Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy

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Objective: To evaluate the incidence of venous thromboembolism (VTE) in transsexual patients and the value of screening for thrombophilia in this population.
Design: Retrospective cohort study.
Setting: Academic research institution.
Patient(s): Two hundred fifty-one transsexuals (162 male-to-female [MtF] and 89 female-to-male [FtM] transsexuals).
Intervention(s): Screening for activated protein C (aPC) resistance, antithrombin III, free protein S antigen, and protein C deficiency.
Main Outcome Measure(s): Incidence of thrombophilic defects and VTE during cross-sex hormone therapy.
Result(s): Activated protein C resistance was detected in 18/251 patients (7.2%), and protein C deficiency was detected in one patient (0.4%). None of the patients developed VTE under cross-sex hormone therapy during a mean of 64.2 ± 38.0 months. There was no difference in the incidence of thrombophilia comparing MtF and FtM transsexuals (8.0% [13/162] vs. 5.6% [5/89], respectively).
Conclusion(s): VTE during cross-sex hormone therapy is rare. General screening for thrombophilic defects in transsexual patients is not recommended. Cross-sex hormone therapy is feasible in MtF as well as in FtM patients with aPC resistance. (Fertil Steril® 2010;93:1267–72. ©2010 by American Society for Reproductive Medicine.)

Key Words: Venous thromboembolism, transsexuals, aPC resistance, protein C deficiency, thrombophilia

Transsexualism is a rare disorder with a prevalence of 1:11,900 males and 1:30,400 females (1). Cross-sex hormone therapy is an established means to provide relief from the dichotomy between body habitus and gender identity in transsexuals and thus is a key medical strategy for these individuals.

Standard hormone therapy for male-to-female (MtF) transsexualism includes estrogens (usually peroral or transdermal 17ß-estradiol), antiandrogens (medroxyprogesterone acetate or cyproterone acetate), and a 5α-reductase inhibitor (finasteride). In female-to-male (FtM) transsexuals, T is the main hormonal agent used for cross-sex hormone therapy (2).

Adverse effects of cross-sex hormone therapy for both MtF and FtM transsexuals include venous thromboembolism (VTE). For MtF transsexuals, rates of VTE of up to 20% have been reported (2). However, a recent retrospective survey showed VTE in 6%–8% of MtF transsexuals using ethinylestradiol (3). VTE as a possible adverse effect in FtM transsexuals on cross-sex hormone therapy is believed to be due to an increase in platelet aggregation and hematocrit (4, 5).

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The risk of VTE in transsexual patients on cross-sex hormone therapy is correlated to the dosage of the hormone applied as well as to the presence of other risk factors such as smoking, age over 35, and carriage of genetic polymorphisms (6, 7). It is well accepted that a general screening strategy for thrombophilia among women seeking oral contraception is not cost-effective (8). In transsexuals, however, higher dosages of sex hormones are used, and a genetic predisposition to thrombophilia may have more severe clinical consequences in conjunction with cross-sex hormone therapy.

As all transsexuals undergo screening for thrombophilia at our institution, we retrospectively evaluated the incidence of thrombophilia and VTE during cross-sex hormone therapy to assess the practical value of thrombophilia screening in this population.

MATERIALS AND METHODS

We assessed the incidence of VTE in transsexuals undergoing cross-sex hormone therapy and the base-line incidence of abnormal hemostatic variables, that is, aPC-resistance, antithrombin III activity, free protein S antigen, and protein C activity, by chart review. In this retrospective cohort study, we included a total of 251 transsexuals (162 MtF and 89 FtM transsexuals) presenting to the Department of Obstetrics and Gynecology of the Medical University of Vienna, Vienna, Austria, during the years 1995–2007.

After the diagnosis of transsexualism was established, all patients were screened for aPC-resistance, antithrombin III

activity, free protein S antigen, and protein C activity before the administration of cross-sex hormone therapy. All screened patients underwent cross-sex hormone therapy and thus were included in the study. Data on hemostatic variables and on regular follow-up visits were available for all patients. To assess the incidence of VTE, patients were specifically asked for clinical symptoms of thrombosis at each visit as part of our follow-up routine.

All parameters were done within the routine diagnostic work-up of patients in our outpatient clinic. There was no specific Institutional Review Board approval.

Determination of Hemostatic Variables

In all patients, venous blood was obtained at the first visit to our outpatient clinic. Venous blood was collected by puncture of the antecubital vein into vacutainer tubes containing 0.1 mol/L sodium citrate. The aPC resistance, protein C activity, and protein S antigen were determined in the central laboratory of the Vienna General Hospital. These parameters are included in routine thrombophilia screening at our department and are in accordance with international consensus statements such as the one published in 2005 by the European Genetics Foundation (9). The routine screening for thrombophilia including protein S antigen, protein C activity, aPC-resistance, and antithrombin III activity has been used for screening in transsexual patients before the start of cross-sex hormone therapy. The test for aPC resistance (COATEST APC Resistance; Coachrom Diagnostica, Milan, Italy) is a second-generation coagulation test. These tests have been reported to give a sensitivity and specificity for the factor V Leiden mutation very close to 1 (10, 11). Thus, and for cost reasons, we screened for aPC resistance without additional testing for factor V Leiden mutation.

Determination of aPC resistance was performed by use of a commercially available assay (COATEST APC Resistance, Coachrom Diagnostica). Antithrombin III activity (STA antithrombin III; Diagnostica Stago, Asnières sur Seine, France) and protein C activity (COAMATIC protein C, Chromogenix AB) were determined by the STA analyzer (Diagnostica Stago). Free protein S antigen was determined by ELISA according to the manufacturer's instructions (Asserachrom protein S; Diagnostica Stago).

The interassay variability coefficients for aPC resistance, antithrombin III activity, free protein S antigen, and protein C activity in our laboratory were 3%–5%, 2%–5%, <5%, and 2.6%–3.6%, respectively. The intraassay variability of aPC resistance is 2%; the intraassay variability coefficients of the other factors have not been evaluated.

Cross-Sex Hormone Therapy

Standard MtF cross-sex hormone therapy at our department includes transdermal 17ß-estradiol (2 × 100 μg/week), oral cyproterone acetate (50 mg/day), and oral finasteride (5 mg every other day) and is reduced to the administration of transdermal 17ß-estradiol (2 × 100 μg/week) after sex-reassignment surgery. Our standard FtM cross-sex hormone therapy includes IM T undecanoate (1000 mg every 12 weeks) and oral lynestrenole (5 mg daily) and is reduced to the administration of T undecanoate (1000 mg every 12 weeks) after sex-reassignment surgery. Patients were seen every 3 months before and every 12 months after sex-reassignment surgery.

Statistical Analysis

Statistical analysis was carried out by the χ^2-test and Fisher's exact test using the Statistical Package for Social Sciences, version 10.0.7 (SPSS, Chicago). $P<.05$ was considered statistically significant.

RESULTS

Two-hundred fifty-one patients were included in this study. Of these, 162 and 89 were MtF and FtM transsexuals, respectively. Patient characteristics are described in Table 1. Thrombophilic defects were detected in 18 (7.2%) of 251 patients.

TABLE 1

Patient characteristics.

	MtF (n = 162)	FtM (n = 89)
Age, y	36.6 (±10.9)	26.9 (±7.3)
BMI	22.7 (±3.9)	23.1 (±4.1)
Previous thrombophilic event	5 (3.1)	0 (0)
Family history of thrombosis	8 (6.3)	3 (3.4)
Smoking	96 (59.3)	62 (69.7)
Arterial hypertension	35 (21.6)	14 (15.7)
Dyslipidemia	62 (38.3)	29 (32.6)
Diabetes mellitus	2 (1.2)	0 (0)
Previous cross-sex hormone therapy	60 (37.0)	2 (2.2)
Cross-sex surgery before initiation of cross-sex hormone therapy	24 (14.8)	6 (6.7)

Note: Data in parentheses are percents unless otherwise indicated.

Ott. Venous thrombosis in transsexuals. Fertil Steril 2010.