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Original Article

DIFFERENTIAL ENDOCRINE AND METABOLIC EFFECTS OF TESTOSTERONE SUPPRESSIVE AGENTS IN TRANSGENDER WOMEN

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ABSTRACT

Objective: Suppression of testosterone secretion and/or action in transgender women using cyproterone acetate (CPA), spironolactone, or gonadotropin-releasing hormone analogues (GA) is achieved through various mechanisms. Our objective was to characterize possible differential effects of these compounds on metabolic and endocrine variables.

Methods: We conducted a historic cohort study of transgender patients treated in a tertiary referral center. A longitudinal analysis of treatment naïve patients and a cross-sectional analysis of the whole cohort at the last visit was carried out.

Results: Among 126 transgender women (75 treatment-naïve), CPA was the predominant androgen suppressive therapy (70%), followed by spironolactone (17.6%), and GA (10.2%). Among those who were treatment-naïve, the increase in serum prolactin levels over baseline was greater at 3 months following CPA initiation (mean change 397 ± 335 mIU/L) than following spironolactone (20.1 ± 87 mIU/L) or GA initiation (64.6 ± 268 mIU/L; $P = .0002$). Prolactin levels remained higher in the CPA-treated group throughout follow-up, irrespective of estradiol levels, which were similar between the groups. A worse metabolic profile was associated with treatment with CPA than with spironolactone or GA. In the CPA compared to the spironolactone and GA groups, high-density lipoprotein-cholesterol levels were lower (47.1 ± 10.4, 54.4 ± 12.2, and 60.3 ± 13, respectively; $P = .0076$), while body mass index levels (24.3 ± 5, 21.7 ± 2.3, and 20.7 ± 3.1 kg/m^2; $P = .03$), and systolic (117 ± 12.1, 109 ± 12.2, and 105 ± 13.3 mm Hg; $P = .01$) and diastolic (74 ± 9, 65.6 ± 5.5, and 65.4 ± 11 mm Hg; $P = .0008$) blood pressure levels were higher at the last visit.

Conclusion: Treatment of transgender women with CPA was associated with hyperprolactinemia and a worse cardiovascular risk profile than treatment with spironolactone or GA. **(Endocr Pract. 2020;26:883-890)**

Abbreviations:
BMI = body mass index; **CPA** = cyproterone acetate; **E2** = estradiol; **FSH** = follicle-stimulating hormone; **GA** = gonadotropin-releasing hormone analogues; **LH** = luteinizing hormone

INTRODUCTION

Transgender individuals feel a mismatch between their assigned gender at birth and their gender identity (1,2). Gender-affirming therapy consists of suppression of endogenous hormone secretion coupled with cross-sex hormone administration (1-3). Testosterone suppression in trans women may be achieved with spironolactone, cyproterone acetate (CPA), or long-acting gonadotropin releasing hormone (GnRH) analogues (GA) (1). Spironolactone and CPA compete with dihydrotestosterone for androgen-receptor binding (4). Spironolactone also inhibits enzymes involved in androgen biosynthesis (5), while CPA inhibits pituitary luteinizing hormone (LH) secretion (4), leading to

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a decrease in androgen secretion by the testes. Long-acting GA suppress the hypothalamo-pituitary gonadal axis but are devoid of a direct peripheral anti-androgenic effect.

Recent clinical guidelines (1) do not recommend one anti-androgen preparation over the other, for the treatment of adult trans women. Given that the available compounds differ in their anti-androgenic mechanisms, we hypothesized that they may also differ in their efficacy to suppress testosterone and in their safety profiles. Investigation of this hypothesis is hampered by the lack of availability of CPA in the United States, where the anti-androgen of choice is spironolactone. On the other hand, CPA is widely used in Europe.

Furthermore, recent studies have suggested differential effects of spironolactone and CPA on prolactin levels (6-9), but direct comparisons within the same study population are not available. We therefore compared treatment outcomes and related side effects of 3 testosterone suppressive agents in a single population of transgender women who were treated with a pre-established protocol in a university-affiliated tertiary medical center.

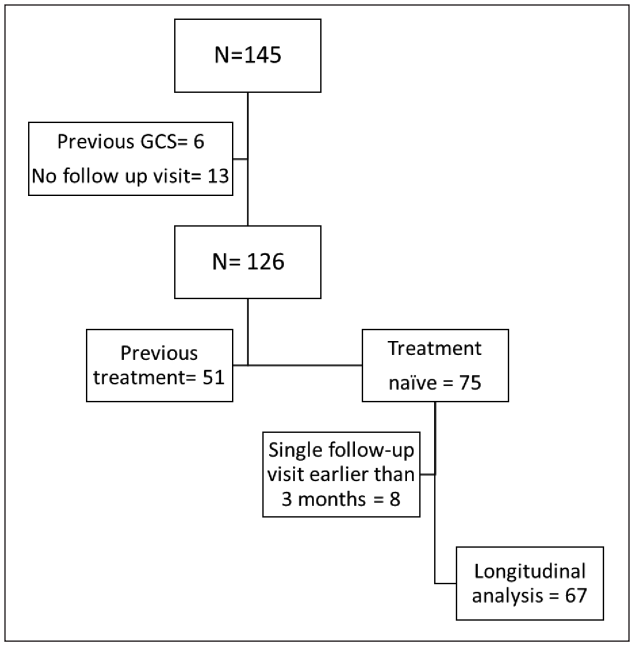

Fig. 1. Patient disposition. *GCS* = gender confirming surgery.

METHODS

The transgender outpatient clinic at our institution is a referral center for transgender care. Services are provided to a population of over 9 million people in Israel and the West Bank. We conducted a retrospective analysis of transgender women treated in our department between January, 2003, and December, 2013. Due to substantial changes in the treatment protocol, data from 2014 onwards are not included. Data of both previously treated and treatment naïve patients were analyzed (Fig. 1). At least 1 follow-up visit was required for inclusion in the final analysis. People who had already undergone gender confirmation surgery were excluded.

Our study was approved by the institutional ethics committee of the Tel Aviv-Sourasky Medical Center, in compliance with the Declaration of Helsinki. Written consent was waived for extracting retrospective data from clinical records.

Estradiol, testosterone, LH, follicle-stimulating hormone (FSH), and prolactin serum levels were analyzed using chemiluminescence immunoassays on the Centaur automated machine (Siemens Healthcare GmbH, Erlangen, Germany).

Statistical Analysis

A cross-sectional analysis of the entire study population was performed for individuals with at least 6 months of follow-up information. The nonparametric Kruskal-Wallis test was used for the comparative analysis of continuous variables between treatment groups, according to the type of androgen suppressive therapy. The Mann-Whitney *U* test was used to compare the same variables according to the route of estrogen treatment delivery. The unpaired Student's *t* test was used to compare demographic data of treatment-naïve and previously treated patients.

Regression models were built using the Fisher exact test for dichotomic variables and a linear model for continuous variables. Prolactin levels were analyzed according to visit and treatment type, and adjusted for the estradiol levels measured during the same visit. The Wilcoxon signed rank test was used to determine changes in prolactin levels from baseline to the final evaluation. In addition, standard descriptive statistics are provided. *P* values of <.05 were considered to indicate statistical significance. The results are presented as means ± SD. The data analysis was performed with SAS 9.3 software (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

Of 145 transgender women identified, 126 (75 treatment-naïve) were included in this analysis (Fig. 1). Treatment-naïve patients were younger and the mean follow-up period was significantly longer compared with previously treated patients (Table 1).

Patients previously treated with ethinylestradiol or conjugated estrogens were switched to β-estradiol-based preparations during their first visit in our department. Treatment-naïve patients received oral or transdermal β-estradiol preparations. Treatment was titrated to achieve estradiol levels within the normal cisgender premenopausal range (1). Smokers and individuals over the age of 40 years were preferentially treated with transdermal estrogen (26% of the total cohort), either estradiol gel (0.06%, 2.5 to 5 mg/day), or patches (50 to 200 μcg twice a week). The oral β-estradiol daily dose ranged from 2 to 8 mg.

Table 1
Sociodemographic Characteristics of the Study Population

	Treatment-naïve patients	Previously treated patients	*P* value
Number	75	51	
Age (years)	27.0 (8.8)[a]	30.9 (9.9)[a]	.05
Follow-up (months)	22.3 (24)[a]	14.7 (18.7)[a]	.0086
Academic education Secondary education	18.7% 30.7%	23.5% 37.3%	.999
Currently employed Missing data	65.3% 17.3%	68% 9.8%	.43
Marital status Married Divorced Single	 9.6% 6.8% 83.6%	 10.0% 6.0% 84.0%	.25
Recreational drugs	12.0%	17.6%	.56
Smoking	36.0%	47.1%	.28
Psychiatric medications	12.0%	13.7%	.64

[a]Mean (SD).

Overall, CPA was the predominant adjunct androgen suppressive therapy (70%, daily dose range 10 to 100 mg/day), while spironolactone and GA were used by 17.6% (daily dose range 50 to 200 mg) and 10.2% (monthly triptorelin 3.75 mg or goserelin 3.6 mg) of patients, respectively. Thirty-six percent of those treated with CPA received daily dosages lower than 30 mg. The mean ages were similar among the anti-androgen treatment groups.

Longitudinal Analysis

Overall

Sixty-seven treatment-naïve patients were followed prospectively (Fig. 1), every 3 months during the first year of treatment, every 6 months during the second year, and yearly thereafter. The number of patients available for analysis decreased during the follow-up period, and statistical power was lost beyond the 12th month visit. Thus, only data collected up to this point were analyzed.

During the study period, testosterone, LH, and FSH levels decreased significantly (Table 2), and estradiol levels increased (not shown). Despite significant increases in weight and body mass index (BMI) over time (Fig. 2 *A* and *B*), systolic blood pressure decreased, while diastolic blood pressure remained unchanged (Fig. 2 *C* and *D*). Both hematocrit and creatinine levels (Fig. 2 *E* and *F*) decreased, while the lipid profile remained unchanged (not shown).

Outcomes According to the Type of the Adjunct Anti-Androgen Modality

Hypothalamo-Pituitary Gonadal Axis

Treatment with estrogen combined with CPA or GA effectively inhibited the hypothalamo-pituitary-gonadal axis. LH and FSH levels were suppressed after 3 months of treatment, while testosterone dropped to values within or below the normal female range (Table 2). The same degree of gonadotropin and testosterone suppression was maintained at 12 months (Fig. 3 *A* and Table 2). In contrast, the decrease in gonadotropin and testosterone levels was significantly less under spironolactone treatment; dose up-titration was thus required. The increase in estradiol levels was similar when estrogen was combined with any of the other anti-androgens (Table 2).

Prolactin Levels

A significant increase in serum prolactin levels in individuals treated with CPA was already evident at 3 months (mean changes of 397 ± 255 mIU/L for CPA, 20 ± 88 mIU/L for spironolactone, and 65 ± 268 mIU/L for GA; $P<.05$). Prolactin levels remained significantly higher over time in the CPA-treated group than in the other 2 groups (Fig. 3 *B*), whose levels remained within the normal range with no interaction with time. Prolactin levels were significantly higher at 6 months in individuals who received CPA doses over 30 mg/day (711 ± 379 mIU/L) than among those treated with lower doses (495 ± 316 mIU/L; $P = .045$), suggesting a dose-dependent response. A correlation of estradiol (E2) with prolactin was observed in spironolactone-treated ($r = 0.72$, $P = .017$) and GA-treated ($r = 0.66$, $P = .07$) patients, but not in CPA-treated patients ($r = 0.06$, $P = .61$), in whom prolactin levels were the highest.

Lipids

High-density lipoprotein cholesterol levels were significantly lower at 12 months among subjects treated with CPA (40 ± 10.4 mg/dL) compared to those treated with spironolactone (57.7 ± 9.2 mg/dL) and GA (60.3 ± 16.4 mg/dL; $P = .03$). No significant changes were observed in low-density lipoprotein cholesterol or triglyceride levels in any of the treatment groups.

Table 2
Hormonal Changes Over Time in the Treatment-Naïve Group According to the Type of Antiandrogen Compound Added to Estrogen Therapy[a]

Anti-androgen	CPA (n = 41)	S (n = 16)	GA (n = 10)	*P* value[b]
Prolactin (mIU/mL)				
Baseline	227.9 (153.5)	220 (101.3)	228.4 (185.6)	.91
3	655.2 (282.3)	268.1 (157.2)	321.8 (212.2)	.0002
6	662.6 (390.6)	316.6 (157.4)	240 (120.9)	.001
12	751.2 (487.1)	283.1 (238)	333.3 (151.5)	.08
E2 (pmol/L)				
Baseline	93.2 (65.4)	116.8 (130.3)	145.1 (40.1)	.06
3	339.6 (515)	357.3 (425.3)	223.5 (143.9)	.911
6	454.6 (423.3)	237.8 (80.5)	242.6 (156.9)	.348
12	464.5 (494.3)	260.2 (74.4)	444 (546.9)	.934
Testosterone (nmol/L)				
Baseline	21.7 (7.2)	15.2 (8.1)	23.3 (7.7)	.015
3	0.9 (1)	10.2 (5.7)	1.1 (0.85)	<.0001
6	1.1 (1.85)	3.5 (1.2)	1.6 (1.3)	.048
12	1.73 (4.28)	4 (7.1)	0.85 (0.8)	.62
LH (IU/L)				
Baseline	4.5 (1.6)	6.5 (3.7)	5.7 (2.1)	.25
3	0.38 (0.87)	4.84 (3.94)	0.27 (0.35)	.0004
6	0.28 (0.89)	4.23 (2.85)	0.4 (0.43)	.001
12	0.38 (1.42)	3.13 (4.52)	0.53 (0.31)	.015
FSH (IU/L)				
Baseline	3.9 (2.9)	6.8 (8.5)	6.7 (5)	.33
3	0.36 (0.78)	3.78 (5.8)	0.45 (0.46)	.0012
6	0.11 (0.3)	3.95 (5.4)	1 (1.5)	.023
12	0.43 (0.94)	3.1 (3.97)	0.37 (0.64)	.39

Abbreviations: CPA = cyproterone acetate; E2 = estradiol; FSH = follicle-stimulating hormone; GA = GnRH analogs; LH = luteinizing hormone; S = spironolactone.
[a]Individuals available for analysis at baseline, 3, 6, and 12 months of treatment with CPA (41,26,21,16), spironolactone (16,8,6,2), and GA (10,5,5,3), respectively.
[b]Comparison between treatment types at each visit. Data is represented as the mean (SD).

Cross-Sectional Analysis

We performed a cross-sectional analysis, according to the anti-androgen preparation started at the first visit in our department. Data were collected from the last available visit, or from the last visit prior to confirmation surgery, provided that patients had a follow-up time of at least 6 months (n = 89, mean follow-up 26 ± 22 months). Treatment with CPA was associated with a worse metabolic profile compared with the other 2 anti-androgenic modalities: high-density lipoprotein levels were lower, while BMI was higher at the last visit (Table 3). Prolactin levels were significantly higher with CPA treatment, while spironolactone was the least effective modality in reducing testosterone levels (Table 3).

The patients treated with transdermal estradiol were older than those who received oral β-estradiol (34.7 ± 11.5 years versus 26.4 ± 9.2 years; *P*<.0001) and heavier (76 ± 19 kg versus 69.1 ± 18 kg; *P* = .035). No differences were observed in clinical or laboratory characteristics between patients who received oral and transdermal estrogen preparations.

DISCUSSION

Treatment of transgender women requires long-term administration of estrogens in combination with an additional anti-androgenic compound. Although the effects of anti-androgen treatment on endocrine and metabolic

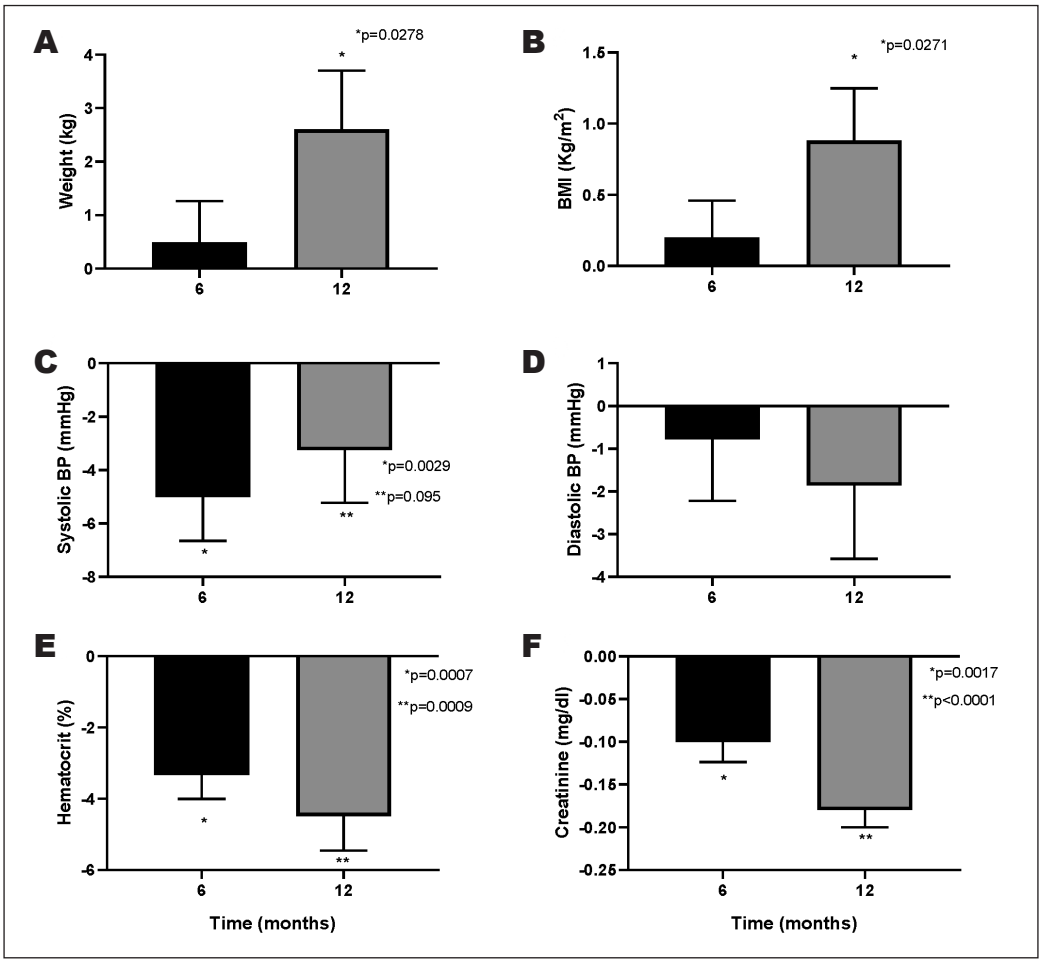

Fig. 2. Effects of cross-sex hormone therapy on weight. *A*, BMI, *B*, systolic, *C*, diastolic, *D*, blood pressure, *E*, hematocrit, and *F*, creatinine in the study population. *BMI* = body mass index; *BP* = blood pressure.

parameters have been studied, this is the first report in which all 3 preparations in current use were compared in the same population.

The differential treatment effect on prolactin levels was the most striking finding: prolactin levels were markedly higher in CPA-treated trans women than in those treated with GA or spironolactone. In contrast, estradiol levels were similar in the 3 groups. This likely excludes a role for circulating E2 in the observed differential, treatment-related effect on serum prolactin. These data do not support the previously prevalent notion that hyperprolactinemia in trans women was secondary to pharmacologic estrogen doses.

The CPA effect on prolactin levels may be mediated through its high-affinity binding to progesterone receptors (PRs) (10), expressed in tuberoinfundibular dopaminergic neurons (TIDA) (11) and human lactotrophs (11). Hence, CPA binding to PRs could induce hyperprolactinemia indirectly by inhibiting the dopaminergic tone in TIDA (11), or by a direct effect on the lactotroph. A rise in prolactin related to CPA treatment has been observed in several experimental (12,13) and clinical (14-18) settings.

Our results are in agreement with previously reported data from centers that use only one type of anti-androgen medication per protocol. Dittrich et al (19) reported no increase in prolactin levels in transgender women treated with GA. Spironolactone was not associated with increased prolactin levels in a recent study by Bisson et al (9). In contrast, 2 other studies reported an increase in prolactin levels under combined estrogen and CPA treatment (7,8). In their retrospective analysis, Fung et al (8) found higher prolactin levels in CPA- than in spironolactone-treated trans women after 12 months of treatment (8). Although 2 anti-androgen modalities were compared, there was considerable heterogeneity in their study population, which was compiled from highly dissimilar medical care systems (8). In another report, prolactin levels were also higher in CPA- than in GA-treated patients after 12 months of treatment (20).

In contrast to the above-mentioned studies, we directly compared the 3 anti-androgen preparations currently used in transgender women. Our results are strengthened by the conduct of the study in a single center and the use of a uniform protocol in a homogeneous population. We were able to show a clear time course of hormonal changes.

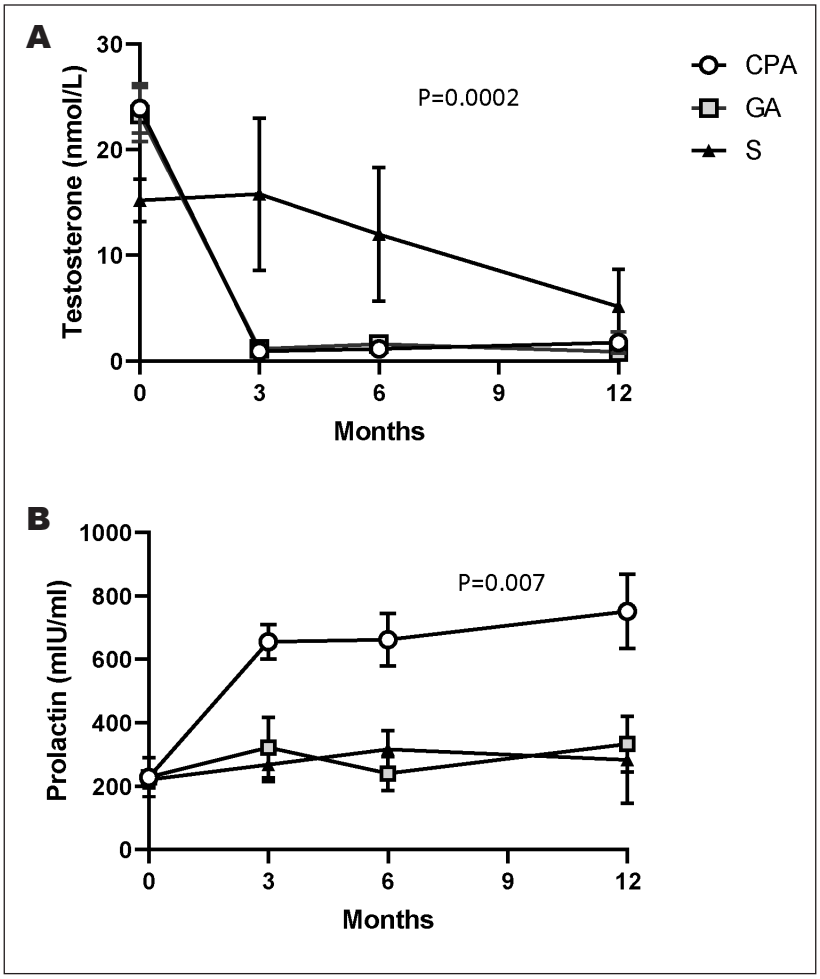

Fig. 3. Differential effects of cyproterone acetate (CPA), GnRH analogs (GA), and spironolactone (S) on: *A*, testosterone and *B*, prolactin levels in transgender women during a 12-month treatment period.

Table 3
Cross-Sectional Analysis of Trans Women with at Least 6 Months of Follow-up (n = 89) at the Last Visit, According to the Type of Antiandrogen Therapy

Anti-androgen	CPA (n = 67)	S (n = 12)	GA (n = 10)	*P* value
Prolactin (miU/mL)	593 (323)	222 (93)	240 (182)	<.0001
E2 (pmol/L)	473 (393)	277 (200)	435 (131)	.17
Testosterone (nmol/L)	1.7 (3.8)	6.9 (8.9)	1.3 (2.8)	.002
Total cholesterol (mg/dL)	159 (30.8)	162 (35.3)	167 (34.9)	.752
HDL cholesterol (mg/dL)	47.1 (10.4)	54.4 (12.2)	60.3 (13.0)	.0076
LDL cholesterol (mg/dL)	93.6 (26.4)	84.0 (25.6)	87.8 (28.7)	.59
Triglycerides (mg/dL)	95.6 (40.5)	86.8 (28.2)	96.3 (41.6)	.822
BMI (kg/m^2)	24.3 (5)	21.7 (2.3)	20.7 (3.1)	.03
Systolic BP (mm Hg)	117.0 (12.1)	109.5 (12.2)	105.0 (13.3)	.01
Diastolic BP (mm Hg)	74.0 (9)	65.6 (5.5)	65.4 (11)	.0008

Abbreviations: BMI = body mass index; BP = blood pressure; CPA = cyproterone acetate; E2 = estradiol; GA = GnRH analogs; HDL = high-density lipoprotein; LDL = low-density lipoprotein; S = spironolactone.
Data is represented as the mean (SD).

Accordingly, gonadotropin and testosterone suppression, together with a rise in prolactin levels in the CPA-treated group, were already detected at 3 months after treatment initiation and maintained throughout the follow-up. In contrast, most other studies considered these effects only at a timepoint of 12 months after treatment initiation. Comparing the 3 anti-androgenic preparations in our study enabled clearly dissociating the differential effect of CPA on prolactin levels from circulating estradiol.

Another notable finding was the inferior suppressive effect of spironolactone on testosterone levels, compared with CPA and GA. This is in accordance with research published by Angus et al (21), which showed less suppression of testosterone with spironolactone treatment than with CPA. In that study, only 40% of the patients had testosterone levels within the normal range for cisgender women. It could be hypothesized that increasing the estrogen dose would result in a further decrease in testosterone levels. Even if true, a higher estrogen dose could increase treatment-associated complications. Alternatively, in regions were CPA is not available, treatment with GA should be considered, particularly for patients for whom testosterone suppression under spironolactone treatment is inadequate.

Discrepancies have been reported among studies that examined the effects of cross-sex hormone therapy on cardiovascular risk factors and morbidity in the transgender population (22). In contrast with the increased incidence of thromboembolic events that has been consistently found across studies, cardiovascular outcomes relative to the general population have not been uniform (23-25). Higher incidences of stroke, myocardial infarction, and cardiovascular mortality (26) compared with controls have been reported in trans women, particularly when high doses of ethinylestradiol (100 μg/day) and CPA (100 mg/day) were used (27). In contrast, other studies have shown similar (28) and even lower (26) cardiovascular mortality among trans women than in control populations. In our cohort, feminizing therapy was associated with an increase in weight and BMI, similar to other reports (21,29). The lower high-density lipoprotein cholesterol (HDLc) levels observed in patients treated with CPA compared to those treated with other anti-androgens is in accordance with the reports by Fung et al (8) and Gava et al (20), who compared CPA with spironolactone and GA, respectively.

The mechanism by which CPA negatively affects cardiovascular risk factors is unclear. A decrease in HDLc levels has been associated mainly with progestagens that have androgenic properties (30). This is clearly not the case with CPA. The possible role of the CPA-associated increase in prolactin levels in this setting is intriguing, but awaits direct testing. A large population-based study that used the Health Improvement Network database in the United Kingdom may be relevant to this context; an increase in the adjusted incidence rate ratio for cardiovascular diseases (31) was observed in male, but not female, patients with prolactinomas.

One limitation of our study is its retrospective design, which raises the possibility that the data collected from patients' files may be incomplete or inaccurate. An additional confounder is the relatively large proportion of trans women who were previously treated when first seen in our department. By performing a separate analysis in treatment-naïve patients, we tried to account for possible heterogeneity or bias present in the group of previously treated subjects. Finally, serum steroid levels were determined by means of chemiluminometric immunoassays and not state-of-the-art liquid chromatography mass spectrometry assays, whereupon the measured figures could be less accurate.

CONCLUSION

In conclusion, in a large cohort of transgender women who were receiving affirming hormone therapy, treatment with CPA was associated with hyperprolactinemia and a worse cardiovascular risk profile compared to treatment with spironolactone or GnRH analog. Whether these are clinically relevant differences that may affect cardiovascular outcomes remains to be determined.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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