased seminal volume, motility and abnormal testicular biopsies. These studies included a small number of patients and often lacked a control population (15, 16). More recent studies followed a number of postpubertal men after hypothyroidism was induced for three months. Moderate semen abnormalities, such as decreased sperm volume and forward motility were observed, insufficient however to cause infertility (17). Other studies showed a decreased seminal volume, sperm motility and abnormal testicular biopsies. After treatment with levothyroxine, the semen parameters tended to normalize (17, 18).

In the present study, the prevalence of TAI was almost doubled in men with abnormal semen compared with that in men with normal semen, although this was not statistically significant. This could be due to the small number of patients with TAI in group 1 ($n = 1$) or a beta error. Furthermore, no correlation between the MAR test and TAI could be detected. The association of TAI and sperm antibodies has been investigated in two studies. An increased incidence of thyroid antibodies in men with sperm autoantibodies compared with men without sperm antibodies was shown independent from a history of genital tract obstruction. These studies postulated that TAI and other organ-specific antibodies were probably related to a common immune dysregulation (19, 20). More recently, Trummer *et al.* (21) investigated prospectively the impact of thyroid dysfunction and autoimmunity on semen in a large cohort of subfertile men. In the latter group, TAI was found in 7.5% of the men and elevated thyroid antibody titers were significantly correlated with asthenozoospermia. Subclinical hypothyroidism was present in 3% of the cases, but was not correlated with altered semen density, sperm motility or morphology (21).

In conclusion: although in the literature some evidence exists that thyroid disorders and thyroid autoimmunity can influence sperm parameters (as a

Table 2 Descriptive analysis of sperm abnormalities.

	O	A	T	A + T	O + A	O + T	O + A + T
<i>n</i>	4	7	108	29	3	13	89
%	1.5	2.7	42.6	11.5	1.2	5.1	35.2

O, oligospermia; A, asthenospermia; T, teratozoospermia.

surrogate endpoint of male infertility), no increased prevalence of thyroid disease was detected in a large cohort of men with altered semen compared with men with normal semen. Therefore, there does not seem to be any justification to recommend systematic screening for thyroid function and thyroid autoimmunity in men of subfertile couples consulting a tertiary referral center.

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