LGBT Health
Volume 4, Number 5, 2017

DOI: 10.1089/lgbt.2016.0190

Transient Elevated Serum Prolactin in Trans Women Is Caused by Cyproterone Acetate Treatment

Justine Defreyne, MD,[1] Nienke Nota, MD,[2,3] Cecilia Pereira, MD,[4] Thomas Schreiner, MD, PhD,[5] Alessandra D. Fisher, MD, PhD,[6] Martin den Heijer, MD, PhD,[2,3] and Guy T'Sjoen, MD, PhD[1,7]

Abstract

Purpose: Hormone treatment in trans women in Europe usually consists of the administration of estrogens and antiandrogens, for example, cyproterone acetate (CPA). Mild serum prolactin elevations during follow-up are attributed to estrogen therapy. This analysis evaluates whether CPA contributes to the elevation of prolactin in trans women receiving gender affirming hormones.
Methods: This study is part of the endocrine part of the European Network for the Investigation of Gender Incongruence (ENIGI). Belgian data were selected for this substudy. Trans women who initiated gender affirming hormone treatment and underwent orchiectomy were prospectively evaluated. Trans women were treated with oral CPA 50 mg in combination with estrogen substitution. Postsurgery, estrogen was reinitiated in an unchanged dose. Sex steroids, gonadotropins, and prolactin were compared at baseline, pre- and postsurgery in patients receiving orchiectomy, and at baseline, 12, and 18 months in patients who did not undergo orchiectomy.
Results: One hundred and seven trans women participated in this analysis, with a mean age of 31.5 years. An increase in serum prolactin levels was seen in the group undergoing orchiectomy (23.72 μg/L) and not undergoing orchiectomy (23.05 μg/L) at the preoperative and 12-month visit, compared with baseline (9.42 μg/L, $P = 0.002$ and 9.94 μg/L, $P < 0.001$, respectively). After orchiectomy, a decline in prolactin levels (10.17 μg/L, $P < 0.001$) occurred.
Conclusions: CPA is likely to cause a temporary increase in serum prolactin, with prolactin levels returning to normal after orchiectomy and CPA discontinuation.

Keywords: clinical care, clinical research, gender dysphoria, gender identity, gender transition, transgender

Introduction

The transgender population that is actively seeking endocrine treatment is increasing.[1] However, transgender care is not a strong part of the medical curriculum and many physicians might not know how to interpret certain test results.[2] The current treatment regimens for trans women in Europe usually involve hormone therapy as well as gender affirming surgery. Hormone treatment in Europe generally consists of estrogens (estradiol valerate) and antiandrogens (cyproterone acetate, CPA).[3] In trans women, the use of an antiandrogen agent is necessary to suppress testosterone levels and decrease masculine secondary sexual characteristics, until orchiectomy has been performed. The World Professional Association for Transgender Health (WPATH) Standards of Care[4] requires at least 1 year of gender affirming hormonal therapy before orchiectomy can be performed, although exceptions are allowed in the case of medical contraindications or other compelling reasons. CPA is an androgen receptor antagonist that is a synthetic derivative of 17-OH progesterone. CPA reduces serum testosterone levels by acting as a direct antagonist on the peripheral androgen receptor and by its progestational and weak glucocorticoid activity that inhibits luteinizing hormone (LH) release.[5]

In the literature, elevations in serum prolactin levels are reported in up to 20% of trans women treated with estrogens and are sometimes associated with enlargement of the

[1]Department of Endocrinology, Ghent University Hospital, Ghent, Belgium.
Departments of [2]Endocrinology and [3]Internal Medicine, VU University Medical Center, Amsterdam, the Netherlands.
[4]Department of Endocrinology and Metabolism, San Juan de Dios Hospital, Santiago, Chile.
[5]Department of Endocrinology, Oslo University Hospital, Oslo, Norway.
[6]Sexual Medicine and Andrology Unit, Department of Experimental, Clinical and Biomedical Sciences, University of Florence, Florence, Italy.
[7]Center for Sexology and Gender, Ghent University Hospital, Ghent, Belgium.

pituitary gland.[6,7] Previously, this prolactin elevation was thought to be caused only by an estrogen-mediated decreased effectiveness of dopamine-mediated inhibition of prolactin secretion from the pituitary gland.[8,9] Articles concluding that not only estrogens but also CPA therapy may lead to an increase in serum prolactin levels are scarce[10,11] and prospective data are not available.

There have been case reports of prolactinomas occurring after long-term or high-dose estrogen therapy;[12–16] however, these findings were not reported in large cohorts of estrogen-treated transgender persons. As high levels of estrogen are known to enlarge the pituitary gland, physicians may fear prolonged high doses of estrogen causing prolactinomas in transgender persons. Therefore, the Clinical Practice guidelines of the Endocrine Society for the endocrine treatment of transgender persons recommend monitoring serum prolactin levels at baseline and then at least annually during the transition period and biannually thereafter,[7] whereas the Endocrine Society Clinical Practice Guidelines on pituitary incidentaloma[17] do not suggest assessing serum prolactin levels routinely.

Another common cause of drug-induced elevated serum prolactin is the use of certain antidepressive and antipsychotic agents. Mental health issues are frequently observed in transgender persons, and studies report that transgender adults are burdened by mental health concerns, including mood disorders, suicidal and nonsuicidal self-injury, and anxiety disorders.[18] There is a marked decrease in psychoneurotic distress (including anxiety, depression, interpersonal sensitivity, and hostility) after the initiation of gender affirming hormone therapy.[19]

Prolonged elevated prolactin levels can induce erectile dysfunction in men and loss of sexual desire in both sexes.[20] In cisgender women, hyperprolactinemia is usually reflected on the gonadotroph axis (hypogonadotropic hypogonadism), with alterations in gonadotropin-releasing hormone (GnRH) pulsatility, decreased levels of estradiol, and menstrual abnormalities. In trans women, these effects are not described because of the anatomical situation or the concurrent hormone treatment.[21] High levels of prolactin can cause galactorrhea, which is reported in 9%–14% of trans women receiving estrogen therapy.[22] However, the galactorrhea seen in trans women is usually very mild and transient.[23]

In this article, we wanted to verify whether CPA contributes to the elevation of prolactin in trans women receiving gender affirming hormones or if this effect can be attributed to the administration of estrogens. We also aimed to assess the clinical relevance of the observed elevation in serum prolactin levels.

Methods

This research is part of the ''European Network for the Investigation of Gender Incongruence'' (ENIGI), a collaboration of four major West European gender identity clinics (Amsterdam, Ghent, Florence, and Oslo), a study group created to obtain more transparency in diagnostics and treatment of gender dysphoria.

From February 15, 2010 to August 23, 2016, 187 trans women were included in the ENIGI study at the Ghent University Hospital in Belgium. All patients were 16 years old or older and underwent a standardized diagnostic procedure to confirm the diagnosis of gender incongruence/gender dysphoria before initiating treatment.[3] Patients were included in the ENIGI endocrine protocol when they started medical treatment for gender incongruence. Every patient was treated in accordance with the WPATH Standards of Care, Version 7.[4] Exclusion criteria were previous use of gender affirming hormones, insufficient knowledge of the native languages (Dutch or French), use of medication known to induce elevations of serum prolactin, and preexisting conditions known to cause hyperprolactinemia.[24] At the start of the study, patients received oral and written information about the ENIGI endocrine protocol by the physician. Written informed consent was obtained according to the Ethics Committee of the Ghent University Hospital, which approved all aspects of the study.

To analyze if a prolactin elevation occurred in trans women, we chose to include only those who had at least 1 year of follow-up, which resulted in 153 cases. The complete study protocol of the endocrine part of the ENIGI study can be found in Dekker et al.[3] The short-term follow-up currently consists of a visit at baseline and after 3, 6, 9, 12, 18, 24, and 36 months of gender affirming hormone therapy.

In trans women, the hormone treatment consists of CPA 50 mg in one daily dose, usually in combination with an oral estradiol agent, estradiol valerate (Progynova®, Bayer, Germany) 2 mg twice daily. In patients older than 45 years of age, estradiol was administered transdermally in the form of estradiol patches (Dermestril®, Besins, Belgium) in a dose of 100 μg/24 hours, to avoid the increased risk for thrombosis from oral estrogens caused by the first pass effect of the liver. In case of nontolerance, 1.5 mg of transdermal 17-β E2 gel twice daily (Oestrogel®, Besins) was given. After orchiectomy, estrogen alone is continued in an unchanged dose.

At baseline and during each follow-up visit, standard clinical measurements are assessed, including body weight and height, which is further detailed in Dekker et al.[3] Routine questioning on the occurrence of galactorrhea was included. These clinical measures are filled out on a standardized form.

Upon each visit, venous blood samples are obtained after overnight fasting. Competitive chemiluminescent immunoassays were run for estradiol (E170 Modular, Roche; LOQ 25 pg/mL), prolactin (IMMULITE® 2000XPi, Siemens; LOQ 0.5 ng/mL), serum testosterone (E170 Modular, Roche; LOQ 10 ng/dL), LH (E170 Modular, Roche; LOQ 0.1 mIU/mL), follicle-stimulating hormone (FSH) (E170 Modular, Roche; LOQ 0.1 mIU/mL), and sex hormone-binding globulin (SHBG) (E170 Modular, Roche; LOQ 0.35 nM). The free testosterone concentration was calculated from the total serum hormone concentration, serum SHBG, and serum albumin, using a validated equation derived from the mass action law. Tests for excluding macroprolactinemia (estimating the monomeric component after protein precipitation with polyethylene glycol) were performed in patients with prolactin levels >50 ng/mL. There were no patients with elevated prolactin levels due to macroprolactinemia.

We chose to analyze whether prolactin differed in patients undergoing orchiectomy (group A) versus patients not undergoing orchiectomy (group B). We decided to compare these two groups at different times. We compared the patients' prolactin at their first visit (M0), at their last visit preoperatively (group A) versus 12-month checkup (group B) and at the first postoperative visit (group A) versus 18-month

checkup (group B). We chose the 12 and 18 months visits because these correlated best with the last preoperative and first postoperative visit, respectively, as the mean time between initiation of therapy and orchiectomy was 17.5 months.

It has been described that serum prolactin can be correlated with body mass index (BMI) and/or age.[25] Because our patients' serum prolactin levels did not correlate to their BMI and age, we did not control for these parameters. Reference ranges for prolactin are 1–17 μg/L in cisgender men and 6–30 μg/L in cisgender women. In our laboratory, reference ranges for prolactin are shown according to one's legal sex, which can only be changed after gonadectomy. Hyperprolactinemia is defined as an elevated prolactin, above the reference ranges for one's sex. However, to the knowledge of the authors of this article, there are currently no reference ranges for prolactin levels in trans women.[26] Therefore, we decided to use cisgender male reference ranges for prolactin at the first visit and cisgender female reference ranges for prolactin after initiation of hormone therapy to define hyperprolactinemia.

Data were analyzed using IBM SPSS 23.0 software (IBM Corporation, Armonk, New York) and were verified for normal distribution using the Shapiro–Wilk test. Patients were divided into two groups: those who underwent orchiectomy (group A) and those who did not (yet) undergo orchiectomy (group B). Differences between groups were analyzed using unpaired *t*-tests (for normally distributed data) and Mann–Whitney U tests (for nonnormally distributed data). To evaluate prolactin differences over time, we performed one-way ANOVA with repeated measurements in case of normally distributed data; for nonnormally distributed data, we performed Friedman tests with post hoc analysis by means of Wilcoxon signed-rank tests with an applied Bonferroni correction.

Results

One hundred and fifty-three trans women had 1 year of follow-up (Fig. 1). Reasons for not including study patients in this analysis were dropout/lost to follow-up ($N=33$), use of medication known to induce elevation in serum prolactin levels ($N=10$; 8 because of selective serotonin reuptake inhibitors (SSRIs), 2 because of antihistamines), current conditions known to elevate serum prolactin levels ($N=0$), and patients in whom prolactin was not assessed during at least three visits ($N=3$). This resulted in 107 test cases. The mean age of participants in our study population was 31.5 years old with a mean BMI of 23.2 kg/m^2, which was not different between groups undergoing versus not undergoing orchiectomy. Regarding hormone status at baseline, our two groups were also quite similar (Table 1).

None of the trans women in our study population was diagnosed with prolactinoma during the investigated time period. None of our patients reported galactorrhea. During the investigated time period, 58 (54.2%) trans women underwent orchiectomy (group A), whereas 49 (45.8%) did not (yet) undergo orchiectomy (group B). Orchiectomy generally took place after 17.5 months, and at the same time, CPA was interrupted. After initiation of hormone therapy, we noticed an increase in serum estrogen levels and a decrease in serum testosterone and free testosterone levels

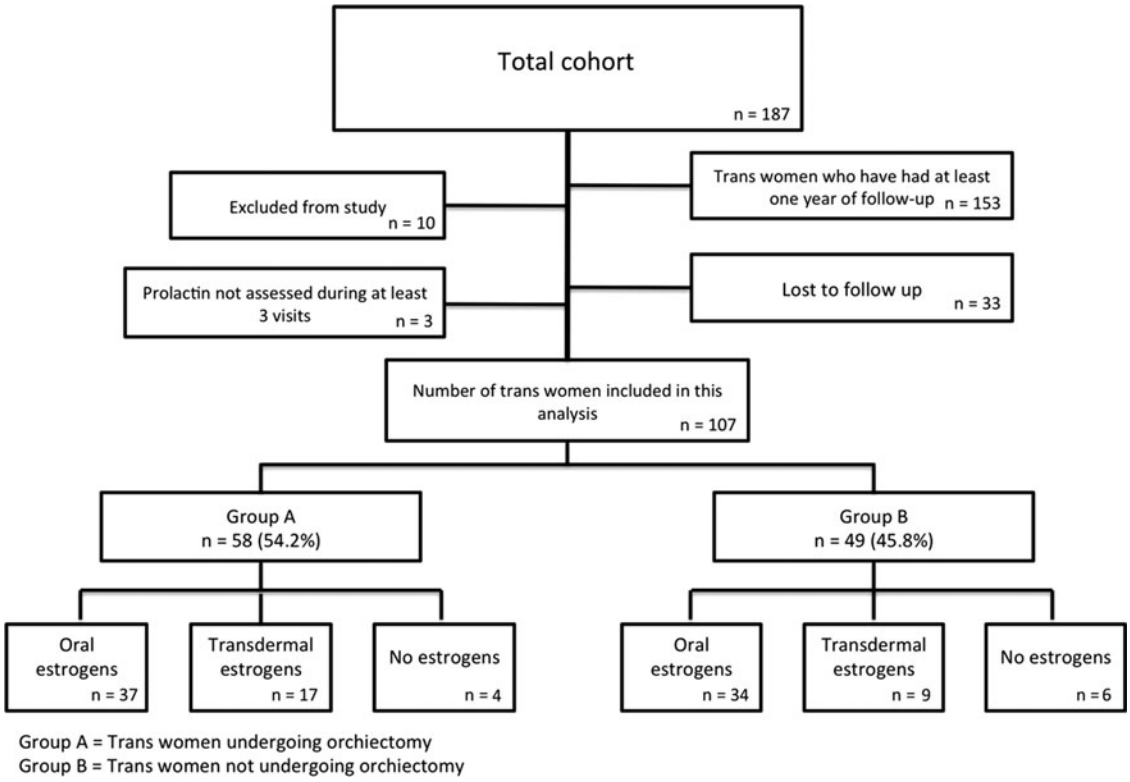

FIG. 1. Flowchart of the study population.

Table 1. Baseline Characteristics of the Study Population

	Total	*Group A*	*Group B*	P-*value*
Baseline characteristics				
Number of cases (%)	107 (100%)	58 (54.2%)	49 (45.8%)	
Age (years)	31.48 ± 12.35	32.35 ± 12.83	30.75 ± 11.95	0.444
Weight (kg)	73.42 ± 14.80	72.26 ± 12.43	73.72 ± 17.21	0.808
Height (m)	1.779 [1.732–1.823]	1.773 [1.720–1.819]	1.791 [1.751–1.827]	0.579
BMI (kg/m^2)	23.22 ± 4.55	23.26 ± 3.70	23.12 ± 5.38	0.669
Type of estrogen therapy				
Oral	71 (66.4%)	37 (63.8%)	34 (69.3%)	0.352
Transdermal	26 (24.3%)	17 (29.3%)	9 (18.3%)	0.424
Baseline laboratory				
Prolactin (μg/L)	9.65 ± 9.21	9.42 ± 8.64	9.94 ± 9.94	0.785
LH (U/L)	4.85 ± 2.13	4.78 ± 2.19	4.87 ± 2.09	0.599
FSH (U/L)	4.48 ± 4.17	4.86 ± 4.50	4.12 ± 3.84	0.930
E2 (ng/L)	29.91 ± 11.80	30.35 ± 9.71	29.37 ± 13.87	0.853
SHBG (ng/dL)	38.85 ± 18.15	39.65 ± 16.27	38.31 ± 20.17	0.509
Testosterone (ng/dL)	501.25 [390.03–625.93]	543.30 [417.60–629.70]	475.30 [363.05–617.13]	0.137
FT (ng/dL)	10.2 [8.51–12.00]	10.30 [8.56–12.00]	10.05 [8.05–11.45]	0.282

Group A is defined as patients undergoing orchiectomy, group B is defined as patients not undergoing orchiectomy. Tests for normality were performed by Shapiro–Wilk. For normally distributed values, mean values ± standard deviations are shown. For values that are not normally distributed, median values and IQR [P25 and P75] are shown, unless otherwise specified. For normally distributed values, unpaired Student's *t* test was used to quantify differences between both groups. For nonparametric values, the Mann–Whitney U test was performed, and for categorical variables, we used the Chi-square test.

LH, luteinizing hormone; FSH, follicle-stimulating hormone; E2, estradiol; SHBG, sex hormone-binding globulin; FT, free testosterone.

upon the second visit in both groups. We also noticed a suppression of serum LH and FSH levels after initiation of therapy. In group A, there was an increase in serum LH and FSH after orchiectomy and discontinuation of CPA therapy (Fig. 2).

We noticed higher levels of serum estrogen in groups with transdermal estrogen application, compared with groups on oral administration of estrogens ($P < 0.001$ for preoperative values, $P = 0.003$ postorchiectomy, $P = 0.028$ at month 12 [M12], and $P < 0.001$ at month 18 [M18]) (data not shown). There was no difference in the serum estradiol values before and after orchiectomy or between the 12- and 18-month visits. However, we did notice a difference in the serum LH and FSH levels before and after orchiectomy, whereas there was no difference in the group not undergoing orchiectomy. In the study population, mean serum prolactin at baseline was 9.65 ± 9.21 μg/L, and this was similar among both groups (Table 1).

Seven patients (6.6%) had an elevated prolactin at baseline, with a maximum reported value of 72.40 μg/L. In all of these patients, this elevation of serum prolactin at baseline decreased after their first visit. We noticed an increase in serum prolactin after 12 months of hormone therapy and at the preoperative visit in both groups, compared with baseline ($P < 0.001$ and $P = 0.002$, respectively), (as shown in Fig. 3 and Table 2). We assessed whether prolactin levels were different in group A versus group B at different times. After orchiectomy and discontinuation of CPA, we noticed a return to baseline OF prolactin levels ($P < 0.001$), whereas we also described a decline in serum prolactin levels in group B ($P < 0.001$), although the decline was not as severe as in group A.

At baseline and preorchiectomy and at the 12-month visit, we found no difference in serum prolactin levels in group A versus group B, whereas the postoperative serum prolactin levels (group A) were lower than the 18-month serum prolactin levels (group B) ($P = 0.008$) (Table 3). In addition, we observed a positive relationship between serum estradiol levels and serum prolactin levels after 12 months of gender affirming hormone therapy and preorchiectomy (Spearman's rho 0.348, $P < 0.001$). After orchiectomy and after 18 months of gender affirming hormone therapy, we no longer found a correlation between serum estradiol levels and serum prolactin levels.

Discussion

In this prospective analysis, we assessed whether mild elevated serum prolactin in trans women is associated with use of CPA. We described a decline in serum prolactin in the first postoperative laboratory analysis in the group of trans women undergoing orchiectomy. We suggest that this is caused by stopping the CPA, unrelated to the administration of estrogens, as estrogens are continued with an unchanged dose after orchiectomy and the estradiol levels are not significantly lower.

The mechanism behind the CPA- induced increase in serum prolactin is not well understood. One suggested mechanism is drug-induced secondary hypogonadism, with CPA suppressing the pulsatile GnRH release, resulting in low LH and FSH levels, which may lead to elevated serum prolactin levels.[27] Other articles reporting progesterone-induced hyperprolactinemia are scarce[28,29] and also support the hypothesis of a progesterone-mediated suppressing of the GnRH release, in addition to a progesterone-induced reduction of hypothalamic dopamine. However, these articles do not specify which type of progesterone caused the documented elevation in serum prolactin levels.

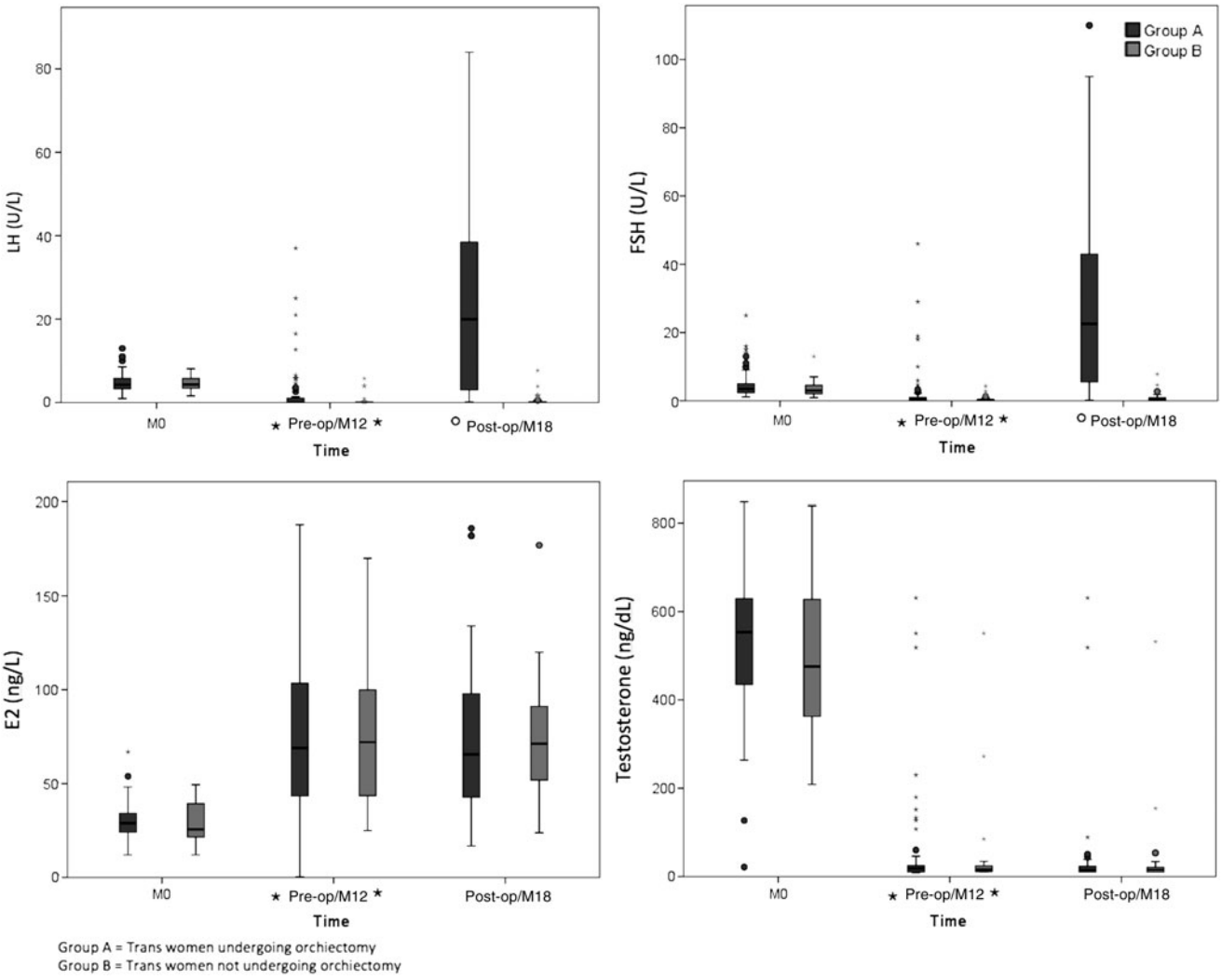

FIG. 2. Effects of hormone therapy in trans women. Figure 2 shows the evolution of serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogen (E2), and testosterone levels in time in trans women undergoing versus not undergoing orchiectomy during the first visit (1), preoperative or at the 12-month visit (Preop/M12) (2) and postoperative or after 18 months (Postop/M18) (3). The symbol * indicates a significant difference ($P < 0.05$) between the first and second visit, ° indicates a significant difference ($P < 0.05$) between the first and third visit.

We also described low serum LH and FSH levels after initiation of hormone therapy, which increased again after orchiectomy, whereas there was no increase in the trans women who did not undergo orchiectomy. As all patients were treated with the same dosage of estrogens (which is supraphysiological in menopausal women), we hypothesize that the lack of free testosterone may be a causal factor for the higher LH and FSH levels, when these are no longer suppressed by CPA. We hypothesize that estrogens cannot (sufficiently) suppress LH and FSH levels in trans women. The groups presented in this study are too small to test this hypothesis at this point and further research may be needed.

As other studies suggest, an elevation in prolactin levels during estrogen treatment may occur. Asscheman et al.[6] followed 214 trans women treated with ethinyl estradiol (100 μg/day) and CPA (100 mg/day). They documented an elevated serum prolactin above normal in all subjects (>30 μg/L), which decreased by more than 50% spontaneously or after dose reduction of oral estrogens. In addition, they observed a higher incidence of prolactin levels greater than 1000 mU/L in trans women with high doses of estrogens and advanced age at the start of treatment. Therefore, they concluded that estrogen administration in trans women causes elevations in serum prolactin levels. Gooren et al.[30] followed 142 trans women, treated with CPA 100 mg/day. After 3 months, ethinyl estradiol 100 μg/day was added to the treatment. They observed a rise in serum prolactin levels during the first 15 months of hormone treatment, which was already apparent after 3 months of therapy with CPA alone, but increased further after adding ethinyl estradiol 100 μg/day.

In our study population, we noticed higher serum estrogen levels in patients treated with transdermal estrogens compared with those taking oral estrogen therapy, which did not result in higher levels of serum prolactin. We described a decline in serum prolactin levels in trans women who underwent orchiectomy and stopped CPA, whereas in the

FIG. 3. Serum prolactin levels in trans women with or without orchiectomy. Boxplots for the evolution of prolactin levels (mean ± SD) in time in trans women with (group A) versus without (group B) orchiectomy during the first visit (1), preoperative or at the 12 month visit (2) and postoperative or after 18 months (3). The symbol * indicates a significant difference ($P < 0.05$) between the first and second visit, ° indicates a significant difference ($P < 0.05$) between the second and third visit.

trans women who were receiving hormone treatment but did not undergo orchiectomy, the increase in serum prolactin levels induced by hormone therapy persisted. After orchiectomy, antiandrogens were stopped in our study protocol, whereas trans women not undergoing orchiectomy continued both estrogens and antiandrogens. Therefore, we conclude that the elevated prolactin in our trans women ($N = 19$, 17.8%) could be attributed to the administration of CPA, rather than the estrogen treatment.

These findings have previously been documented by Sofer et al.,[10] Nota et al.,[11] and Gava et al.[31] Sofer et al.[10] described 124 trans women who were followed for 18 months. Estrogen treatment was titrated to achieve estradiol levels in the normal premenopausal range. Antiandrogenic treatment consisted of GnRH-analogs (10.2%), CPA (70%), or spironolactone (17.6%). They noticed an increase in prolactin levels compared with baseline, which was already apparent 3 months after initiation of CPA treatment. By 18 months, the mean increase in serum prolactin levels in the group receiving CPA treatment was greater than the increase in serum prolactin levels in the group taking spironolactone. They observed no increase in serum prolactin levels in patients treated with GnRH-analogs, but the number of patients in this group was too small for analysis. Gava et al.[31] followed 40 trans women for 1 year. Twenty trans women were treated with CPA 50 mg daily and transdermal estradiol 1 mg or 2 mg daily, whereas the other twenty trans women received leuprolide acetate 3.75 mg

TABLE 2. COMPARATIVE DATA ON TRANS WOMEN WITH OR WITHOUT ORCHIECTOMY

	Group A			*Group B*			*Group A versus group B*	
	Preorchiectomy	*Postorchiectomy*	P-*value*	*Month 12 (no orchiectomy)*	*Month 18 (no orchiectomy)*	P-*value*	*Preorchiectomy versus M12* (P-*value*)	*Postorchiectomy versus M18* (P-*value*)
Number of cases (%)	35 (32.7%)	36 (33.6%)		30 (28.0%)	20 (18.7%)			
Weight (kg)	73.0 [68.0–78.5]	74.00 [62.25–83.75]	0.546	76.0 [63.0–88.5]	74.90 [63.73–86.38]	0.231	0.865	0.580
BMI (kg/m^2)	23.35 [22.16–26.00]	23.38 [21.83–26.71]	0.690	23.41 [20.15–27.87]	23.39 [19.92–28.92]	0.469	0.604	0.293
Prolactin (µg/L)	23.72 ± 13.52	10.17 ± 5.64	<0.001*	23.05 [13.38–29.85]	14.10 [11.78–18.65]	<0.001*	0.579	0.008*
LH (U/L)	2.05 ± 3.95	20.00 [5.7–39.75]	<0.001*	0.71 ± 1.55	1.01 ± 1.85	1.000	0.042*	<0.001*
FSH (U/L)	1.62 ± 3.69	33.21 ± 32.56	<0.001*	0.59 ± 0.95	1.15 ± 1.92	0.328	0.061	<0.001*
E2 (ng/L)								
Total	148.79 ± 265.44	102.16 ± 146.83	0.282	101.61 ± 101.98	107.16 ± 147.72	0.457	0.979	0.701
Oral	64.51 ± 33.45	63.38 ± 46.14	0.813	73.86 ± 34.55	63.013 ± 24.24	0.210	0.708	0.908
Transdermal	296.73 ± 367.53	166.91 ± 188.85	0.120	763.34 ± 311.64	272.96 ± 217.82	0.713	0.428	0.234
SHBG (nM)	47.0 [27.1–70.1]	50.08 ± 25.68	<0.001*	46.70 [31.68–36.03]	43.70 [35.86–48.88]	0.243	0.685	0.031*
Testosterone (ng/dL)	81.27 ± 142.45	53.97 ± 129.69	0.023*	58.47 ± 113.14	54.31 ± 116.95	0.804	0.483	0.966
FT (ng/dL)	4.90 ± 14.76	3.72 ± 16.89	0.271	1.01 ± 2.36	0.86 ± 1.78	0.244	0.133	0.465

Group A is defined as patients undergoing orchiectomy, group B is defined as patients not undergoing orchiectomy. Tests for normality were performed by Shapiro–Wilk. For normally distributed values, mean values ± standard deviations are shown. For values that are not normally distributed, median values and IQR [P25 and P75] are shown, unless otherwise specified. For normally distributed values, unpaired Student's *t* test was used to quantify differences between both groups. For nonparametric values, the Mann–Whitney U test was performed, and for categorical variables, we used the Chi-square test. Statistically significant differences between both groups are indicated by $^*P < 0.05$.

TABLE 3. COMPARATIVE DATA ON SERUM PROLACTIN LEVELS IN TRANS WOMEN WITH (GROUP A) OR WITHOUT (GROUP B) ORCHIECTOMY

	Group A				*Group B*				*Group A versus group B*	
	Baseline	*Preorchiectomy*	*Postorchiectomy*	*P-value*	*Baseline*	*Month 12 (no orchiectomy)*	*Month 18 (no orchiectomy)*	*P-value*	*Preorchiectomy versus M12 (P-value)*	*Postorchiectomy versus M18 (P-value)*
Prolactin (μg/L)	9.42 ± 8.64	23.72 ± 13.52	10.17 ± 5.64	<0.001*	7.84 [6.25–9.80]	23.05 [13.38–29.85]	14.10 [11.78–18.65]	<0.001*	0.579	0.008*

Group A is defined as patients undergoing orchiectomy, group B is defined as patients not undergoing orchiectomy. Tests for normality were performed by Shapiro–Wilk. For normally distributed values, mean values ± standard deviations are shown. For values that are not normally distributed, median values and IQR [P25 and P75] are shown, unless otherwise specified. For normally distributed values, unpaired Student's *t* test was used to quantify differences between both groups. For nonparametric values, the Mann–Whitney U test was performed. To evaluate the difference in serum prolactin levels, a multivariate ANOVA analysis was used for normally distributed values and a Friedman analysis was used for nonparametric values. Statistically significant differences between both groups are indicated by $^*P < 0.05$.

(a GnRH-analog) intramuscularly, monthly, with the same estrogen dose. After 1 year, they observed an increase in serum prolactin levels (compared with baseline) in the group receiving CPA, whereas there was no difference in serum prolactin levels in the group treated with leuprolide acetate. These findings also suggest that the observed elevation in serum prolactin levels in trans women can be attributed to the CPA treatment.

In three case reports describing trans women with prolactinoma, estrogen doses were not controlled by a physician, with patients surpassing the maximum doses.[6,14,15] However, some case reports do mention patients adhering to adequate hormone doses presenting with hyperprolactinemia.[12,13,16] These patients presented with symptoms suggestive of hyperprolactinemia, including mastodynia, hemicranial migraine, headaches, asthenia, galactorrhea double vision, right-sided third nerve palsy, and generalized weight gain. Magnetic resonance imaging (MRI) revealed a macroprolactinoma. Bunck et al.[13] reported one asymptomatic patient adhering to adequate hormone doses, whose serum prolactin levels increased after 15 years of hormone therapy (CPA 50 mg twice a day plus ethinyl estradiol 50 μg twice a day), with a 8 mm diameter focal hypointense lesion of the pituitary gland on MRI. Therefore, we suggest that hormone therapy in trans women is safe and does not induce prolactinoma if the patient adheres to the prescription dose.

During the first visit with the endocrinologist, there might be an elevation in serum prolactin levels, which was the case in 7.3% of our participants at one point during the investigated time period. This elevation is probably caused by the stress of starting the transitioning process and experiencing the new medical environment. Therefore, it is not clinically relevant. As the CPA-induced elevation in serum prolactin is only moderate without clinical implications in our study population, we advise against measuring serum prolactin levels at baseline and serially, in contrast with the Endocrine Society Clinical Practice Guidelines on the endocrine treatment of transgender persons, which suggest monitoring at baseline and annually.[7] However, if the patient presents with symptoms (headache, blurry vision, galactorrhea, etc.) or biochemical signs (e.g., baseline low serum testosterone) suggestive of prolactinoma, further diagnostic steps should be taken; serum prolactin should be assessed and a brain MRI scan can be planned.

As for the strengths of this study, this is the first prospective analysis, to the knowledge of the authors of this article, that suggests that CPA can induce elevated serum prolactin, as the only published article mentioning CPA-induced elevated serum prolactin levels in trans women was a retrospective analysis.[11] In this study, we excluded patients using certain medications known to induce elevations in serum prolactin levels and all of our patients underwent the same hormone treatment, with the only variation being the administration mode of the estrogens. Patients' variables were measured during standardized visits.

Some limitations of this study should be considered. As CPA is not currently approved by the Food and Drug Administration in the United States, the results of this analysis cannot be extrapolated to the entire transgender population receiving antitestosterone treatment. Other antiandrogen agents (e.g., spironolactone or GnRH-analogs) have

not been included in this analysis. In addition, we were not able to perform multivariate analyses, as our data did not match all assumptions to proceed with multivariate analyses.

Conclusion

It is important to know how to interpret certain laboratory results in transgender persons seeking physician-controlled hormone therapy. The endocrinologist should be aware that CPA can induce mild serum prolactin elevations in trans women. However, as long as this elevation is mild and the patient does not present with symptoms suggestive of hyperprolactinemia, we suggest that further diagnostic actions are not needed. It is our opinion that our findings may lead to an improvement in the follow-up of trans women taking CPA. Unless the patient presents symptoms or biochemical signs suggestive of prolactinoma, serially monitoring serum prolactin levels is not necessary in trans women, as the observed increase in serum prolactin levels in trans women is transient and not clinically relevant. Not annually assessing serum prolactin levels may cause less concerns and stress in both patients and hormone prescribing physicians. In addition, it may lead to less laboratory and technical imaging costs.

Acknowledgments

We thank all endocrinology residents who have made a valuable contribution to the ENIGI study: Roef Greet, Boer Mirra, Carpentier Marijn, Van Huffel Liesbeth, Vandewalle Sara, Moernaut Loes, Vermeersch Sabine, Aers Xavier-Philippe, Vereecke Gert-Jan, Verroken Charlotte, Van Caenegem Eva, Wierckx Katrien, Versele Emmanuelle, and Vantomme Bram. We also thank Corneille Jocelyne, for proofreading the article and our study nurses, Toye Kaatje and Kestens Natascha, for handling the extensive administration of the study. In addition, we thank all participants in the ENIGI study protocol.

J. Defreyne was funded by an FWO (Fonds Wetenschappelijk Onderzoek) grant: FWO TBM T001816 N.

Author Disclosure Statement

Guy T'Sjoen received scientific grants from Bayer Schering Pharma AG. No competing financial interests exist for any other authors.

References

1. Wylie K, Knudson G, Khan SI, et al.: Serving transgender people: Clinical care considerations and service delivery models in transgender health. Lancet 2016;388:401–411.
2. Wilczynski C, Emanuele MA: Treating a transgender patient: Overview of the guidelines. Postgrad Med 2014;126: 121–128.
3. Dekker MJ, Wierckx K, Van Caenegem E, et al.: A European Network for the Investigation of Gender Incongruence: Endocrine part. J Sex Med 2016;13:994–999.
4. Coleman E, Bockting W, Botzer M, et al.: Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. Int J Transgend 2012;13: 165–232.
5. Wierckx K, Mueller S, Weyers S, et al.: Long-term evaluation of cross-sex hormone treatment in transsexual persons. J Sex Med 2012;9:2641–2651.
6. Asscheman H, Gooren LJ, Assies J, et al.: Prolactin levels and pituitary enlargement in hormone-treated male-to-female transsexuals. Clin Endocrinol (Oxf) 1988;28:583–588.
7. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al.: Endocrine treatment of transsexual persons: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2009;94:3132–3154.
8. Gudelsky GA, Nansel DD, Porter JC: Role of estrogen in the dopaminergic control of prolactin secretion. Endocrinology 1981;108:440–444.
9. Pérez RL, Machiavelli GA, Romano MI, Burdman JA: Prolactin release, oestrogens and proliferation of prolactin-secreting cells in the anterior pituitary gland of adult male rats. J Endocrinol 1986;108:399–403.
10. Sofer Y, Sharon N, Yaron M, et al.: High prolactin levels in transsexual women are related to the anti-androgen treatment modality. [Abstract; Poster 0111] Poster session presented at the Endocrine Society's 96th Annual Meeting and Expo, Chicago, June 21–24, 2014.
11. Nota NM, Dekker MJ, Klaver M, et al.: Prolactin levels during short- and long-term cross-sex hormone treatment: An observational study in transgender persons. Andrologia 2016 [Epub ahead of print]; DOI: 10.1111/and.12666.
12. Serri O, Noiseux D, Robert F, Hardy J: Lactotroph hyperplasia in an estrogen treated male-to-female transsexual patient. J Clin Endocrinol Metab 1996;81:3177–3179.
13. Bunck MC, Debono M, Giltay EJ, et al.: Autonomous prolactin secretion in two male-to-female transgender patients using conventional oestrogen dosages. BMJ Case Rep 2009;2009. pii: bcr02.2009.1589.
14. Cunha FS, Domenice S, Câmara VL, et al.: Diagnosis of prolactinoma in two male-to-female transsexual subjects following high-dose cross-sex hormone therapy. Andrologia 2015;47:680–684.
15. Gooren LJ, Assies J, Asscheman H, et al.: Estrogen-induced prolactinoma in a man. J Clin Endocrinol Metab 1988; 66:444–446.
16. García-Malpartida K, Martín-Gorgojo A, Rocha M, et al.: Prolactinoma induced by estrogen and cyproterone acetate in a male-to-female transsexual. Fertil Steril 2010;94: 1097.e13–e15.
17. Freda PU, Beckers AM, Katznelson L, et al.: Pituitary Incidentaloma: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2011;96:894–904.
18. Reisner SL, Poteat T, Keatley J, et al.: Global health burden and needs of transgender populations: A review. Lancet 2016;388:412–436.
19. Heylens G, Verroken C, De Cock S, et al.: Effects of different steps in gender reassignment therapy on psychopathology: A prospective study of persons with a gender identity disorder. J Sex Med 2014;11:119–126.
20. Corona G, Mannucci E, Fisher AD, et al.: Effect of hyperprolactinemia in male patients consulting for sexual dysfunction. J Sex Med 2007;4:1485–1493.
21. Touraine P, Plu-Bureau G, Beji C, et al.: Long-term follow-up of 246 hyperprolactinemic patients. Acta Obstet Gynecol Scand 2001;80:162–168.
22. Oriel KA: Clinical update: Medical care of transsexual patients. J Gay Lesb Med Assoc 2000;4:185–194.

23. Molitch ME: Medication-induced hyperprolactinemia. Mayo Clin Proc 2005;80:1050–1057.
24. Torre DL, Falorni A: Pharmacological causes of hyperprolactinemia. Ther Clin Risk Manag 2007;3:929–951.
25. Roelfsema F, Pijl H, Keenan DM, Veldhuis JD: Prolactin secretion in healthy adults is determined by gender, age and body mass index. PLoS One 2012;7:e31305.
26. Roberts TK, Kraft CS, French D, et al.: Interpreting laboratory results in transgender patients on hormone therapy. Am J Med 2014;127:159–162.
27. Futterweit W: Endocrine therapy of transsexualism and potential complications of long-term treatment. Arch Sex Behav 1998;27:209–226.
28. Rakoff JS, Rigg LA, Yen SS: The impairment of progesterone-induced pituitary release of prolactin and gonadotropin in patients with hypothalamic chronic anovulation. Am J Obstet Gynecol 1978;130:807–812.
29. Rakoff JS, Yen SS: Progesterone induced acute release of prolactin in estrogen primed ovariectomized women. J Clin Endocrinol Metab 1978;47:918–921.
30. Gooren LJ, Harmsen-Louman W, van Kessel H: Follow-up of prolactin levels in long-term oestrogen-treated male-to-female transsexuals with regard to prolactinoma induction. Clin Endocrinol (Oxf) 1985;22:201–207.
31. Gava G, Cerpolini S, Martelli V, et al.: Cyproterone acetate vs leuprolide acetate in combination with transdermal oestradiol in transwomen: A comparison of safety and effectiveness. Clin Endocrinol (Oxf) 2016;85:239–246.

Address correspondence to:
Justine Defreyne, MD
Department of Endocrinology
Ghent University Hospital
De Pintelaan 185
Ghent 9000
Belgium

E-mail: justine.defreyne@ugent.be