ORIGINAL RESEARCH—INTERSEX AND GENDER IDENTITY DISORDERS

Long-Term Evaluation of Cross-Sex Hormone Treatment in Transsexual Persons

Katrien Wierckx, MD,* Sven Mueller, S.C., PhD,† Steven Weyers, MD, PhD,‡ Eva Van Caenegem, MD,* Greet Roef, MD,* Gunter Heylens, MD,§ and Guy T'Sjoen, MD, PhD*§

*Department of Endocrinology, University Hospital Ghent, Ghent, Belgium; †Department of Experimental-Clinical and Health Psychology, Ghent University, Ghent, Belgium; ‡Department of Gynaecology and Obstetrics, University Hospital Ghent, Ghent, Belgium; §Department of Sexology and Gender Problems, University Hospital Ghent, Ghent, Belgium

DOI: 10.1111/j.1743-6109.2012.02876.x

ABSTRACT

Introduction. Long-term effects and side effects of cross-sex hormone treatment in transsexual persons are not well known.

Aim. The aim of this study is to describe the effects and side effects of cross-sex hormone therapy in both transsexual men and women.

Main Outcome Measures. Hormone levels were measured by immunoassays. Physical health was assessed by physical examination and questionnaires on general health and specific side effects, areal bone parameters by dual energy X-ray absorptiometry.

Methods. Single center cross-sectional study in 100 transsexual persons post-sex reassignment surgery and on average 10 years on cross-sex hormone therapy.

Results. Transsexual men did not experience important side effects such as cardiovascular events, hormone-related cancers, or osteoporosis. In contrast, a quarter of the transsexual women had osteoporosis at the lumbar spine and radius. Moreover, 6% of transsexual women experienced a thromboembolic event and another 6% experienced other cardiovascular problems after on average 11.3 hormone treatment years. None of the transsexual women experienced a hormone-related cancer during treatment.

Conclusion. Cross-sex hormone treatment appears to be safe in transsexual men. On the other hand, a substantial number of transsexual women suffered from osteoporosis at the lumbar spine and distal arm. Twelve percent of transsexual women experienced thromboembolic and/or other cardiovascular events during hormone treatment, possibly related to older age, estrogen treatment, and lifestyle factors. In order to decrease cardiovascular morbidity, more attention should be paid to decrease cardiovascular risk factors during hormone therapy management. **Wierckx K, Mueller, S, Weyers S, Van Caenegem E, Roef G, Heylens G, and T'Sjoen G. Long-term evaluation of cross-sex hormone treatment in transsexual persons. J Sex Med 2012;9:2641–2651.**

Key Words. Hormone Therapy; Transsexualism; Side Effects; Gender Identity Disorder; Thrombosis; Osteoporosis

Introduction

The current treatment regimens for transsexual persons usually involve hormonal therapy as well as sex reassignment surgery (SRS). In 1986, at the start of our multidisciplinary team, a dual-phase hormonal schedule was used. First, during the reversible part, sex-specific features were suppressed using cyproterone acetate 50–100 mg, together with starting the real-life test. Cyproterone acetate is a synthetic derivative of 17-hydroxyprogesterone and acts primarily as an androgen receptor antagonist. It has also a progestational and weak glucocorticoid

activity that inhibits luteinizing hormone (LH) releasing and in turn reduces testosterone levels. After 6 months up to 1 year treatment with cyproterone acetate, cross-sex hormones were added [1]. Recently, we changed our hormonal protocol, and we now prescribe antiandrogens (mostly cyproterone acetate 50 mg) and estrogens simultaneously to the majority of transsexual women (male-to-female transsexual persons). However, some transsexual women favor a slower procedure, and they receive the dual-phase hormonal protocol.

Also, the type and doses of estrogens have changed during the past years. Currently, at the start of cross-sex hormone treatment, ethinyl estradiol and conjugated estrogens are rarely prescribed, and below the age of 40, estradiol valerate 4 mg daily is now recommended. After the age of 40, transdermal estrogens (17-β estradiol gel 2 mg daily or 17-β estradiol patch 100μg twice a week) is usually recommended. In transsexual men (female-to-male transsexual persons), testosterone administration has been and is currently started after suppression of the menstruation by a progestin.

The goals of hormonal treatment are to induce the development of the secondary characteristics of the new sex and to diminish those of the natal sex [2]. Consequently, transsexual men are treated with testosterone to induce virilization, which includes the development of a male hair growth pattern and body composition, cessation of menses, a deepening of the voice, and clitoral enlargement. To obtain feminization, transsexual women at our center receive a combination of antiandrogen therapy and estrogen therapy. Feminization consists of breast formation, reduction of masculine hair growth, and a more female fat distribution.

A number of studies demonstrated the efficacy of several hormonal preparations to induce masculinization and feminization in transsexual persons [3–6]. After SRS, which usually involves gonadectomy, hormone treatment is continued life-long to maintain virilization and feminization in transsexual men and women, respectively, and to avoid signs or symptoms of hormone deficiency.

Follow-up data on the long-term effects and side effects of hormone treatment on physical health are still scarce in this specific population [7,8] and, as no randomized controlled trials are available, the optimal formulations and dosages of cross-sex hormone treatment are unknown at present. Current treatment modalities for hormonal replacement therapy are similar to those of hypogonadal persons and aim at hormone values in the normal physiological range [2]. Sustained supraphysiological levels of both testosterone and estrogen increase the risk for serious adverse reactions such as thrombosis, whereas subphysiological levels may induce the effects known from hypogonadal states. Although based on limited evidence, a serum concentration of LH within the normal range may be a reliable marker of adequate dosing [8,9]. In this study, we will describe the long-term effects and side effects of hormonal therapy in a relatively large number of transsexual men and women.

Methods

Study Population and Study Procedures

We performed two independent studies. First, in 2007, all Dutch-speaking transsexual women who underwent SRS at least 6 months before recruitment and who consulted a member of the gender team for treatment or follow-up during 2006 were invited by mail (N = 70). We had no further inclusion criteria, and we included 50 transsexual women in our study. The others did not respond (N = 17) or declined to participate because they wished not to be reminded of their past (N = 3) [9,10]. Second, in 2010, all Dutch-speaking transsexual men who underwent SRS between 1987 and 2009 at our hospital (N = 79) received a written invitation in which they were asked to confirm their participation by telephone or electronic mail. Fifty individuals agreed to participate [11–13]. Two participants could not be reached because of change of address. The others were not willing to participate.

All transsexual women underwent SRS (orchidectomy and phallectomy in combination with vaginoplasty) at least 6 months before recruitment and after at least 2 years of hormonal treatment. All but two women received breast augmentation. Before SRS, hormonal therapy had been initiated using antiandrogen therapy (cyproterone acetate 50–100 mg/day) up to a maximum of 1 year, followed by the addition of exogenous estrogen administration (different formulations). Post-SRS, all but three participants received estrogen treatment. On average, transsexual women were 6.3 years after SRS, with a minimum of 6 months and a maximum of 32.2 years.

All transsexual men except for one underwent ablative SRS (hystero-oophorectomy and mastectomy) at least 2 years before inclusion in this study. Almost all (N = 46) participants underwent phal-

loplasty, eight of whom had a previous metaidoioplasty, one person had metaidoioplasty alone, and three participants expressed no wish for further genital surgery. All started testosterone therapy at least 2 years before SRS. On average, participants were 8.7 years after SRS, with a minimum of 9 months and a maximum of 22 years.

Study Procedures

Transsexual women received questionnaires on medical history, dermatological features, changes in voice, quality of life, sexual functioning, surgical results, and psychological functioning during their hospital visit. They completed their study protocol between March and June 2007.

Transsexual men who agreed to participate in the study received questionnaires on medical history, dermatological changes, voice, quality of life, sexual functioning, fertility wish, surgical results, and psychological functioning by regular mail. Subsequently, they visited Ghent University Hospital between November 2009 and April 2010 for further evaluation. Both studies were approved by the ethical review board of Ghent University Hospital, Belgium. All participants gave written informed consent for participation in the study.

Main Outcome Measures

Medical History and Examination

As sex steroid treatment is known to be associated with specific side effects, data relevant to the long-term use of estrogen and testosterone therapy were collected from both samples. A self-constructed questionnaire was completed concerning medical history, experience of adverse effects (such as hormone-related cancers and thromboembolic and other cardiovascular events), current and past hormonal treatment, medication use, and smoking habits. Information was compared with data from medical files for accuracy and corrected if necessary.

Anthropometry, Areal Bone Mineral Density, and Body Composition

Body weight and anthropometrics were measured in light indoor clothing without shoes. Standing height was measured using a wall-mounted Harpenden stadiometer (Holtain, Ltd, Crymuch, UK). Areal BMD at the lumbar spine, at the proximal femur (total hip region), and at both distal forearms were measured using dual energy X-ray absorptiometry (DXA) with a Hologic QDR-4500A device (software version 11.2.1; Hologic, Bedford, MA, USA). *T*- and *Z*-scores for areal BMD were calculated using controls provided by the National Health and Nutrition examination Survey-III (NHANES-III) study group for the hip [14] and by the manufacturer for the lumbar spine, distal forearm, and total body BMD [15]. Male references were used in transsexual women and female references for transsexual men as all participants underwent normal pubertal development, with well-known effects on bone mass and size. The coefficient of variation (CV %) was <1% as calculated from daily spine phantom measurements.

Biochemical Determinations

Venous blood samples were obtained between 08.00 AM and 12.00 AM after overnight fasting. All blood samples were stored at –80°C until batch analysis. Commercial kits for radioimmuno assay were used to determine the serum concentrations of total testosterone (T) and sex hormone binding globulin (SHBG) (Orion Diagnostica, Espoo, Finland); estradiol (E_2) (Clinical Assay, Diasorin s.r.l., Saluggia, Italy), according to a modified protocol that doubles the serum amount [16]; LH, insulin-like growth factor, C-terminal telopeptides of type I collagen (CTX) as a marker of bone resorption, protocollagen 1 aminoterminal propeptide (P1NP), which reflects bone formation (electrochemiluminiscence immunoassay [ECLIA]; Modular, Roche Diagnostics, Mannheim, Germany). Insulin-like growth factor-binding protein 3 (IGFBP3) was determined by an extraction method (DSL-5600; Diagnostic System Laboratories, Webster, TX, USA). The intra- and interassay coefficients of variation for all assays were ≤10%. For all measurements, samples from transsexual men and transsexual women were assayed in a same assay run. Serum free T was calculated from the total serum hormone concentration, serum SHBG, and serum albumin, using a validated equation derived from the mass action law [15]. We defined supra- and subphysiological levels of T, estradiol, and LH as hormone levels exceeding the upper or lower limit of the reference ranges according to values from our local laboratory. Hematocrit, total cholesterol, and creatinin were measured using routine clinical chemistry methods. Prolactin and prostate-specific antigen (PSA) were additionally investigated in transsexual women.

Statistical Analysis

Descriptive statistics are expressed as means and standard deviations, or, in case of a non-normal

Table 1 General characteristics and biochemical levels of the study population

	Transsexual men (N = 50)	Transsexual women (N = 50)	*P* value
Age at time of the interview (years)	37 ± 8.2	43.0 ± 10.4	***0.003***
Age at SRS (years)	30 ± 8.2	36.7 ± 9.8	***0.001***
Height (cm)	165 ± 6.7	175.1 ± 8.3	***<0.001***
Weight (kg)	67.5 ± 11.5	77.8 ± 18.3	***0.01***
Use of hormone therapy (%)	100	94.0	0.24
Testosterone (ng/dL)[a]	631.1 [466.0–1019.2]	29.6 [21.8–38.2]	***<0.001***[a]
Free testosterone (ng/dL)[a]	15.5 [9.2–25.0]	0.3 [0.18–0.49]	***<0.001***[a]
Estradiol (pg/mL)[a]	34.4 [24.7–49.7]	50.9 [27.7–73.7]	0.012[a]
SHBG (nmol/L)[a]	30.1 [22.5–38.5]	66.1 [48.0–110.3]	***<0.001***[a]
LH (U/L)[a]	3.7 [0.2–28.5]	27.0 [17.5–39.4]	0.001[a]
Creatinin (mg/dL)[a]	0.9 [0.9–1.0]	0.8 [0.7–0.9]	***<0.001***
Hematocrit %	48.8 ± 2.8	41.0 ± 2.4	***<0.001***
IGF1 (ng/mL)	225.5 ± 65	229.1 ± 103	0.713
PSA (ng/mL)[a]	—	0.003 [0.03–0.09]	—
Prolactin (ng/mL)[a]	—	9.1 [6.0–12.2]	—

All statistical significant results are placed in bold and are italicized.
Data are presented as mean ± standard deviation or median (first to third quartiles) in case of non-Gaussian distribution. Categorical variables using chi-square-test; Linear variables using Linear regression analysis [a]adjusted for age, height, and weight
SRS = sex reassignment surgery; SHBG = sex hormone binding globulin; LH = luteinizing hormone; IGF1 = insulin-like growth factor; PSA = prostate-specific antigen

distribution, medians (first to third quartiles). Between-group differences of categorical variables were calculated with χ^2 tests, or a Fisher exact test was used. Differences between both groups of linear variables were calculated using the student *T*-test or linear regression analysis while covarying for age, weight, and/or height. Significance was set at $P < 0.5$ (two-tailed). Data were analyzed using PASW-software, v.18 (SPSS Inc., Chicago, IL, USA). For all analyses, missing values were excluded.

Results

General Characteristics

General characteristics of the study population (N = 100) are summarized in Table 1. All transsexual men were on testosterone replacement therapy for about 10 years (Figure 1); in total 496 hormone treatment years. Three transsexual women were not on estrogen therapy because of previous thromboembolic events and were therefore excluded from further hormonal, bioche-

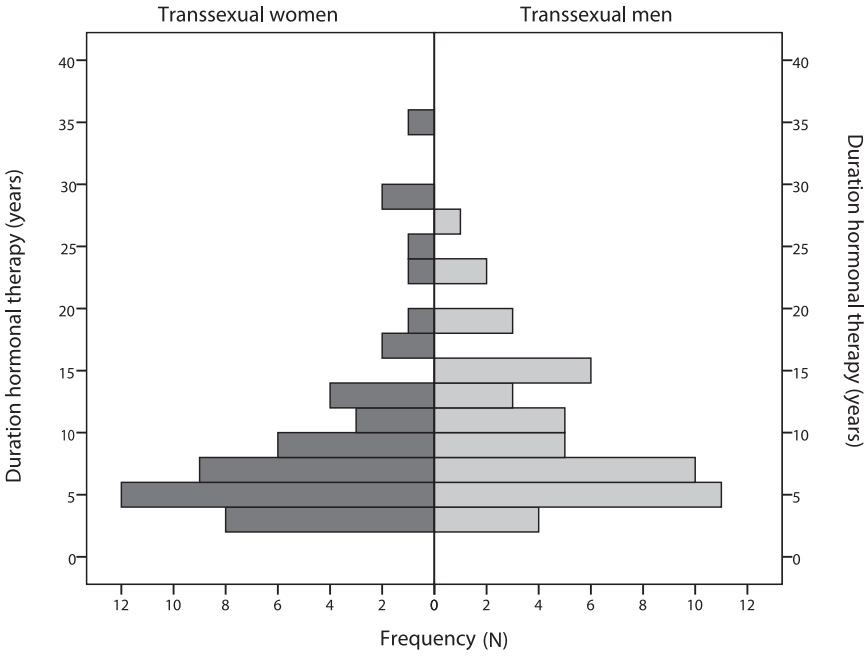

Figure 1 Distribution of duration of cross-sex hormone therapy.

mical, and bone measurements. The remaining transsexual women were on average 9.2 years on hormone therapy (in total 473 hormone treatment years). Most transsexual men used intramuscular testosterone treatment (parental testosterone esters 250 mg/2 or 3 weeks; N = 35 or testosterone undecanoate 1000 mg/12 weeks; N = 7), while seven men applied transdermal testosterone gel (50 mg daily). One participant used both oral testosterone undecanoate 40 mg (daily) and transdermal testosterone gel 50 mg daily. Transsexual women used transdermal estradiol (17-β estradiol gel 1.5 mg/24u: N = 22; estradiol patch 50 μg/24u: N = 3) or oral estrogens (estradiol valerate 2 mg: N = 19; estriol 2 mg: N = 1; ethinyl estradiol 50 μg: N = 1; ethinyl estradiol 120 μg: N = 1). Participants using ethinyl estradiol (N = 2) were excluded from estradiol analysis as this compound is not measured in the assay.

Hormonal and Biochemical Parameters

Given that the goal of hormone treatment in transsexual men and women is to obtain hormonal concentrations in the normal physiological range for natal men and women, respectively, hormonal levels differed significantly between both groups (Table 1). At the time of measurement, 8.9% of transsexual men exhibited levels below the reference values of our laboratory (testosterone <321 ng/dL), whereas 26.7% exceeded the upper limit of 1005 ng/dL. Sixty-three percent of transsexual women had estrogen levels below the lower limit (estradiol <55 pg/mL) and 11.5% above the upper limit (200 ng/L). When compared directly, transsexual women had higher LH levels compared with transsexual men (85% vs. 42%, respectively).

In 14 transsexual men (28.5%), we observed hematocrit levels above 50%, eight of whom (16.3%) had erythrocytosis (hematocrit levels above 52%) with one participant having a hematocrit level of 55%. Hematocrit levels in transsexual men were negatively associated with LH levels (linear regression: $P = 0.021$; $\beta = -0.35$), but not with other hormonal parameters (testosterone, SHBG) or age (data not shown). Hematocrit levels were significantly higher in participants who used conventional intramuscular testosterone esters compared with those who used intramuscular testosterone undecanoate or transdermal testosterone (linear regression: $P = 0.042$; $\beta = 0.29$).

Four transsexual women (8.2%) had slightly elevated prolactin levels (range: 21.4–30.5 ng/mL) compared with the normal male range at our laboratory (4–17 ng/mL). Only one transsexual woman had a prolactin level above the normal female range (6–30 ng/mL). None had elevated PSA levels.

Hormone-Related Cancers

Transsexual men did not experience hormone-related cancers during hormone treatment, whereas one transsexual woman had a macroprolactinoma. As this patient's macroprolactinoma was diagnosed before the start of cross-sex hormone treatment, she was excluded from prolactin analyses.

Cardiovascular Risk Factors

Cardiovascular risk factors were comparable in both groups, although transsexual women evidenced lower mean arterial blood pressure and lower serum triglycerides levels (Table 2). A similar number of transsexual men and women were overweight (24% vs. 22%) or obese (14% vs.14%). Three transsexual women had a body mass index above 35 kg/m^2 as compared with none of the transsexual men. Hypercholesterolemia (cholesterol ≥ 190 mg/dL) was observed in 60% of transsexual women and 64% of men. A compa-

Table 2 Cardiovascular risk factors

	Transsexual men (N = 50)	Transsexual women (N = 50)	*P* value
Current smoking (%)	34.7	36.0	0.39
Smoking years	11.6 ± 14.0	15.7 ± 14.3	0.15
Sports activity (%)	50.0	40.0	0.32
Body mass index (kg/m^2)	24.8 ± 3.8	25.3 ± 5.4	0.80
Total cholesterol (mg/dL)	199.1 [185.0–220.0]	198.0 [168.0–227.3]	0.44[a]
Triglycerides (mg/dL)	114.5 [85.5–182.0]	83.0 [64.3–127.8]	***0.001***[a]
Systolic blood pressure (mm Hg)	124.7 ± 14.4	124.8 ± 16.6	0.208
Diastolic blood pressure (mm Hg)	81.3 ± 10.7	77.1 ± 10.1	***0.002***[a]
Mean arterial blood pressure (mm Hg)	95.8 ± 10.1	93.0 ± 11.2	***0.008***[a]

All statistical significant results are placed in bold and are italicized.
Data are presented as mean ± SD or median (first to third quartiles) in case of non-Gaussian distribution. Categorical variables using chi-square-test; Linear variables using Linear regression analysis [a]adjusted for age, and weight

Table 3 Thromboembolic and other cardiovascular events in transsexual women (N = 6)

Event	Age at event (year)	Duration of hormone therapy at event (years)	Type of estrogen therapy at event (all oral administration, daily intake)	Smoking years at event	Current smoker
DVT‡	52	21	Conjugated estrogens 0.625 (Premarin®, Pfizer, New York, NY, USA)	18	No
Cerebral thrombosis§	58	20	Ethinyl estradiol 50 μg	45	Yes
Cerebral thrombosis	46	1	Cyproterone acetate 50 mg	—	Yes
TIA at SRS‡	33	2	Conjugated estrogens 0.625 + cyproterone acetate 50 mg	18	No
Peripheral arterial disease	46	8	Estradiol valerate 2 mg†		
Venous ulcer	45	7	Ethinyl estradiol 20 μg		
MI	43	21	Estrogen therapy*	18	Yes

*Not further specified
†Diagnosis of type 2 diabetes 9 years before event
‡Same participant
§Homozygeous carrier mutant methylhydrofolatereductase allele
DVT = deep venous thrombosis; MI = myocardial infarction; TIA = transient ischemic attack; SRS = sex reassignment surgery

rable number of transsexual women and men had an elevated blood pressure at the time of investigation and/or used antihypertensive medication (26% vs. 28%).

Thromboembolic and Cardiovascular Events

No transsexual men reported cardiovascular events such as myocardial infarction (MI), cerebrovascular disease, or deep venous thrombosis. Three transsexual women experienced thromboembolism (two cerebral and one deep venous thrombosis) during hormone treatment (Table 3). One participant experienced deep venous thrombosis and pulmonary embolism before starting of cross-sex hormone treatment. Estrogen treatment was given in combination with anticoagulants.

Additionally, four transsexual women experienced other cardiovascular diseases: transient ischemic attack (TIA) (N = 1), venous ulcer (N = 1), and MI (N = 2). One participant experienced MI prior to hormone therapy. Another transsexual woman underwent surgery for peripheral arterial disease during the course of hormone treatment, but the presence of diabetes mellitus was a likely cause in this woman. All participants except one, who experienced thromboembolic or other cardiovascular events, were smokers at the time of event (on average 24 smoking years).

Areal Bone Mineral Density Using DXA

Transsexual women experienced significantly more osteoporosis and osteopenia as compared with transsexual men. In transsexual men, no osteoporosis (T-scores ≤ -2.5) was diagnosed, while in transsexual women, osteoporosis was observed in 23.4% of patients at the lumbar spine, 8.7% at femoral neck, 2.1% at the total hip, and 25.5% at the left radius. In addition, the mean Z-scores in transsexual women were negative at all sites (at the lumbar spine: -1.0 ± 1.4, total hip: -0.4 ± 1.0, femoral neck: -0.7 ± 1.0, distal radius: -1.3 ± 1.3, and total body: -1.0 ± 1.0).

No differences in bone density were found between patients using transdermal or oral estrogen administration (data not shown). Finally, no associations were found in bone mineral density at lumbar spine, femoral neck, total hip and serum testosterone, LH, or estradiol levels in both transsexual women and men (data not shown).

Compared with the normal male range at our laboratory (<0.58 ng/dL), all but four transsexual women had normal CTX levels (range: 0.62–1.24 ng/dL), while two transsexual women had higher P1NP levels above the normal male range (102 ng/mL) (range: 106–125 ng/mL).

Discussion

This study presents follow-up data on physical health after hormone therapy and SRS (on average after 10 treatment years) in transsexual men and women. We demonstrate that at our center, transsexual men are less at risk for severe side effects than transsexual women. In addition, we found that none of the transsexual men experienced cardiovascular events or hormone-related cancers. These findings are in line with previous studies, which demonstrated that cross-sex hormone treatment was acceptably safe in the short- and medium-term for transsexual men [17,18]. However, risks may become more apparent as subjects grow older and the duration of hormone exposure increases [6,18]. Moreover, the presence of several cardiovascular risk factors such as obesity, poorer lipid profile, or elevated serum

hematocrit raises the concern for possible future cardiovascular events [4].

Several risks factors were present in a substantial part of our group of transsexual men at the time of investigation: being overweight (24%), obesity (14%), hypercholesterolemia (64%), smoking (30%), erythrocytosis (14.3%), and elevated blood pressure (22.5%). Long-term studies are needed to provide specific data on the effects of hormonal treatment in transsexual men on cardiovascular health [6]. A healthier lifestyle may reduce the impact of these risk factors, while some risk factors such as erythrocytosis are related to the specific pharmacokinetic effects of the type of testosterone therapy [19,20] and can be avoided. In contrast with previous findings in natal men [20], older age was not associated with a higher risk of erythrocytosis during testosterone administration. However, in comparison with the study by Coviello et al. [20], none of our transsexual men were aged between 60 and 75 years.

Transsexual women showed a similar number of cardiovascular risk factors compared with transsexual men in the current sample. Except for smoking, which occurred more in the transgender participants, similar or even less cardiovascular risk factors were present in comparison with the general Belgian population [21–25]. Nevertheless, 12% of transsexual women experienced thromboembolic and/or other cardiovascular complications during hormone treatment after a mean duration of 11.4 hormone treatment years. For a comparable duration of hormone treatment years, cross-sex hormone treatment seems to have more harmful effects in transsexual women than in men. This is in line with Asscheman et al. [26], who observed higher cardiovascular mortality after an average of 20 years of cross-sex hormone therapy in transsexual women, but not transsexual men, as compared with the general population. Whether these thromboembolic and other cardiovascular events are caused by cross-sex hormone therapy, older age of transsexual women, or represent the preexisting sex differences in cardiovascular events, remains to be determined. Long-term prospective studies in a larger study sample are needed in this regard.

The incidence of venous thrombosis in the present study (2% or estimated 21/10,000 user years) was lower than the one reported by Van Kesteren et al. [17]. Their study [17] showed that 6.4% (58/10,000 user years) in their group of transsexual women experienced a deep venous thrombosis or pulmonary embolism thrombosis during hormonal therapy, which was a 20-fold increased incidence compared with the general Dutch male population. However, a more appropriate control group might be women using estrogens and/or progestagens such as hormone replacement therapy (HRT) or oral contraceptives (OCs). OC therapy and HRT are both associated with an increased risk of venous thromboembolism [27,28]. A recent Danish population study [29] found that the incidence of venous thromboembolism in women using OC was 3.01/10,000 user years, which is still significantly lower than the risk observed in transsexual women.

The estrogen levels of many of our transsexual women were below the normal female range. This may be a reason why relatively few transsexual women experienced venous thrombosis and pulmonary embolism compared with other centers. However, inadequate estrogen levels can cause side effects known from hypogonadal states. As we felt the need to increase the estrogen dosage in our treatment protocol in the past years, we chose 17-β estradiol as this formulation is thought to induce less changes in hemostatic factors [30]. Currently, more attention is also paid to monitor LH levels especially when estradiol levels cannot be measured by the immunoassay. Also, in the presence of low bone density, clearly supraphysiological LH levels will influence our decision on estrogen dosage.

We observed a higher incidence of cerebrovascular disease in our transsexual women compared with the general male and female population [31]. Both OC and HRT are known to increase the risk for cerebrovascular disease [32,33]. However, other factors such as smoking, hypercholesterolemia, or hypertension are even more detrimental [34]. Indeed, the majority of transsexual women who experienced cerebrovascular complications had other important risk factors besides estrogen therapy including genetic predisposition, smoking, and hypercholesterolemia. Although we always strongly recommend to all transsexual women to quit smoking, it appeared that many individuals continued despite prior experience of a thromboembolic or cardiovascular event. In our clinical experience, it remains difficult to convince transsexual women to discontinue smoking but also to adopt a healthier lifestyle. Importantly, during and after transition, more attention should be paid to treat cardiovascular risk factors such as hypercholesterolemia and hypertension.

One patient developed a TIA at SRS, and perioperative thromboses in transsexual women have

been described in other centers as well [17,35]. As surgery and immobilization are well-known risk factors for development of thrombosis, we currently advise to discontinue hormonal therapy at least 2 weeks before SRS or other elective surgery and to restart at mobilization. However, the existing evidence regarding the necessity to discontinue hormonal therapy before surgery in transsexual women remains limited. Also, the time period hormonal therapy should be discontinued is presently unknown. In our current treatment regimens especially ethinyl estradiol is no longer used given possible association with higher thromboembolic risks [30,35].

With regard to hormone-related cancers, it should be noted that all transsexual men treated at our center receive bilateral mastectomy, hysterectomy, and ovariectomy, within 1 year of testosterone treatment, so that risk of development of related cancers in these areas is very low. However, breast cancer has been reported in one transsexual man after bilateral mastectomy under long-term hormone treatment as well as development of an ovarian cancer in another transsexual man during hormone treatment and before ovariectomy [36,37]. None of the transsexual women developed hormone-related cancers during hormone therapy. So far, only a few case reports of prolactinomas, breast cancers, and prostate carcinomas in transsexual women have been reported [38]. Nevertheless, it deserves mention that the incidence of hormone-related cancers can increase as the duration of hormone exposure increases [38]. Moreover, it is possible that transsexual persons feel uncomfortable with medical exams concerning their native sex such as prostate examinations in transsexual women or gynecological examinations in transsexual men leading to an underinvestigation of cancers in these subjects. However, with appropriate care, these medical checkups are possible [39].

All transsexual women had normal PSA levels and only one participant developed a slightly elevated prolactin level compared with normal female range. This is in line with Dietrich et al. [40], who did not find an increase in prolactin levels in 60 transsexual women treated with monthly injections of gonadotropin-releasing hormone analogue (GnRH) analogs and oral estradiol valerate 6 mg daily, but it is in contrast with Asscheman et al. [35], who observed that more than 50% of transwomen experienced elevated prolactin levels under cross-sex hormone treatment (mostly cyproterone acetate 100 mg and 100 μg ethinylestradiol daily). The time course and exact mechanism of increased prolactin levels during cross-sex hormone treatment in transsexual women has not been fully elucidated. Type and dose of HRT are likely to be at least partly responsible for the observed differences, but head-to-head comparisons of different treatment regimens are to be performed.

Finally, long-term bone health is also a matter of concern in the treatment of transsexual persons. In line with most [41–43] but not all studies [44], we found that cross-sex hormone therapy maintained areal bone mineral density in all transsexual men, possibly due to a direct effect of testosterone on bone and/or an indirect effect of testosterone after aromatization to estradiol. In contrast to most other studies [45–48], but consistent with previous results from our center [49], we observed a high prevalence of osteoporosis and osteopenia in our group of transsexual women. However, the prevalence of osteoporosis and osteopenia is also dependent based on which gender (natal or desired) is used as a reference. As all our transsexual men and women underwent normal puberty, with well-known effects on bone mass and size, we generally recommend the use of the natal gender as a reference. Although this can be debated especially in adolescent transsexual persons. Data on bone health in transsexual women compared with control men are extensively described elsewhere [10]. Multiple causes might explain the high number of osteoporosis in our transsexual women compared with other centers. First, it is possible that our treatment regimen in the past using cyproterone acetate alone up to a maximum 1 year without concomitant use of exogenous estrogen therapy has led to a decrease in bone mineral density as cyproterone acetate decreases testosterone levels. Previous studies in men treated for prostate cancer [50,51] support these findings and show a decrease in BMD during androgen deprivation therapy. Moreover, men with prostate cancer treated with androgen deprivation therapy exhibited a higher fracture risk compared with those not receiving this therapy [52,53]. In sex offenders, treatment with cyproterone acetate was also associated with significant bone loss [54]. Second, given the use of a cross-sectional design in the present investigation, it cannot be ruled out that our study group differed at baseline because of cultural differences in physical activity, height, or calcium intake. Lower levels of physical activity in Belgium as compared with other European as well as non-European countries have been described in both

female and male adults and adolescents [55–57]. Finally, low estrogen levels and high gonadotrophines in our participants might indicate inadequate estrogenization. However, the rather high SHBG levels and the absence of clinical symptoms of insufficient treatment such as hot flushes do not support this hypothesis. The normal values for markers of bone turnover in this study population are also not suggestive for a state of estrogen deficiency with active bone loss, characterized by an increased bone turnover. Future prospective studies examining bone health in transsexual women may clarify the current findings. Studies comparing treatment regimens of cyproterone acetate with or without concomitant estrogen administration, as well as multicenter studies with adjustment for confounding effects (e.g., physical activity, height and calcium intake), may solve these questions.

Our study has several limitations. The relatively small sample size disallows us to provide accurate prevalence and incidence rates of morbidity. Comparisons with the general population therefore need to be interpreted with caution. Also, some adverse events based on biochemical variations and osteoporosis may be explained to some extent by increased screening. Third, as in all follow-up studies, selection bias of our participants cannot be excluded. Participants who agreed to this study may have a more favorable outcome than those who refused to participate. Fourth, as older age is associated with a higher morbidity, it should be noted that transsexual women in our sample were on average 6 years older than transsexual men. However, given that transsexual men mostly seek treatment at younger ages, transsexual women will be older if a comparable duration of hormone therapy is evaluated [58]. Finally, the nature of the cross-sectional design implies that we cannot draw any causative conclusions. In addition, given the absence of a baseline measurement, we cannot rule out that some of the findings were already present before cross-sex hormone therapy. Yet, despite these limitations, we feel that the present data contribute to the investigation of the effects and side effects of hormone therapy in transsexual persons, especially as follow-up data on hormone administration in this specific group remain scarce.

Conclusions

In conclusion, we have shown that after an average of 10 years of cross-sex hormone treatment, transsexual men did not experience important side effects such as hormone-related cancers or cardiovascular events. Osteoporosis was also absent in transsexual men. On the other hand, a substantial number of transsexual women suffered from osteoporosis at the lumbar spine and distal arm. Twelve percent of transsexual women experienced thromboembolic and/or other cardiovascular events during hormone treatment, possibly related to older age, estrogen treatment, and lifestyle factors. In order to decrease cardiovascular morbidity, more attention should be paid to decrease cardiovascular risk factors during hormone therapy management.

Acknowledgment

The authors are indebted to Griet De Cuypere, MD, PhD; Els Elaut, MSc, Birgit Van Hoorde, MSc; Piet Hoebeke, MD, PhD; Stan Monstrey, MD, PhD; for referral of participants. We thank Kaatje Toye for her help and assistance.

Corresponding Author: Katrien Wierckx, MD, Department of Endocrinology, University Hospital Ghent, Ghent 9000, Belgium. Tel: 0032 9 332 19 66; Fax: 0032 9 332 38 00; E-mail: katrien.wierckx@ugent.be

Conflict of Interest: E.VC. and K.W. are PhD students funded by the FWO (FWO11/ASP/152) and Bijzonder Onderzoeksfonds of Ghent University (01D20711), respectively.

Statement of Authorship

Category 1

(a) Conception and Design
Katrien Wierckx; Guy T'Sjoen; Gunter Heylens

(b) Acquisition of Data
Katrien Wierckx; Steven Weyers

(c) Analysis and Interpretation of Data
Katrien Wierckx; Greet Roef; Eva Van Caenegem; Sven Mueller

Category 2

(a) Drafting the Article
Katrien Wierckx; Guy T'Sjoen; Greet Roef

(b) Revising It for Intellectual Content
Steven Weyers; Gunter Heylens; Katrien Wierckx; Eva Van Caenegem; Guy T'Sjoen

Category 3

(a) Final Approval of the Completed Article
Katrien Wierckx; Sven Mueller; Greet Roef; Eva Van Caenegem; Steven Weyers; Guy T'Sjoen

References

1 De Cuypere G, T'Sjoen G, Beerten R, Selvaggi G, De Sutter P, Hoebeke P, Monstrey S, Vansteenwegen A, Rubens R. Sexual and physical health after sex reassignment surgery. Arch Sex Behav 2005;34:679–90.
2 Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM. Endocrine treatment of transsexual persons: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2009;94:3132–54.
3 Moore E, Wisniewski A, Dobs A. Endocrine treatment of transsexual people. A review of treatment regimes, outcomes and adverse effects. J Clin Endocrinol Metab 2003;88:3467–73.
4 Tangpricha V, Ducharme SH, Barber TW, Chipkin SR. Endocrinologic treatment of gender identity disorders. Endocr Pract 2003;9:12–21.
5 Gooren L. Hormone treatment of the adult transsexual patient. Horm Res 2005;64(2 suppl):31–6.
6 Gooren LJ, Giltay EJ. Review of studies of androgen treatment of female-to-male transsexuals: Effects and risks of administration of androgens to females. J Sex Med 2008;5:765–76.
7 Gooren L. Care of transsexual persons. N Engl J Med 2011;364:1251–7.
8 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.
9 Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental and sexual health among transsexual women. J Sex Med 2009;6:752–60.
10 T'Sjoen G, Weyers S, Taes Y, Lapauw B, Toye K, Goemaere S, Kaufman JM. Prevalence of low bone mass in relation to estrogen treatment and body composition in male-to-female transsexual persons. J Clin Densitom 2009;12:306–13.
11 Wierckx K, Van Caenegem E, Elaut E, Vandepeer F, Dedecker D, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. J Sex Med 2011;8:3379–88.
12 Wierckx K, Elaut E, Van Caenegem E, Van de peer F, Dedecker D, Vanhoudenhove E, T'Sjoen G. Sexual desire in female-to-male transsexual persons: An exploration of the role of testosterone replacement. Eur J Endocrinol 2011;165: 331–7.
13 Wierckx K, Van Caenegem E, Pennings G, Elaut E, Van de peer F, Dedecker D, Weyers S, De Sutter P, T'Sjoen G. Reproductive wish in transsexual men. Hum Reprod 2012;27:483–7.
14 Looker AC, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, Johnston Jr CC, Lindsay R. Updated data on proximal femur bone mineral levels of US adults. Osteoporos Int 1998;8:468–90.
15 Szulc P, Claustrat B, Munoz F, Marchand F, Delmas PD. Assessment of the role of 17 beta-oestradiol in bone metabolism in men: Does the assay technique matter ? The MINOS study. Clin Endodocrinol 2001;61:447–57.
16 Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 1999;84:3666–72.
17 Van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol 1997;47:337–42.
18 Traish AM, Gooren LJ. Safety of physiological testosterone therapy in women: Lessons from female-to-male transsexuals (FTM) treated with pharmacological testosterone therapy. J Sex Med 2010;7:3758–64.
19 Dobs AS, Meikle AW, Arver S, Sanders SW, Caramelli KE, Mazer NA. Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. J Clin Endocrinol Metab 1999;84:3469–78.
20 Coviello A, Kaplan B, Lakshman K, Chen T, Singh A, Bhasin S. Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. J Clin Endocrinol Metab 2008;93:914–5.
21 Duvigneaud N, Wijndaele K, Matton L, Deruemaeker P, Philippaerts R, Lefevre J, Thomis M, Duquet W. Socio-economic and lifestyle factors associated with overweight in Flemisch adult men and women. BMC Public Health 2007;7:23–33.
22 Belgische Gezondheidenquête. Rapport 2- leefstijl en preventie. 2008.
23 Duprez D, Helshoecht PV, Eynde WV, Leeman M. Prevalence of hypertension in the adult population of Belgium: Report of a worksite study. J Hum Hypertens 2002;16:47–52.
24 De Henauw S, De Bacquer D, de Smet P, Kornitzer M, De Backer G. Trends and regional differences in coronary risk factors in two areas in Belgium: Final results from the MONICA Ghent-Charleroi Study. J Cardiovasc Risk 2000; 7:347–57.
25 Mullie P, Clarys P, Hulens M, Vansant G. Distribution of cardiovascular risk factors in Belgian army men. Arch Environ Contam Toxicol 2010;65:135–9.
26 Asscheman H, Giltay EJ, Megens J, de Ronde W, Trotsenburg MA. A long term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol 2011;164:635–42.
27 Vandenbroucke JP, Rosing J, Bloemenkamp KW, Middeldorp S, Helmerhorst F, Bouma BN, Rosendaal FR. Oral contraceptives and the risk of venous thrombosis. N Engl J Med 2001;344:1527–35.
28 Canonico M, Plu-Bureau G, Lowe GDO, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: Systematic review and meta-analysis. BMJ 2008;336:1227–36.
29 Lidegaard Ø, Nielsen LH, Skovlund CW, Skjeldestad FE, Løkkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestagens and oestrogen doses: Danish cohort study, 2001–9. BMJ 2011;343: d6423.
30 Toorians AW, Thomassen MC, Zweegman S, Magdeleyns EJ, Tans G, Gooren LJ, Rosing J. Venous thrombosis and changes of hemostatic variables during cross-sex treatment in transsexual people. J Clin Endocrinol Metab 2003;88:5723–9.
31 Buntinx F, Devroey D, Van Casteren V. The incidence of stroke and transient ischaemic attacks is falling: A report from the Belgian sentinel stations. Br J Gen Pract 2002;52:813–7.
32 Kemmeren J, Tanis B, van den Bosch M, Bollen E, Helmerhorst F, van der Graaf Y, Rosendaal F, Algra A. Risk of arterial thrombosis in relation to oral contraceptives (RATIO) study: Oral contraceptives and the risk of ischemic stroke. Stroke 2002;33:1202–8.
33 Sare G, Gray L, Bath P. Association between hormone replacement therapy and subsequent arterial and venous vascular events: A meta-analysis. Eur Heart J 2008;29:2031–41.
34 Lindenstrøm E, Boysen G, Nyboe J. Life style factors and risk of cerebrovascular disease in women. Copenhagen City Heart Study Stroke 1993;24:1468–72.
35 Asscheman H, Gooren LJG, Eklund PL. Mortality and morbidity in transsexual patients with cross-gender treatment. Metabolism 1989;38:869–73.
36 Ganly I, Taylor EW. Breast cancer in a trans-sexual man receiving hormone replacement therapy. Br J Surg 1995;82:341.
37 Hage JJ, Dekker JJ, Karim RB, Verheijen RH, Bloemena E. Ovarian cancer in female-to-male transsexuals: Report of two cases. Gyanecol Oncol 2000;76:413–45.

38 Mueller A, Gooren L. Hormone-related tumors in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol 2008;159:197–202.
39 Weyers S, Decaestecker K, Verstraelen H, Monstrey S, T'Sjoen G, Gerris J, Hoebeke P, Villeirs G. Clinical and transvaginal sonographic evaluation of the prostate in transsexual women. Urology 2009;74:191–6.
40 Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckman W, Mueller A. Endocrine treatment of male-to-female transsexuals using gonadotropin-releasing hormone agonist. Exp Clin Endocrinol Diabetes 2005;113:586–92.
41 Ruetsche AG, Kneubuehl R, Birkhaeuser MH, Lippuner K. Cortical and trabecular BMD in transsexuals after long-term cross-sex hormone treatment: A cross-sectional study. Osteoporos Int 2005;16:791–8.
42 Turner A, Chen TC, Barber TW, Malabanan AO, Holick MF, Tangpricha V. Testosterone increases bone mineral density in female-to-male transsexuals: A case series of 15 subjects. Clin Endocrinol (Oxf) 2004;61:560–6.
43 Mueller A, Haenerle L, Zollver H, Claasen T, Kronawitter D, Oppelt PG, Cupisti S, Beckman MW, Dittrich R. Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. J Sex Med 2010;7:3190–8.
44 Van Kesteren P, Lips P, Gooren LJ, Asscheman H, Megens J. Long-term follow up of bone mineral density and bone metabolism in transsexuals treated with cross-sex hormones. Clin Endocrinol (Oxf) 1998;48:347–54.
45 Mueller A, Dittrich R, Binder H, Binder H, Kuehnel W, Maltaris T, Hoffmann I, Beckmann MW. High dose estrogen treatment increases bone mineral density in male-to-female transsexuals receiving gonadotropin-releasing hormone antagonist in the absence of testosterone. Eur J Endocrinol 2005;153:107–13.
46 Lips P, Asscheman H, Uitewaal P, Netelenbos JC, Gooren L. The effect of cross-gender hormonal treatment on bone metabolism in male-to-female transsexuals. J Bone Miner Res 1989;4:657–62.
47 Haraldsen IR, Haug E, Falch J, Egeland T, Opjordsmoen S. Cross-sex pattern of bone mineral density in early onset gender identity disorder. Horm Behav 2007;52:334–43.
48 Sosa M, Jodar E, Arbelo E, Domínguez C, Saavedra P, Torres A, Salido E, de Tejada MJ, Hernández D. Bone mass, bone turnover, vitamin D and estrogen receptor gene polymorphism in male-to-female transsexuals: Effect of estrogenic treatment on bone metabolism of the male. J Clin Densitom 2003;6: 297–304.
49 Lapauw B, Taes Y, Simoens S, Van Caenegem E, Weyers S, Goemaere S, Toye K, Kaufman JM, T'Sjoen G. Body composition, volumetric and areal bone parameters in male-to-female transsexual persons. Bone 2008;43:1016–21.
50 Greenspan SL, Coates P, Sereika SM, Nelson JB, Trump DL, Resnick NM. Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. J Clin Endocrinol Metab 2005;90:6410–7.
51 Diamond TH, Higano CS, Smith MR, Guise TA, Singer FR. Osteoporosis in men with prostate carcinoma receiving androgen-deprivation therapy: Recommendations for diagnosis and therapies. Cancer 2003;100:892–9.
52 Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation therapy for prostate cancer. N Engl J Med 2005;104:1633–7.
53 Smith M, Boyce S, Moyneur E, Duh M, Raut M, Brandman J. Risk of clinical fracture after gonadotropin-releasing hormone agonist therapy for prostate cancer. J Urol 2006;175: 136–9.
54 Gooren LJ. Clinical review: Ethical and medical considerations of androgen deprivation treatment of sex offenders. J Clin Endocrinol Metab 2011;96:3628–37.
55 Bauman A, Bull F, Chey T, Craig C, Ainsworth B, Sallis B, Bowles H, Hagstromer M, Sjostrom M, Pratt M, the IPS Group. The international prevalence study on physical activity: Results from 20 countries. Int J Behav Nutr Phys Act 2009;6:21–32.
56 Sjöström M, Oja P, Hagströmer M, Smith BJ, Bauman AE. Health-enhancing physical activity across European Union countries: The Eurobarometer study. J Public Health 2006;14:291–300.
57 Currie C, Roberts C, Morgan A, Smith R, Settertobulte W, Samdal O, Rasmussen V, eds. 2004. Young People's Health in Context: International report from the HBSC 2001/02 survey.
58 Nieder TO, Herff M, Cerwenka S, Preuss WF, Cohen-Kettenis PT, De Cuypere G, Haraldsen IR, Richter-Appelt H. Age of onset and sexual orientation in transsexual males and females. J Sex Med 2011;8:783–79.