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Overt hypothyroidism is associated with the presence of uterine leiomyoma: a retrospective analysis

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ABSTRACT

Objective: A possible correlation between uterine leiomyoma and thyroid disease was reported decades ago. We aimed to evaluate the possible associations between the presence of uterine leiomyomas and (i) the presence of overt hypothyroidism, (ii) the level of anti-thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (TG-Ab), and (iii) thyroid stimulating hormone (TSH) levels.
Study design: In a retrospective study, all 215 sterile women who underwent reproductive surgery (hysteroscopy and laparoscopy/laparotomy) at our department from January 2007 to January 2011 were included. All leiomyomas suspected on gynecologic ultrasound were verified during surgery. As risk factors for uterine leiomyomas, thyroid parameters, age, African heritage, age at menarche, parity, and body mass index were included.
Results: One or more uterine leiomyomas were found in 51 cases (23.7%). After multivariate analysis, three parameters remained significant, with African heritage the most important (odds ratio, OR, 27.80), followed by overt hypothyroidism (OR 3.10) and increasing age (OR 1.23). Larger leiomyomas were found in women with overt hypothyroidism than in those without overt hypothyroidism (median, 70 mm; range, 5–88 vs. median, 30 mm; range, 2–93, respectively; $p = 0.007$).
Conclusions: Overt hypothyroidism, but not autoantibodies against the thyroid gland, was associated with the presence of uterine leiomyoma in our study.

1. Introduction

Uterine leiomyomas are benign tumors of the uterine smooth muscle cells. They are clinically apparent in up to 25% of reproductive-age women. Heavy or abnormal uterine bleeding, pelvic pain, infertility, and recurrent pregnancy loss are generally associated with leiomyomas [1].

Although leiomyomas are the most common gynecologic tumors in premenopausal women, their etiology is still under investigation. To date, genetic and epigenetic factors, sex steroids, growth factors, cytokines, chemokines, and extracellular matrix components are important factors thought to be involved in the pathogenesis of leiomyomas. The fact that fibroids occur during the reproductive period and regress after menopause indicates a dependency on the influence of ovarian hormones [2].

In addition to uterine leiomyomas, thyroid gland dysfunction is commonly observed within the subfertile population. Thyroid function is suspected to be crucially involved in reproductive processes and dysfunction. Primarily, hypothyroidism has been proposed to be associated with several etiologies of infertility, including impaired ovulation, fertilization, and implantation, as well as a risk factor for miscarriage and late pregnancy complications [3]. The most prevalent cause of subclinical or overt hypothyroidism and one of the most common autoimmune endocrine disorders in the female population is Hashimoto's thyroiditis, characterized by the presence of antibodies against thyroid peroxidase (TPO-Ab) and/or antibodies against thyroglobulin (TG-Ab) [4].

A possible correlation between uterine leiomyoma and thyroid disease was reported decades ago. In 1989, Lange and Meinen focused on thyroid dysfunction in an examination of 79 women who had undergone hysterectomy. Women with leiomyomas had

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pathological TRH-stimulation test results and thyroid antibodies more often than women without leiomyomas [5]. Recent reports on this topic are scarce. A possible relationship between lipoleiomyoma, an unusual uterine fatty tumor, and concomitant metabolic disorders, e.g. diabetes mellitus and hypothyreosis, has also been described [6,7].

Given the high prevalence and clinical relevance of both diseases and the indications in the literature of a possible link, we intended to systematically investigate the possible association between uterine leiomyomas and thyroid function, including thyroid antibodies, in a population of subfertile women.

2. Materials and methods

2.1. Study population and design

In a retrospective study, all women with primary or secondary sterility who underwent reproductive surgery by hysteroscopy and laparoscopy/laparotomy at the Medical University of Vienna, Department of Gynecology and Obstetrics, Vienna, Austria, from January 2007 to January 2011, were included. The study aims were to evaluate possible associations between the presence of uterine leiomyomas and (i) the presence of overt hypothyroidism (primary objective), (ii) the level of anti-thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (TG-Ab), and (iii) thyroid-stimulating hormone (TSH) levels, in women who had not been pre-treated with thyroid hormone supplementation (secondary objectives). At the initial visit, overt hypothyroidism was defined as follows: (i) if TSH and levo-thyroxin (T4) were >5.0 μIU/ml and <64.5 nmol/l, respectively, or (ii) if the woman was under treatment with thyroid hormone supplementation due to overt hypothyroidism as defined above. If women were pre-treated, medical records providing TSH and T4 levels were obtained in order to verify the diagnosis of overt hypotyhroidism.

Data were retrieved by retrospective chart review. In accordance with a recent comprehensive review [8], we included the following available parameters as risk factors for uterine leiomyomas in addition to thyroid parameters (TSH, TPO-Ab, TG-Ab): age, African heritage, age at menarche, parity and body mass index (BMI). In addition, we noted the type of sterility (primary/secondary).

No patient had received hormonal therapy for myomas before the operation. All women were premenopausal. The Institutional Review Board of the Medical University of Vienna approved the study.

2.2. Diagnosis of uterine leimomyomas

All women underwent preoperative transvaginal ultrasound examination, performed by highly experienced operators. Gynecological transvaginal ultrasound examinations are subject to internal quality assurance. All myomas suspected on gynecologic ultrasound could be verified during surgery. The exact size of the leiomyomas—the secondary outcome parameter—was retrieved either from histologic reports if the tumor had been removed, or from preoperative ultrasound.

Submucosal uterine leiomyomas were considered relevant for infertility [9].

2.3. Laboratory analyses

Hormonal parameters were assessed within the three months prior to surgery in a morning-fasted state. Samples were obtained during the first six days of the menstrual cycle. All serum parameters were determined using commercially available assays. At our department, the normal ranges are 0.44–3.77 μU/ml for TSH, 0–34 IU/ml for TPO-Ab, and 0–33 IU/ml for TG-Ab.

2.4. Statistical analysis

Nominal variables are reported as numbers and frequencies, and continuous variables as median and range. Statistical analyses were performed with the SPSS software package, version 19 (SPSS, Chicago). A logistic regression model with Wald's tests was used to test the statistical significance of all coefficients. Adjusted odds ratios (OR) are given, including the 95 percent confidence interval (95% CI). To evaluate factors predicting leiomyoma size, a generalized linear model with Poisson link function was used. Differences between groups were tested with the Wilcoxon rank sum test with continuity correction. Differences were considered statistically significant if p was <0.05.

3. Results

A total of 215 women were included. Forty-six patients (21.4%) had missing values which affected only the parameters "age at menarche" and "body mass index". Table 1 shows general patient characteristics. Eleven of the 16 women (68.8%) with overt hypothyroidism had been pre-treated with thyroid hormone supplementation for a median of six months (range, 2–17) at the time of the initial visit. One or more uterine leiomyomas were found in 51 cases (23.7%). The localization of the leiomyomas was as follows: there were 20 submucosal (39.2%) and 30 subserosal leiomyomas (58.8%) as well as one leiomyoma in the broad ligament (2.0%). Intra-abdominal abnormalities associated with infertility that were diagnosed/confirmed during surgery are listed in Table 2. In the group of patients with uterne leiomyoma, 31 (60.8%) underwent surgery for diagnostic reasons, which was comparable to the group of patients without uterine leiomyomas (n = 80, 48.8%, p = 0.134).

Details on the analysis of parameters associated with the presence of uterine leiomyoma are provided in Table 3. After

Table 1
Patient characteristics.

Number		215
Age (years)		32 (18–43)[a]
BMI (kg/m^2)		23.1 (17.8–40.9)[a]
Type of sterility	Primary	122 (56.7)[b]
	Secondary	93 (43.3)[b]
African heritage		6 (2.8)[b]
Parity		0 (0–2)[a]
Age at menarche		12 (9–15)[a]
Patients with overt hypothyroidism		16 (7.4)[b]
TSH at initial visit (μU/ml)		1.0 (0.4–5.2)[a]
TPO-Ab at initial visit (IU/ml)		0 (0–588)[a]
TG-Ab at initial visit (IU/ml)		0 (0–1653)[a]

[a] Values are provided as median (range).
[b] Values are provided as numbers (frequencies).

Table 2
Final surgical diagnosis of factors associated with female infertility.

	Patients with leiomyomas (n = 51)	Patients without leiomyomas (n = 164)	p
Submucosal uterine leiomyoma	20 (39.2)	0 (0)	<0.001
Ovarian cysts	6 (11.8)	36 (22.0)	0.109
Polycystic ovary syndrome (laparoscopic drilling)	2 (3.9)	42 (28.8)	<0.001
Endometriosis	28 (54.9)	114 (78.1)	0.054
Tubal factor (both tubes completely blocked)	7 (13.7)	19 (11.6)	0.632
Septate uterus	1 (2.0)	6 (3.7)	1.000
No abnormal findings during surgery	0 (0)	11 (6.7)	0.070

Values are provided as numbers (frequencies); multiple citations possible.