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Original Article

# Uterine and ovarian changes during testosterone administration in young female-to-male transsexuals

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ABSTRACT

*Objective:* Female-to-male transition remains a specific clinical indication for long-term testosterone administration. There is a limited number of studies dealing with the effect of androgen treatment on their female receptive targets (mainly breast and uterus) and the knowledge in this field is scarce and, sometimes, contradictory.
*Materials and Methods:* We performed a prospective study including 12 patients aged between 20 years and 32 years, with a diagnosis of gender dysphoria, treated with parenteral testosterone administration before sexual reassignment surgery.
*Results:* Endometrial histology revealed the presence of active endometrium in 10 cases and secretive endometrium in two cases. Multifollicular ovaries were observed in all cases of active endometrium, while corpus luteum was present in the two cases of secretory endometrium. Fibroids or hypertrophic myometrium were observed in 58% of the patients. Estrogen receptor was very high (59%) in the endometrial epithelial cells and low (17%) in the myometrium. Androgen receptor expression was modest in endometrial epithelial cells (24%) and sustained in myometrium (69%). Ki67 expression is steadily present in all uterine compartments, varying from 8% in epithelial endometrium to 2% in the myometrium.
*Conclusion:* Our data suggest that long-term testosterone administration to female-to-male patients during reproductive age induces a low proliferative active endometrium, associated with some hypertrophic myometrial changes.


## Introduction

In recent years, a number of therapeutic protocols have included androgens as part of the traditional postmenopausal hormonal therapy [1,2], although there are few efficacy data.

Female-to-male (FtM) transition remains a specific clinical indication for testosterone administration. There is a limited number of studies dealing with long-term treatments and the effect of androgens on their targets (mainly breast and uterus) and the knowledge in this field is scarce and, sometimes, contradictory.

Theoretically, after androgen treatment, the uterine changes of postmenopausal women may be different from those occurring in women taking long-term androgen therapy during reproductive age [3]. A point that still needs to be adequately addressed regards the uterine changes induced by long-term testosterone administration during the reproductive age.

Therefore, the purpose of this study was to determine the type of histological and steroid receptor changes in the endometrium and myometrium of FtM transgender individuals undergoing long-term testosterone therapy, prior to hysterectomy during the process of sexual reassignment surgery.

## Materials and methods

We performed a prospective study including 12 patients aged between 20 years and 32 years, with a diagnosis of gender

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dysphoria, performed according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) [4]. All patients were recruited at our Department of Obstetrics and Gynecology between 2011 and 2013 and were eligible for total hysterectomy with bilateral salpingo-oophorectomy during sexual reassignment surgery.

Patients underwent colposcopy with cytologic examination, and pelvic ultrasound in order to exclude genital tract pathologies contraindicating hormonal treatment.

Serum concentrations of free testosterone, total testosterone, 17-β estradiol, sex hormone binding globulin (SHBG), as well as hematocrit and Ferriman and Gallwey score, were evaluated before treatment, after the initiation of hormonal treatment but before surgery, and after the surgical sex reassignment procedure.

Cross hormonal therapy started preliminarily with parenteral administration of 100 mg testosterone enanthate along a 5.8 ± 3.8-month period every 2 weeks and was then implemented with intramuscular administration of testosterone enanthate at a dose of 200–250 mg every 2–3 weeks [5].

Recruited patients received androgen treatment during a period of 31.9 ± 14.3 months—the time needed to obtain the permission of the Court to proceed to hysterectomy with bilateral salpingo-oophorectomy—which was performed by laparoscopic approach in all patients.

Testosterone concentrations were measured every 3 months for the 1st year and then every 6 months in subsequent years. The goal was to maintain serum testosterone concentration < 55 ng/dL.

A mean time lapse of 12 months of testosterone treatment was needed for whole phenotypic masculinization. After oophorectomy or after masculinization has been reached, interval of testosterone administration was reduced to 3–4 weeks, maintaining the levels of serum testosterone within half the normal masculine levels.

The modulation of testosterone administration was based on levels of circulating androgens, the degree of satisfaction of masculinizing changes and absence of overdose symptoms such as hypertension and restlessness.

Follow-up consisted mainly of the following: (1) anamnestic surveys (menstrual history before and after the initiation of treatment with androgens, occurrence of amenorrhea, recurrence of bleeding); (2) measuring the degree of androgenization (Ferriman–Gallwey score, changes in tone of voice, appearance of alopecia and seborrhea); (3) arterial blood pressure measurement; (4) waist circumference and hip ratio; (5) evaluation of changes in body weight (body mass index calculation); and (6) work up with interest on the metabolic balance and hormonal changes (follicle-stimulating hormone, luteinizing hormone, total and free testosterone, SHBG, 17-β estradiol, insulin, thyroid-stimulating hormone, and erythropoietin).

Hormonal concentrations, hematocrit values, and Ferriman–Gallwey score taken into account in the present study are those obtained at the last evaluation just before performing the hysterectomy.

After surgery, every uterus was embedded in 10% buffered formalin and sent for pathological examination. The pathologist was asked to focus on the endometrial (epithelial and stromal) and myometrial histologic characteristics as well as to perform an immunohistochemical study of receptors for estrogens, progesterone, and androgens, but also for the proliferation marker Ki67.

The following immunohistochemical probes were used to study the above mentioned molecules: a monoclonal antibody clone 6F11 (Novocastra; Leica Biosystems, Newcastle-Upon-Tyne, UK), was used for estrogen receptors, with 1:50 dilution, and antigenic unmasking in citrate; a monoclonal antibody clone 1A6 (Novocastra), was used for progesterone receptors, with 1:40 dilution, and antigenic unmasking in citrate; a monoclonal antibody clone AR441 (Dako, Ely, UK), was used for androgen receptors, with 1:10 dilution, antigen unmasking in EDTA; a monoclonal antibody clone Mib-1 (Dako), was used for Ki67, with 1:25 dilution, antigen unmasking in citrate [6,7]. The immunohistochemical evaluation was based on the percentage of positive cells, similarly to breast cancer evaluation of steroidal receptors.

*Definitions*

The description of the endometrium also included cyclical changes, if present, as described by Noyes [8].

Endometrium was classified as inactive when tubular glands lined with cuboidal epithelium and low nucleus–cytoplasm ratio were present, in the absence of secretory or proliferative activity, separated by compact stroma. Active or proliferative endometrium was defined by presence of compact cellular stroma and tubular endometrial glands lined by column epithelium, with some of the glands showing pseudostratification and occasional mitosis.

The histological definition of ovary micropolycystic-like was made in the presence of numerous cystic follicles with a diameter between 5 mm and 10 mm, delimited by the granulosa cells and below a thickened ovarian cortex, associated with stromal hyperplasia.

*Statistical analysis*

The data on continuous variables with normal distribution were presented as mean ± SD, and compared between study groups using Student *t* test. Categorical data were assessed by Chi-square. A two-sided $p$ value < 0.05 was considered significant. Statistical analysis was done using SPSS version 20 (SPSS Inc., Chicago, IL, USA).

## Results

Amenorrhea occurred 8–12 months after starting of the therapy and had a mean duration of 21.8 ± 8.7 months before the hysterectomy.

Free testosterone and total testosterone concentrations progressively increased from basal value, reaching a peak at 6 months ($p < 0.001$) after testosterone administration. Concentrations of 17-β estradiol were reduced after testosterone administration due to inhibition of folliculogenesis, reaching postmenopausal concentrations at 6 months after initiation of androgen therapy (116.5 ± 62.3 pg/mL vs. 51.6 ± 18.6 pg/mL, respectively). Basal hematocrit values were significantly lower than those after 6 months of androgen treatment as well after year of therapy (39.9 ± 2.3 vs. 43.7 ± 2.8 vs. 44.6 ± 2.2, respectively; $p = 0.01$ for all comparisons). Ferriman–Gallwey score progressively increased from pretreatment value until 1 year after surgery (4.5 ± 3.7 vs. 9.9 ± 4.2 vs. 14.2 ± 4.4 vs. 16.6 ± 8.65 vs. 17.3 ± 8.96, respectively; $p < 0.001$ for all comparisons). Remarkably, Ferriman–Gallwey score increased from 4.5 ± 3.7 before treatment to 16.6 ± 8.65 soon after the surgery. As a result of the direct inhibition exercised by androgens on its synthesis in the liver, SHBG concentrations underwent a slight but significant decrease (43.8 ± 4.6 vs. 21.9 ± 5.6; $p = 0.001$; Table 1).

Table 2 summarizes the results of the histological examinations of uterus and ovaries removed obtained from the 12 patients after surgery. Endometrial histology revealed the presence of active endometrium in 10 cases and secretive endometrium in two cases. Multifollicular ovaries were observed in all cases of active endometrium, while corpus luteum was present in the two cases of secretory endometrium. Fibroids or hypertrophic myometrium has been observed in 58% (7/12) of the patients.