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Original Article

SERUM HORMONE CONCENTRATIONS IN TRANSGENDER INDIVIDUALS RECEIVING GENDER-AFFIRMING HORMONE THERAPY: A LONGITUDINAL RETROSPECTIVE COHORT STUDY

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ABSTRACT

Objective: To examine the association of various gender-affirming hormone therapy regimens with blood sex hormone concentrations in transgender individuals.
Methods: This retrospective study included transgender people receiving gender-affirming hormone therapy between January 2000 and September 2018. Data on patient demographics, laboratory values, and hormone dose and frequency were collected. Nonparametric tests and linear regression analyses were used to identify factors associated with serum hormone concentrations.
Results: Overall, 196 subjects (134 transgender women and 62 transgender men), with a total of 941 clinical visits, were included in this study. Transgender men receiving transdermal testosterone had a significantly lower median concentration of serum total testosterone when compared with those receiving injectable preparations (326.0 ng/dL vs 524.5 ng/dL, respectively, $P = .018$). Serum total estradiol concentrations in the transgender women were higher in those receiving intramuscular estrogen compared with those receiving oral and transdermal estrogen (366.0 pg/mL vs 102.0 pg/mL vs 70.8 pg/mL, respectively, $P < .001$). A dose-dependent increase in the hormone levels was observed for oral estradiol ($P < .001$) and injectable testosterone ($P = .018$) but not for intramuscular and transdermal estradiol. Older age and a history of gonadectomy in both the transgender men and women were associated with significantly higher concentrations of serum gender-affirming sex hormones.
Conclusion: In the transgender men, all routes and formulations of testosterone appeared to be equally effective in achieving concentrations in the male range. The intramuscular injections of estradiol resulted in the highest serum concentrations of estradiol, whereas transdermal estradiol resulted in the lowest concentration. There was positive relationship between both oral estradiol and injectable testosterone dose and serum sex hormone concentrations in transgender people receiving GAHT.
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Introduction

Many transgender and gender nonbinary (TGGNB) people receive gender-affirming hormone therapy (GAHT) to align their gender identity with their secondary sexual characteristics.[1] Other ways in which TGGNB people affirm their gender identity include social transitioning, voice therapy, and gender affirmation surgery.[2] The goal of GAHT is to closely mirror the sex steroid concentrations

Abbreviations: BMI, body mass index; GAHT, gender-affirming hormone therapy; IQR, interquartile range; SHBG, sex hormone–binding globulin; TGGNB, transgender and gender nonbinary; VTE, venous thromboembolism.

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found within the reference range of the affirmed gender.[3] Over a period of 2 to 3 years, GAHT typically results in physical changes expected for the affirmed gender. In transfeminine individuals, GAHT leads to an increased volume of breast tissue, redistribution of subcutaneous fat, and changes in the skin and hair. In transmasculine individuals, GAHT causes deepening of the voice, an increase in muscle mass, redistribution of subcutaneous fat, and increased facial and body hair.[4-6]

Although GAHT is considered safe under medical supervision,[7-11] evidence indicates that TGGNB people may experience potential adverse effects, such as polycythemia secondary to testosterone administration and venous thromboembolism (VTE) owing to estrogen use.[9,12] The Endocrine Society's guidelines suggest monitoring and adjusting hormone medications to maintain the hormone levels within the desired sex-specific physiologic range of the affirmed gender to minimize these risks.[1,2] However, published data on hormone dosing and corresponding blood concentrations are limited in the literature.[7,13,14] It is important for clinicians to have a better understanding of the impact of the dose of hormone preparation, route of administration, and frequency of dosing on blood hormone levels to ensure the safety of GAHT regimens.[11,15]

The purpose of this study was to examine the effect of various GAHT regimens on blood hormone concentrations in transfeminine and transmasculine individuals receiving care at a single center. We included all subjects who were receiving GAHT over a 15-year period and collected data on the details of their hormone regimen and hormone concentrations.

Methods

Study Population

This was a retrospective study of patients identifying as transgender who received GAHT at the Emory Clinic and Emory University Hospital between January 1, 2000, and September 6, 2018. The protocol for this study was approved by the Emory Institutional Review Board. All the subjects were treated in accordance with the Endocrine Society's clinical practice guidelines for the treatment of gender-dysphoric/gender-incongruent people.[2,11] Transgender women received estrogen in various types of preparations, which were administered via oral, intramuscular, and transdermal routes. Some transgender women also received testosterone-lowering agents, such as spironolactone. Transgender men were prescribed testosterone, which, in most instances, was administered as an intramuscular injection.

Data Collection

Information collected from medical records included patient demographic characteristics (gender identity, current age, age at hormone initiation, and race/ethnicity), clinical and general health-related variables (body mass index [BMI] and history of gonadectomy), and details of GAHT (medication type, dose, frequency, and route of administration). Transdermal preparations of sex steroid hormones included patches and gels. All the subjects underwent regular hormone testing during outpatient visits. Serum total estradiol level was determined using tandem mass spectrometry as a send-out test to ARUP Laboratories, and testosterone analyses were performed using tandem mass spectrometry at Emory Medical Laboratories in both the transgender men and women. Based on the guidelines of the Endocrine Society, blood tests were performed every 3 to 6 months in subjects initiating on GAHT and approximately 6 to 12 months in subjects who had already been on a stable regimen 2 years after the initiation of GAHT. The dates and results of the hormone level tests were obtained from the laboratory reports.

Statistical Analysis

The data were analyzed using SPSS Statistics version 20 (IBM Corp). Descriptive statistics was used to summarize the demographic data. Means ± SDs and medians ± interquartile ranges (IQRs) were used to describe the distributions of continuous variables, while categorical variables were characterized in terms of frequencies and proportions. Differences between the groups were compared using the X^2 test for categorical variables. Owing to skewed distributions of hormone levels, nonparametric Kruskal-Wallis or Mann-Whitney *U* test was used to compare the serum concentrations of testosterone across the categories of transgender men and estradiol concentrations across the categories of transgender women. In addition, simple linear regression models were used to examine the relationship between GAHT dose and serum sex hormone levels. Dose-response analyses were performed separately for each route of hormone administration. A 2-sided *P* value of <.05 was considered as evidence of statistical significance.

Results

Study Subjects

The study dataset included 244 patients; however, 48 patients had missing data, thus leaving 196 subjects in the final cohort. These subjects included 134 transgender women and 62 transgender men. After excluding visits in which subjects were not on GAHT, the outpatient clinic visits were divided into 2 groups: 647 transfeminine and 294 transmasculine hormone treatment visits (Fig. 1).

Table 1 presents the baseline demographic characteristics of the study participants. The transgender men were younger than the transgender women, with 31% (19/62) versus 11% (15/134) aged <21 years and 24% (15/62) versus 43% (57/134) aged ≥35 years in the 2 respective groups ($P = .001$). The race/ethnicity distributions (60% non-Hispanic Whites in both the groups, $P = .927$) and percentages of subjects undergoing gonadectomy in the transgender women and men were similar (21.6% vs 29.0%, $P = .283$). Compared with the transgender women, the transgender men included a greater proportion of participants with a BMI of ≥30 kg/m^2 (42% [26/62] vs 30% [40/134]), but the difference was not statistically significant ($P = .095$).

Factors Influencing Blood Sex Steroid Hormone Concentrations

As shown in Table 2, more advanced age and a history of gonadectomy were associated with higher sex hormone levels in both transgender men and women. For example, the median serum testosterone concentrations in transgender men who did and did not undergo gonadectomy were 603 ng/dL (IQR: 437-936) and 481 ng/dL (IQR: 276-686), respectively ($P = .030$). The corresponding median (IQR) estradiol concentrations were 186 pg/mL (114-359) for transgender women who underwent gonadectomy and 116 pg/mL (63-276) for transgender women who did not undergo the procedure ($P < .001$). There was also a statistically significant difference in the serum estradiol concentrations in transgender women on antiandrogen therapy compared with the concentrations in transgender women not taking antiandrogen therapy (120 pg/mL vs 163 pg/mL, $P = .006$).

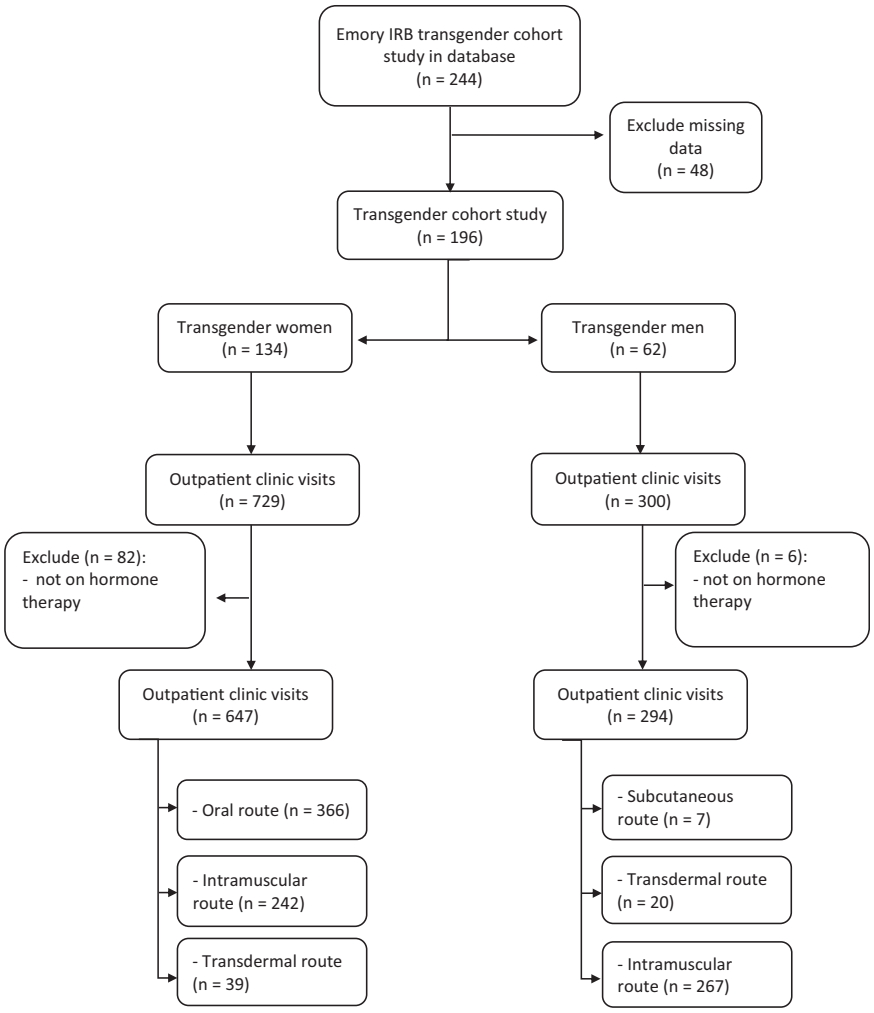

Fig. 1. Flow diagram of study participants. *IRB* = institutional review board.

Table 1
Characteristics of Transgender Subjects at Cohort Entry

Participant characteristics	Transgender men (n = 62) n (%)	Transgender women (n = 134) n (%)	*P* value[a]
Age (y)			
<21	19 (30.6)	15 (11.2)	.001
21-34	28 (45.2)	62 (46.3)	
≥35	15 (24.2)	57 (42.5)	
BMI category (kg/m^2)			
<25 (normal/underweight)	22 (35.5)	63 (47.0)	.092
25-29.9 (overweight)	14 (22.6)	27 (20.1)	
≥30 (obese)	26 (41.9)	44 (32.8)	
Race/ethnicity			
Non-Hispanic White	37 (59.7)	80 (59.7)	.927
African American	11 (17.7)	27 (20.1)	
Other/unknown	14 (22.6)	26 (20.1)	
History of gonadectomy			
Yes	18 (29.0)	29 (21.6)	.283
No	44 (31.0)	105 (78.4)	

Abbreviations: BMI = body mass index.
[a] X^2 test

Gender-Affirming Hormone Therapy Regimens

The majority of the blood test values came from transgender men taking injectable testosterone, with approximately half of the transgender men using an equivalent dose of >75 mg/week (Table 3). Injectable testosterone represented both intramuscular testosterone in 97.5% (267/274) of the observations and subcutaneous testosterone in 2.5%. Transgender men receiving transdermal GAHT had a significantly lower median concentration of total serum testosterone compared with those who were receiving injectable preparations (326.0 ng/dL vs 524.5 ng/dL, respectively). Higher doses of injectable testosterone were associated with higher hormone concentrations, with median (IQR) levels of 442.5 (257.5-644.3) for ≤50 mg/week, 483.0 (317.8-645.3) for 51 to 75 mg/week, and 588.0 (380.3-840.3) for >75 mg/week (*P* for trend = .018). In contrast, the difference between the levels associated with lower and higher doses of transdermal testosterone levels was not statistically significant (*P* = .66).

Table 4 summarizes the serum concentrations of total estradiol according to the route and dose of GAHT among the transgender women. Oral and intramuscular preparations of estradiol were more common than transdermal preparations among the transgender women (n = 366, 242, and 39, respectively). Among transgender women taking oral estradiol, the majority of the subjects received a dose of 15 to 30 mg/week (167/366 [45.6%]) or >30 mg/week (133/366 [36.3%]). Among transgender women taking intramuscular estradiol, the majority received a dose of ≥10 mg/week. There were 488 visits (488/643 [75.9%]) of transgender women using antiandrogenic agents,

Table 2
Sex Steroid Hormone Concentrations in Transgender Men and Women According to Demographic Characteristics

Participant characteristics	Testosterone levels in transgender men Median (IQR)	*P* value[a]	Estradiol levels in transgender women Median (IQR)	*P* value[a]
Age (y)				
<21	446.5 (255.7-652.0)	.027	76 (50.2-153.5)	.001
21-34	508.0 (314.0-685.5)		123.0 (70.7-294.0)	
≥35	563.0 (364.0-864.0)		146.0 (74.0-309.0)	
BMI category (kg/m^2)				
<25 (normal/underweight)	496.0 (340.0-731.0)	.857	145.0 (70.7-327.0)	.171
25-29.9 (overweight)	515.0 (284.0-729.0)		153.0 (74.0-281.5)	
≥30 (obese)	495.0 (309.5-668.5)		119.5 (66.2-234.5)	
Race/ethnicity				
Non-Hispanic White	515.0 (288.0-755.0)	.160	135.5 (74.9-309.0)	.097
African American	582.0 (398.5-832.0)		119.0 (52.3-466.0)	
Other/unknown	956.0 (352.25-1378.25)		55.8 (42.3-77.5)	
History of gonadectomy				
Yes	603.0 (437.00-936.00)	.030[b]	186.0 (114.0-359.0)	<.001[b]
No	481.0 (276.25-686.25)		116.0 (63.00-276.00)	

Abbreviations: BMI = body mass index; IQR = interquartile range.
[a] Kruskal-Wallis test.
[b] Mann-Whitney *U* test.

Table 3
Serum Concentrations of Total Testosterone in Transgender Men by Route of Administration and Dose[a]

Regimen characteristics	Level (ng/dL) Median (IQR)	Route-specific *P* value[b] by dose
Injectable (n = 274)	524.5 (333.8-756.0)	.018
≤50 mg/week (n = 80)	442.5 (257.5-644.3)	
51-75 mg/week (n = 50)	483.0 (317.8-645.3)	
>75 mg/week (n = 144)	588.0 (380.3-840.3)	
Transdermal (n = 20)	326.0 (85.5-441.0)	.660
≤50 mg/week (n = 13)	303 (61.5-442.0)	
51-75 mg/week (n = 0)	…	
>75 mg/week (n = 7)	349.0 (188.0-447.0)	
***P* value for all routes, by dose**		.006[b]
***P* value for all doses, by route**		<.001[c]

Abbreviations: IQR = interquartile range.
[a] Based on individual visits.
[b] Simple linear regression analysis.
[c] Mann-Whitney *U* test.

Table 4
Serum Concentrations of Total Estradiol in Transgender Women by Route of Administration and Dose[a]

Regimen characteristics	Level (ng/dL) Median (IQR)	Route-specific *P* value[b] by dose
Oral (n = 366)	102.0 (61.8-155.0)	<.001
≤14 mg/week (n = 66)	58.0 (47.6-104)	
15-30 mg/week (n = 167)	90.7 (58.7-138.8)	
>30 mg/week (n = 133)	140.0 (91.6-215.5)	
Intramuscular (n = 242)	366.0 (159.5-629.0)	
≤5 mg/week (n = 24)	155.5 (62.28-605.0)	.481
6-9 mg/week (n = 29)	371.0 (227.5-550.0)	
≥10 mg/week (n = 189)	365.0 (165.3-633.0)	
Transdermal (n = 39)	70.8 (38.1-119.0)	
≤2 mg/week (n = 24)	71.5 (35.1-115.0)	.157
2.1-5 mg/week (n = 9)	105.0 (50.9-159.5)	
>5 mg/week (n = 6)	50.3 (28.9-83.6)	
***P* value for all doses, by route**		<.001[c]

Abbreviations: IQR = interquartile range.
[a] Based on individual visits.
[b] Simple linear regression analysis.
[c] Kruskal-Wallis test.

most of whom were taking spironolactone alone (468/643 [72.8%]) or in addition to progesterone (43/643 [6.7%]). Very few transgender women were taking gonadotropin-releasing hormone analogs (n = 4, 0.7%).

Among the transgender women, the total serum estradiol concentrations were higher in those receiving intramuscular estradiol than in those receiving oral or transdermal estradiol (366.0 pg/mL vs 102.0 pg/mL vs 70.8 pg/mL, respectively, $P < .001$). Women with a higher oral dose of estradiol had a higher concentration of serum estradiol in a dose-dependent fashion, with median (IQR) estimates of 58.0 (47.6-104), 90.7 (58.7-138.8), and 140.0 (91.6-215.5) for doses of ≤14, 15 to 30, and >30 mg/week, respectively (*P* for trend <.001). The same analyses showed little evidence of a dose-response relationship for intramuscular (*P* for trend = .481) and transdermal (*P* for trend = .157) routes of estradiol administration (Table 4).

We examined daily regimens of estradiol and their corresponding serum estradiol concentrations in 3 commonly prescribed ranges for transgender women (Fig. 2). There was again a dose-dependent increase in the serum estradiol concentrations with an increasing dose of estradiol. A total daily dose of estradiol in the range of 4 to 5 mg resulted in an estradiol concentration of 93.5 pg/mL (58.6-146.8), which is near the minimum suggested level for transgender women (Fig. 2).

Discussion

This study reported data on GAHT types and doses and the corresponding blood hormone concentrations among transgender individuals receiving care at a large, specialized clinic in the United States. In both transgender men and women, injectable GAHT was associated with significantly higher serum hormone levels when compared to oral or transdermal preparations. In both transgender men and women, the factors that resulted in higher serum estradiol and testosterone concentrations included older age (>35 years) and a history of gonadectomy.

In our study, intramuscular and subcutaneous testosterone administrations resulted in a median serum total testosterone concentration of approximately 525 ng/dL. This level of serum total testosterone is consistent with the levels found in other cohorts of transgender men.[13,14,16,17] Pelusi et al have reported even higher serum concentrations of total testosterone in transgender men receiving intramuscular and transdermal formulations (median = 739.0 and 589.0 ng/dL, respectively).[18] The higher serum testosterone concentrations found in that study could be explained by the

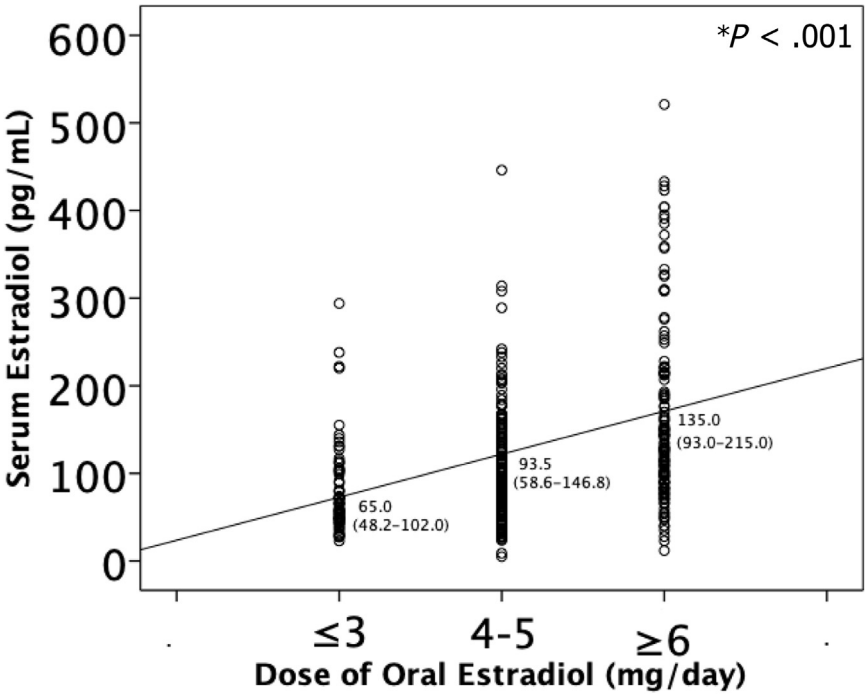

Fig. 2. Total daily dose of oral estradiol and the corresponding serum estradiol concentration in transgender women taking gender-affirming hormone therapy. The serum estradiol concentrations demonstrated a dose-dependent increase with an increasing total daily dose of oral estradiol ($P < .001$, Kruskal-Wallis). A total daily dose of between 4 and 5 mg resulted in a median estradiol concentration of 93.5 pg/mL (interquartile range: 58.6-146.8), which is near the minimum recommended therapeutic range for transgender women.

higher median age and lower BMI of their population compared with those of our study population. In our study, we found that older age was associated with higher serum testosterone concentrations. The relationship between serum total testosterone concentration and BMI remains unclear. One previous study has reported that patients with lower BMI have significantly higher serum testosterone concentrations.[19] In contrast, our data seem to suggest a V-shaped curve, whereby people with a BMI in the range of 25 to 29.9 kg/m^2 had higher hormone concentrations than those whose BMI was <25 kg/m^2 or ≥30 kg/m^2.

The serum estradiol concentrations of the transgender women in our study are also comparable with those reported in previous studies conducted in Europe.[7,13,20] One important distinction between the studies conducted in the United States and studies based in Europe is the use of oral estradiol in combination with cyproterone, which is common in European clinical practice but not in the United States. Cyproterone has been shown to increase sex hormone–binding globulin (SHBG) and serum estradiol concentrations.[21] Some studies have reported a negative correlation between total testosterone level and SHBG,[22,23] while spironolactone is not known to have any impact on serum estradiol concentrations. Interestingly, the serum estradiol concentrations in transgender women receiving testosterone-lowering agents were significantly lower compared with those in transgender women not taking antiandrogen therapy. This is consistent with Leinung et al's study of oral estradiol.[24] The likely explanation for the higher estradiol concentration in the transgender women not taking antiandrogen therapy is that majority of these transgender women had previously undergone gonadectomy.

Monitoring sex steroid hormone concentrations in transgender people receiving GAHT is recommended by the Endocrine Society[2] to decrease the risk of potential complications. VTE and ischemic stroke are serious adverse outcomes in transgender individuals receiving GAHT, especially in transgender women taking oral estradiol.[25,26] The reported incidence of VTE in transgender women ranges from 1% to 6%.[9,10,27,28] One previous study reported that transgender women taking oral estradiol had a rate of VTE that was 3 times higher and a rate of ischemic stroke that was 2 times higher than those for cisgender male referents of the same age and race/ethnicity.[29] Although no studies have examined the association between serum estradiol dose and the risk of VTE in transgender women, it is presumed that higher hormone concentrations would increase the risk. In transgender men, GAHT is associated with a decrease in high-density lipoprotein and an increase in hematocrit, triglycerides, low-density lipoprotein, and inflammatory parameters.[30-33] However, clinical outcomes, such as VTE, cardiovascular disease, and cerebrovascular accidents, do not appear to be increased in this population.[29] Most studies have reported that receiving GAHT under the supervision of medical providers is safe.[7,8] One possible explanation for this safety is that the serum hormone concentrations of TGGNB people are routinely monitored and kept within the recommended ranges. The precise serum hormone levels that produce adequate gender-affirming results (both physical and psychologic), with the lowest risk of complications, are still unknown.[15] However, most guidelines recommend keeping serum hormone levels within physiologic ranges of the affirmed gender.[1,2]

We found that the serum estradiol levels increased in a dose-dependent fashion according to the oral estradiol dose in the transgender women. We also observed that doses of estradiol between 4 and 5 mg/day, primarily in combination with spironolactone, resulted in a median concentration at the minimum level of a recommended range of 100 to 200 pg/mL, and doses of 2 mg/day might not be sufficient to achieve the target concentrations.[2] Clinicians may consider starting at lower doses of oral estradiol and titrating up to 4 to 5 mg daily to reach the recommended therapeutic levels of estradiol. Higher doses of estradiol (≥6 mg) may be reserved for those who still do not reach the target levels, but this may result in supraphysiologic levels of >200 to 300 pg/mL. Injectable estradiol and transdermal estradiol did not result

in a dose-dependent increase in the estradiol concentrations. This may be because injectable estradiol leads to larger fluctuations of estradiol, making the timing of the measurement important, and transdermal estradiol may have significant variability in skin absorption rates among individuals. We also found that intramuscular injections of estradiol led to mean estradiol concentrations above the reference range when given in doses of >5 mg weekly. In addition, the transgender women who underwent gonadectomy had higher serum estradiol concentrations, which supports the common belief that estradiol dose can be decreased following the removal of gonads. Although oral estradiol has many advantages, including ease of administration and low cost, current evidence suggests that it may lead to a higher risk of thrombotic events compared with transdermal estradiol.[9,10,27,28] Our observation that serum estradiol concentrations in transgender women using transdermal estradiol were significantly lower when compared with the concentrations in transgender women taking estradiol via other routes of administration may partly explain this difference in risk.

All routes of testosterone are equally effective in raising serum hormone concentrations to the male reference range; however, injectable testosterone appeared to be more likely to raise the median testosterone concentrations to the range of 400 to 700 ng/dL, as recommended by the Endocrine Society. Intramuscular testosterone was the most popular route among transgender men in our clinic. Testosterone doses of 100 to 200 mg every 1 or 2 weeks resulted in target concentrations. Transdermal preparations resulted in lower serum testosterone concentrations, which were not in the recommended range.

The strengths of this study include the relatively large number of different observations with various hormone preparations and resultant hormone concentrations. Some limitations of this study include variability of the timing of the hormone concentration measurement. In practice, our clinic prefers measuring the trough hormone concentrations in patients taking intramuscular injections to assess the efficacy of the hormone regimen; however, some subjects may not have undergone blood tests at that point. We did not have enough numbers of laboratory tests done on transgender men taking subcutaneous testosterone. Therefore, we were unable to compare the serum testosterone levels in transgender men taking subcutaneous testosterone with those taking intramuscular testosterone. Additionally, serum estradiol concentrations may vary according to the time of day when the oral estradiol dose is ingested. Our cohort primarily used twice-daily dosing when the estradiol doses were >2 mg daily. This may be very important when comparing studies in transgender women on once- to twice-daily doses of estradiol. Furthermore, some transgender women may take estradiol sublingually, as opposed to orally, without informing their physician. We do not have any information regarding this route in our study. Another important point is that we did not have any information on SHBG. Although measurement of SHBG concentration is not recommended by the Endocrine Society, the administration of sex steroids alters SHBG concentrations. Testosterone therapy lowers SHBG concentration, which may result in more bioavailable testosterone, whereas estradiol therapy increases SHBG concentraton, which may result in less bioavailable estradiol. The use of SHBG as a guide to adjust GAHT should be evaluated in future studies. Almost all our subjects were adults, and thus, these findings may not apply to transgender youth. Finally, these results may differ from the findings in Europe because the main antiandrogen used in the United States is spironolactone, as opposed to cyproterone in Europe.

In conclusion, several routes and formulations of sex steroid hormones used in the United States produced target hormone concentrations in our patient population. In the transgender men, all the routes and formulations of testosterone appeared to be equally effective in achieving target hormone concentrations. In the transgender women, there was a dose-dependent increase in the serum estradiol concentration with increasing oral doses of estradiol, with a dose of ≥5 mg daily appearing to be effective in achieving adequate estradiol concentrations. The intramuscular injections of estradiol resulted in the highest serum concentrations of estradiol, whereas transdermal estradiol resulted in the lowest concentration of estradiol. The transgender women undergoing bilateral orchiectomy had higher serum estradiol concentrations, which confirms the expectation that estradiol dose can be lowered after gonadectomy.

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Disclosure

The authors have no multiplicity of interest to disclose.

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