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.

Of 18 patients with a thrombophilic defect, 18 had aPC resistance and one patient was found to have protein C deficiency in addition to aPC resistance. There was no significant difference in the incidence of thrombophilia comparing MtF and FtM transsexuals (8.0% [13/162] vs. 5.6% [5/89], respectively; P=.6). Body mass index (BMI) and age at screening did not differ between patients with and without aPC resistance (BMI, 23.0 ± 4.2 vs. 22.9 ± 2.9 kg/m^2, respectively, P=.1; age 33.9 ± 12.4 vs. 33.1 ± 10.7 years, respectively, P=.8).

No cases of antithrombin III deficiency and protein C deficiency were found. None of the patients in this study developed VTE during cross-sex hormone therapy during a mean duration of 49.6 ± 33.7 (range, 12–135) months of follow-up. Mean follow-up did not differ between MtF and FtM transsexuals (52.5 ± 37.8 vs. 47.3 ± 31.5, respectively; P=.7).

Given the reported incidence of VTE in asymptomatic people with aPC resistance of up to 0.45% (12), the expected incidence in our study collective is about 2.4% over the 64-month follow-up (0.43/18 patients). The actual incidence in our study collective (0/18) does not differ significantly from the expected incidence (P=.5).

MtF Transsexuals

Table 2 describes patient characteristics of the 13 MtF patients with aPC resistance. Twelve of 13 MtF transsexuals presenting with aPC resistance underwent standard cross-sex hormone therapy as described in the Methods section. Patient number 1 was given a cyproterone acetate monotherapy due to the presence of numerous risk factors for VTE including diabetes mellitus and arterial hypertension. Patient number 7 had been admitted for permanent anticoagulation therapy with phenprocoumon due to the presence of a homozygous factor V Leiden mutation and a personal history of VTE before screening. This patient also received standard cross-sex hormone therapy.

If patient number 7 had not received phenprocoumon during cross-sex hormonal treatment and had consequently developed VTE, the resulting 64 months incidence would have been 5.6% (1/18). This incidence would not have been significantly different from the expected incidence in people with aPC resistance (2.4%; P=.3).

Six of 13 MtF transsexuals with aPC resistance underwent sex-reassignment surgery during follow-up and received an E_2 monotherapy afterward.

Sixty of 162 MtF transsexuals (37.0%) reported former hormone self-treatment with cyproterone acetate and/or ethinylestradiol for a median of 15 months (range, 5–21 months) with the last intake up to 4 weeks before initiation of therapy in our institution. In contrast, among MtF transsexuals with a thrombophilic defect, nine (69.2%) of 13 reported former hormone self-treatment. The difference was statistically significant (P=.04). These patients were reevaluated for aPC resistance after 61.6 ± 41.8 months (range, 24–119) after study entry. Normalization of aPC resistance was found in three patients (33.3%).

FtM Transsexuals

Table 3 shows patient characteristics of the five FtM patients with aPC resistance. All patients received standard cross-sex hormone therapy. Patients number 2 and 4 underwent sex-reassignment surgery and therefore received T undecanoate monotherapy afterward. Two of 5 FtM transsexuals with aPC resistance underwent sex-reassignment surgery during follow-up and received T undecanoate monotherapy afterward.

DISCUSSION

In our study, screening for thrombophilic defects identified altered hemostatic variables in 7.2% of transsexual patients. This is within the range of thrombophilic defects found in unselected Caucasian populations (9, 13, 14). Nineteen thrombophilic defects were detected, 18 of which were cases of aPC resistance. One FtM patient had both apC resistance and decreased protein C activity. None of the patients developed VTE under cross-sex hormone therapy.

Besides aPC resistance, other thrombophilic defects, namely, protein C, protein S, and antithrombin deficiency, are found in 0.4%, 0.7%–2.3%, and 0.1% of the population, respectively (15). We found one patient with protein C deficiency, for an incidence of 0.4%, which is in accordance with the reported incidence of protein C deficiency in unselected populations. However, none of our patients had protein S or antithrombin deficiency. This might be due to the small sample size in our study.

Given the reported incidence of VTE in asymptomatic individuals with aPC resistance of up to 0.45% (12), the expected incidence in our study collective is 2.4% over the 64 months at follow-up (0.43/18 patients). The actual incidence in our study collective (0/18) does not significantly differ from the expected incidence. Thus, our patient population represents an average risk group.

Although not statistically significant, MtF transsexuals showed a higher percentage of aPC resistance than FtM transsexuals (8.0% vs. 5.6%, respectively). Significantly more aPC-resistant than non-aPC-resistant MtF transsexuals reported former self-administration of cyproterone acetate; 9/13 MtF patients with aPC resistance reported a former uncontrolled hormone self-treatment with cyproterone acetate and/or ethinylestradiol; 33% of these patients were found to have normal aPC resistance levels after a mean of 61.6 ± 41.8 months. Thus, at least in these cases, it might be considered that aPC resistance was induced by cyproterone acetate. The use of combined oral contraceptives containing cyproterone acetate has been reported to be associated with alterations of aPC resistance, resulting in an 18-fold increased risk for VTE (16).

TABLE 2

Male to female transsexual patients with thrombophilic defects.

Patient no.	Age at screening, y	Chromosomal analysis	Cofactors of thromboembolism	Previous venous thromboembolism	Long-term anticoagulation	aPC resistance (normal >3ng/mL)	Other thrombophilic defects	Previous hormone self-treatment
1	61	46,XY	IDDM, AHT	No	No	1.44	No	CPA
2	35	46,XY	No	No	No	1.48	No	CPA
3	28	46,XY	No	No	No	1.51	No	No
4	21	46,XY	No	No	No	1.66	No	CPA + EE
5	58	46,XY	AHT	No	No	1.51	No	CPA + EE
6	35	46,XY	No	No	No	1.89	No	No
7	36	47,XYY	Smoking	Yes	Phenprocoumon	0.95	No	CPA + EE
8	30	46,XY	No	No	No	1.65	No	CPA
9	22	46,XY	No	No	No	1.60	No	No
10	35	46,XY	Smoking	No	No	1.73	No	CPA
11	38	46,XY	Smoking	No	No	1.63	No	No
12	40	46,XY	No	No	No	1.66	No	CPA + EE
13	50	46,XY	Smoking	No	No	1.89	No	CPA + EE

Note: AHT = arterial hypertension; IDDM = insulin-dependent diabetes mellitus; CPA = cyproterone acetate; EE = ethinylestradiol.

Ott. Venous thrombosis in transsexuals. Fertil Steril 2010.

TABLE 3

Female to male transsexual patients with thrombophilic defects.

Patient no.	Age at screening, y	Chromosomal analysis	Cofactors of thromboembolism	Previous VTE	Long-term anticoagulation	aPC resistance (normal > 3 ng/mL)	Other thrombophilic defects
1	29	46,XX	No	No	No	1.46	No
2	19	46,XX	No	No	No	1.64	No
3	17	46,XX	No	No	No	1.96	No
4	26	46,XX	No	No	No	1.41	Protein C deficiency
5	30	46,XX	No	No	No	1.76	No

Ott. Venous thrombosis in transsexuals. Fertil Steril 2010.

During cross-sex hormone therapy, none of the 251 transsexuals was diagnosed with VTE in our study. All patients with aPC resistance were treated with standard cross-sex hormone therapy for at least 18 months. At our department, ethinylestradiol is not administered to MtF patients because of the increased risk of VTE (3). This is in accordance with international practice using 17ß-estradiol as the estrogen of choice (17). One MtF transsexual with a known homozygous factor V Leiden mutation and a personal history of VTE received constant anticoagulation therapy with phenprocoumon in addition to cross-sex hormone therapy. In regard to the substantially impaired quality of life and the patient's strong wish for cross-sex hormone treatment, the administration of phenprocoumon seemed justified. The decision was made on the basis of an interdisciplinary discussion including experts in hematology and in gynecologic endocrinology.

If this patient had not received phenprocoumon during cross-sex hormonal treatment and had consequently developed VTE, the study results would have been altered. This is considered a study limitation. However, the resulting 64 months' incidence (1/18, 5.6%) would not have been statistically significant from the expected incidence in people with aPC resistance.

Our data indicate that cross-sex hormone therapy is feasible in patients with aPC resistance. Other risk factors of thrombosis should be taken into account, and adequate information should be given to the patient. At our department, for example, all patients with thrombophilia identified during screening are advised to make sure they are adequately hydrated and to wear compression stockings. Information on the need for anticoagulation therapy in high-risk situations such as states of immobility, surgery, and long-distance flights is provided. The suggested activity modifications for patients with aPC resistance are not exceptional. Anticoagulation therapy before long-distance flights and adequate hydration are generally recommended, and anticoagulation therapy before surgery is a routine procedure. However, we cannot rule out that these behavior modifications reduced the risk of thrombosis in this population under close surveillance.

The parameters included in the routine thrombophilia screening at our department are in accordance with international consensus statements, for example, "The European Genetics Foundation: Thrombophilia and Venous Thromboembolism. International Consensus Statement—Guidelines According to Scientific Evidence" (9). The test for aPC resistance (COATEST APC Resistance, Coachrom Diagnostica) is highly sensitive and specific for a factor V Leiden mutation (10, 11). Thus, and for cost reasons, patients with decreased aPC resistance ratios were not genotyped for the factor V Leiden mutation.

Limitations to our study are the possibility of inaccuracies in testing for hemostatic variables as well as the lack of screening for the factor II G20210A mutation, the MTHFR C6//T mutation, homocysteine levels, lupus anticoagulant, and anticardiolipin antibodies.

In summary, our data indicate that cross-sex hormone therapy in FtM and MtF transsexuals with thrombophilia is safe. Since treatment options such as the suggestion of behavior modifications are not considered to be very effective and since it is common practice not to screen for thrombophilic defects in asymptomatic populations (9), general screening for thrombophilic defects in transsexual patients is not recommended and should be restricted to individuals with a personal or family history of VTE.

REFERENCES

1. van Kesteren PJ, Gooren LJ, Megens JA. An epidemiological and demographic study of transsexuals in The Netherlands. Arch Sex Behav 1996;25:589–600.
2. Moore E, Wisniewski A, Dobs A. Endocrine treatment of transsexual people: a review of treatment regimens, outcomes, and adverse effects. J Clin Endocrinol Metab 2003;88:3467–73.
3. Gooren LJ, Giltay EJ, Bunck MC. Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. J Clin Endocrinol Metab 2008;93:19–25.
4. Pilo R, Aharony D, Raz A. Testosterone potentiation of ionophore and ADP induced platelet aggregation: relationship to arachidonic acid metabolism. Thromb Haemost 1981;46:538–42.

5. Nakao J, Change WC, Murota SI, Orimo H. Testosterone inhibits prostacyclin production by rat aortic smooth muscle cells in culture. Atherosclerosis 1981;39:203–9.
6. Beral V. Mortality among oral-contraceptive users. Royal College of General Practitioners' Oral Contraception Study. Lancet 1977;2:727–31.
7. Mohllajee AP, Curtis KM, Martins SL, Peterson HB. Does use of hormonal contraceptives among women with thrombogenic mutations increase their risk of venous thromboembolism? A systematic review. Contraception 2006;73:166–78.
8. Kalev M, Day T, Van de Water N, Ockelford P. Screening for a prothrombotic diathesis in patients attending family planning clinics. N Z Med J 1999;112:358–61.
9. The European Genetics Foundation; The Cardiovascular Disease Educational and Research Trust; The International Union of Angiology; The Mediterranean League on Thromboembolism, Nicolaides AN, Breddin HK, et al. Thrombophilia and venous thromboembolism. International consensus statement. Guidelines according to scientific evidence. Int Angiol 2005;24:1–26.
10. Jorquera JI, Montoro JM, Fernández MA, Aznar JA, Aznar J. Modified test for activated protein C resistance. Lancet 1994;344:1162–3.
11. Trossaërt M, Conard J, Horellou MH, Samama MM, Ireland H, Bayston TA, et al. Modified APC resistance assay for patients on oral anticoagulants. Lancet 1994;344:1709.
12. Langlois NJ, Wells PS. Risk of venous thromboembolism in relatives of symptomatic probands with thrombophilia: a systematic review. Thromb Haemost 2003;90:17–26.
13. Franco RF, Reitsma PH. Genetic risk factors of venous thrombosis. Hum Genet 2001;109:369–84.
14. Rees DC, Cox M, Clegg JB. World distribution of factor V Leiden. Lancet 1995;28:1133–4.
15. Lindhoff-Last E, Luxembourg B. Evidence-based indications for thrombophilia screening. Vasa 2008;37:19–30.
16. van Vliet HA, Winkel TA, Noort I, Rosing J, Rosendaal FR. Prothrombotic changes in users of combined oral contraceptives containing drospirenone and cyproterone acetate. J Thromb Haemost 2004;2:2060–2.
17. Toorians AW, Thomassen MC, Zweegman S, Magdeleyns EJ, Tans G, Gooren LJ, et al. Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people. J Clin Endocrinol Metab 2003;88:5723–9.