

The effect of estrogen therapy on spermatogenesis in transgender women

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Objective: To describe the histopathologic parameters of orchiectomy specimens obtained after gender-affirming surgery from transgender women who used gender-affirming hormone therapy (GAHT), which included estrogen and spironolactone. Our hypothesis was that an increasing duration of GAHT affects testicular health.

Design: Retrospective cohort study.

Setting: Tertiary referral center.

Patient(s): All transgender women (individuals assigned male at birth who identified as female) who underwent orchiectomy with or without vaginoplasty between December 2015 and March 2020.

Intervention(s): GAHT (estrogen and spironolactone) in the setting of patients with orchiectomy with or without vaginoplasty.

Main Outcome Measure(s): Demographic and perioperative data and pathology records were reviewed. The following pathology parameters were recorded: testicular volume, testicular weight, presence of spermatogenesis (active vs. reduced), maturation arrest, testicular atrophy, hyalinization, scarring/fibrosis, and Sertoli cell and Leydig cell phenotypes. The patients were grouped into one of three categories describing the duration of GAHT use: 0–36 months, 37–60 months, and >60 months years. Descriptive statistics were performed and comparisons between outcomes (demographic data and pathology parameters) were made among the GAHT groups.

Result(s): Eighty-five (N = 85) patients underwent orchiectomy during the study period with 85.9% (n = 73) undergoing concurrent vaginoplasty. The mean (SD) age and body mass index of the cohort were 39 ± 16 years and 28.4 ± 5.4 kg/m², respectively. In addition, although this was not statistically significant, patients in the 37–60 and >60-month groups were more likely to smoke marijuana than those in the 0–36-month group (26.3% and 21.2% vs. 4.2%, respectively). Mean testicular weight and volume across the cohort were 60.1 ± 24.9 grams and 65.5 ± 41.1 cm³, respectively. Spermatogenesis was present in 28.2% (n = 24) of specimens with active spermatogenesis noted in 8.2% (n = 7). Hyalinization, scarring/fibrosis, and atrophy were present in 28.2% (n = 24), 20.0% (n = 17), and 25.9% (n = 22) of specimens, respectively. There were no differences in pathology parameters across the GAHT groups. Testicular weight and volume were not associated with any differences in pathology parameters. Additionally, age was not associated with testicular weight, volume, or pathology parameters with the exception of the following: when patients were categorized as either ≤40 years of age (n = 48) vs. >40 years of age (n = 37), patients who were older were more likely to have hyalinization (43.2% vs. 16.7%) as well as atrophy (40.5% vs. 14.6%).

Conclusion(s): The duration of GAHT use was not associated with any differences in orchiectomy pathology parameters in patients undergoing gender-affirming surgery, and some patients may still have some spermatogenesis based on the parameters observed in this study. (Fertil Steril Rep® 2021;2:347–51. ©2021 by American Society for Reproductive Medicine.)

Key Words: Transgender, fertility, orchiectomy, gender-affirming hormones

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Currently, approximately 1.4 million transgender individuals reside in the United States (1). These patients suffer from gender dysphoria, which is a feeling of intense psychological distress as a result of the

incongruence they feel between their assigned sex at birth and their gender identity (2). Treatment for gender dysphoria is multifaceted. Many patients use gender-affirming hormone therapy (GAHT) to achieve congruence between their biologic and affirmed gender. Some patients choose to undergo gender-affirming surgery (GAS), which includes chest surgery, genital surgery, and facial feminization for those who identify as female. Genital surgeries often involve removal of the gonads;

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oophorectomy is commonly performed for transgender men, and orchiectomy is performed for transgender women.

Both GAHT and GAS affect the fertility potential in patients seeking these treatments. The Endocrine Society, World Professional Association for Transgender Health (WPATH), and American Society for Reproductive Medicine (formerly The American Fertility Society) recommend that transgender patients be counseled about their fertility goals and preservation options before they initiate gender-affirming treatments (3–5). According to WPATH guidelines, patients who are considering GAS are required to complete at least 1 year of GAHT before surgical intervention, unless medically contraindicated. Reports show that nearly 80% of transgender patients have considered fertility preservation; however, <10% of patients actually complete fertility preservation before transitioning (6). Current barriers to obtaining this care include the side effects of the hormones used for gonadal stimulation, cessation of ongoing GAHT, and ineffective education on fertility preservation options (7).

Moreover, the effect of GAHT on fertility potential is not well understood (7). At our center, we perform gender-affirming vaginoplasty surgery for transgender women (assigned male at birth), which involves orchiectomy. Patients who present for this surgery vary in age and exposure to GAHT. In theory, antiandrogen treatment in these patients could result in morphological changes in the testes and alterations in spermatogenesis. Review of the literature showed varying effects of GAHT on orchiectomy specimens and sperm health with some reports of complete testicular failure and others of preserved spermatogenesis (8). Currently, <20 publications describe the effect of GAHT on testicular morphology (9). The results in these studies were varied and ranged from occasional spermatogenic activity with evidence of fibrosis and atrophy, preserved spermatogenesis in some patients, and evidence of decreased sperm motility with increasing doses of estrogen (9). Lastly, two studies reported preserved spermatogenesis, including studies by Thiagaraj et al. (10) and Schneider et al. (9). In this latter study, which was the largest (n = 108), 24% of patients had normal spermatogenesis despite GAHT (9). Given these results, there is clearly a wide range of outcomes (9). Moreover, a few studies evaluated the reversibility of the effect of GAHT (1, 11). However, many of these studies had cohorts of <20 patients. The presence of mostly small-scale studies likely adds to the gap in knowledge surrounding GAHT and its effect on fertility.

Sperm cryopreservation and testicular sperm extraction are options for patients seeking GAHT and/or GAS (12). Best practices involve counseling patients regarding these options before they undergo treatment. However, sometimes patients present for GAS, having already been on GAHT, and these patients were either not counseled previously about their options or chose not to engage in fertility preservation at that time (13). Some patients inquire about it before they undergo genital surgery, and it is in these patients that we do not have complete data about the fertility potential given that they were already exposed to antiandrogen and/or exogenous estrogen therapy.

Because of these knowledge gaps, the primary objective of this study was to describe the histopathology of orchiec-

tomy specimens obtained from transgender women undergoing GAS and, in addition, to describe the impact of GAHT on spermatogenesis and testicular architecture in these women. By understanding these concepts, we believe we can better understand the effects on testicular health of transgender women undergoing gender-affirming care and to improve counseling for these patients.

MATERIALS AND METHODS

Study Design and Population

This was an institutional review board-approved retrospective cohort study of transgender women (assigned male at birth) who underwent orchiectomy with or without vaginoplasty surgery for gender affirmation between December 1, 2015, and March 31, 2020, at a tertiary care referral center; surgery was performed by the sole surgical provider at our institution. Patients were identified by their *Current Procedural Terminology Codes* for orchiectomy and their “female” gender marker in the electronic medical record. Once the patients were identified, the operative reports were reviewed to confirm if the inclusion criteria were met. The patients were included if they underwent orchiectomy with or without concurrent vaginoplasty surgery. They were excluded if they were not transgender.

Orchiectomy and vaginoplasty surgeries were performed by one surgeon, who was board-certified in Female Pelvic Medicine and Reconstructive Surgery. Orchiectomy was performed either unilaterally (in cases of previous contralateral orchiectomy) or bilaterally. All orchiectomy specimens were sent to pathology per the institution’s tissue protocol. The pathologists were blinded to the GAHT status of the patients during their review. Once patients were identified, the electronic medical record was queried for patient characteristics and perioperative data. The initial consult and patient history were reviewed, as well as the operative and pathology reports for each patient.

Hypothesis

Based on a review of the current literature, the hypothesis of this study was that the effects of GAHT on testicular parameters, including spermatogenesis, were dependent on the treatment duration. We hypothesized that increasing duration of GAHT therapy decreases markers of testicular functioning.

Outcome Measures and Definitions

The primary outcome measure of the study was the presence of spermatogenesis seen on orchiectomy specimens. The secondary outcomes included additional histopathology parameters of orchiectomy specimens obtained at the time of surgery. These were studied in the context of the duration of GAHT incurred by patients as well as in the context of other patient characteristics.

Definitions of the pathology specimen categories were determined a priori by taking a cross-section of the cohort and doing a cursory review of the reports to notice trends in the way that the pathology was reported. In addition, a review

of the literature was performed to help identify categories that would be essential to our analysis.

Outcome Variables

The following pathology parameters were recorded from the pathology report: testicular volume, testicular weight, presence of spermatogenesis (active vs. reduced), maturation arrest, testicular atrophy, hyalinization, scarring/fibrosis, and Sertoli cell and Leydig cell phenotypes. In the setting of decreased fertility, the presence of Sertoli cell phenotypes represents the absence of spermatogenic cells and an abnormal abundance of Sertoli cells, whereas the presence of Leydig cells phenotypes represents reduced testicular function and increased hyperplasia and hypertrophy of Leydig cells (14, 15). In the setting of this study, normal or active spermatogenesis was defined subjectively by a group of specialized pathologists in our institution as the presence of spermatozoa in all stages of normal differentiation. Similarly, in this context of outcome variables, hypospermatogenesis was the presence of few spermatozoa in the tubules with missing or absent stages of differentiation.

Exposure Variables

The patients were grouped into one of three categories describing the duration of GAHT use: 0–36 months, 36–60 months, and >60 months. Patients in this cohort traditionally used GAHT for at least 1 year before the decision for surgical management in accordance with WPATH guidelines; however, in some patients, GAHT use was medically contraindicated; therefore, patients with <1 year of GAHT use were included in the categorization. The decision to categorize patients in these groups was made post hoc when we were able to see the distribution of the duration of the time on GAHT.

The GAHT regimens included estrogen and spironolactone in our cohort. Estrogen exposure was further clarified into the main formulations (oral, intramuscular/subcutaneous, and transdermal dosing). Data on actual dosages of GAHT were not collected because of the retrospective design of the study. However, typical dosing protocols at our institution were as follows: estrogen–oral (estradiol 2–8 mg daily); estrogen–intramuscular/subcutaneous (estradiol cypionate 2–5 mg every 2 weeks, estradiol valerate 20–40 mg every 2 weeks); estrogen–transdermal (estradiol patch 50–400 mcg every week), and spironolactone (50–300 mg daily).

Other patient characteristics were collected in addition, including age, body mass index (BMI), the presence of medical comorbidities, and tobacco and marijuana use.

Statistical Analysis

Categorical variables were presented as percent (n/N) with 95% confidence intervals where appropriate. Continuous variables were presented as mean \pm SD and median (range). Comparisons between pathology parameters as well as patient characteristics were made among the GAHT groups. In addition, comparisons were made between pathology parameters and other patient characteristics. These comparisons were

done using a Student's *t* test for parametric continuous outcomes, Mann-Whitney *U* test for nonparametric outcomes, and a Fisher's exact test for all categorical outcomes. Multivariate logistic regression was planned to control for any potential confounders found on the univariate analysis. However, no logistic regression was conducted post hoc because there were no statistically significant findings in the univariate analysis. All results $P \leq .05$ were considered statistically significant. Jmp v15.0 was used for all analyses.

RESULTS

Eighty-five ($N = 85$) patients underwent orchiectomy during the study period with 85.9% (73/85) undergoing concurrent vaginoplasty. Only one patient had a previous unilateral orchiectomy for a benign testicular mass. None of the study patients had any documented history of cryptorchidism. Table 1 shows the patient characteristics for all patients. The mean age and BMI of the cohort were 39 ± 16 years and 28.4 ± 5.4 kg/m², respectively. Of the 85 patients, 94.1% (80/85) had a history of GAHT use with 28% (24/85) using GAHT for 0–36 months, 45% (38/85) for 37–60 months, and 27% (23/85) using GAHT for >60 months. The median duration of GAHT use for all patients was 48 (24–60) months. Of the patients, 24.7% (24/85) reported having biological children before orchiectomy.

In addition, Table 1 displays the differences in patient characteristics among the three GAHT duration categories. There were no statistically significant differences among the GAHT groups. Although this was not statistically significant, patients in the 37–60-month and >60 month groups were more likely to smoke marijuana than those in the 0–36-month group (26.3% and 21.2% vs. 4.2%, $P = .09$). However, marijuana use was not associated with any changes in testicular parameters among the GAHT groups (data not shown). Estrogens were used in the following formulations: 81.2% (69/85) oral, 17.6% (15/85) intramuscular or subcutaneous, and 7.1% (6/85) transdermal. Seventy-three (85.9%) patients used spironolactone.

In Table 2, we describe the histopathology parameters for all patients and in addition compare them among the GAHT groups. Mean testicular weight and volume across the cohort were 60.1 ± 24.9 grams and 65.5 ± 41.1 cm³, respectively. Spermatogenesis was present in 28.2% (24/85) of the specimens with active spermatogenesis noted in 8.2% (7/85). Hyalinization, scarring/fibrosis, and atrophy were present in 28.2% (24/85), 20.0% (17/85), and 25.9% (22/85) of the specimens, respectively. Sertoli cell and Leydig cell phenotypes were appreciated in 20.0% (17/85) and 16.5% (14/85) of the specimens, respectively.

Based on these data, there was no association between spermatogenesis and the duration of GAHT, which included a combination of spironolactone and estrogen in our patient cohort. In addition, age was not associated with spermatogenesis in our analysis. There were no statistically significant differences in the other pathology parameters across the GAHT groups. Testicular weight and volume were not associated with any differences in pathology parameters. Additionally, age was not associated with testicular weight or volume or

TABLE 1

Patient characteristics, N = 85.

	All patients (N = 85)	GAHT 0–36 months (n = 24)	GAHT 37–60 months (n = 38)	GAHT > 60 months (n = 19)	P value
Age, y	39 ± 16	37 ± 17	36 ± 15	41 ± 15	.51
BMI, kg/m ²	28.4 ± 5.4	26.9 ± 5.5	27.9 ± 5.3	30.7 ± 5.3	.07
Diabetes	9.4 (8)	20.8 (5)	2.6 (1)	10.5 (2)	.11
Cardiovascular disease	22.4 (19)	20.9 (5)	21.1 (8)	21.1 (4)	.99
Prostate disease	2.4 (2)	0 (0)	2.6 (1)	5.3 (1)	.19
Tobacco use	11.8 (10)	4.2 (1)	6 (15.8)	10.5 (2)	.36
Marijuana use	17.6 (15)	4.2 (1)	26.3 (10)	21.2 (4)	.09
HIV	2.4 (2)	0 (0)	2.6 (1)	5.2 (1)	.54
Biologic children	24.7 (21)	16.7 (4)	23.7 (9)	31.6 (6)	.52
GAHT	94.1 (80)	83.3 (20) ^a	100.0 (38)	100.0 (19)	.007 ^a
Spironolactone	85.9 (73)	70.8 (17)	97.4 (37)	89.5 (17)	
Estrogen	94.1 (80)	87.5 (21)	97.4 (37)	100.0 (19)	
Oral	81.2 (69)	75.0 (18)	84.2 (32)	89.5 (17)	
IM/SC	17.6 (15)	8.3 (2)	26.3 (10)	15.8 (3)	
TD	7.1 (6)	4.2 (1)	7.9 (3)	5.3 (1)	
GAHT duration, months	48 (24–60)	24 (12–24)	48 (36–48)	84 (72–84)	< .0001
Concurrent vaginoplasty	85.9 (73)	85.9 (73)	82.3 (14)	89.5 (34)	.27

Note: Data are presented as mean ± SD, percentage (number), or median (range). BMI = body mass index; GAHT = gender-affirming hormone therapy; HIV = human immunodeficiency virus; IM = intramuscular; SC = subcutaneous; TD = transdermal.

^a Significantly different between 0–36 month, 37–60 month, and >60 month therapy duration groups.

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TABLE 2

Histopathology parameters, N = 85.

	All patients (N = 85)	GAHT 0–36 months (n = 24)	GAHT 37–60 months (n = 38)	GAHT > 60 months (n = 23)	P value
Weight, grams	60.1 ± 24.9	60.1 ± 26.7	60.4 ± 22.2	61.1 ± 25.4	.99
Total volume, cm ³	65.5 ± 41.1	68.9 ± 38.2	68.6 ± 42.3	51.0 ± 32.4	.25
Malignancy	1.2 (1)	0 (0)	2.6 (1)	0 (0)	.56
Any spermatogenesis	28.2 (24)	29.2 (7)	18.4 (7)	39.1 (9)	.07
Active spermatogenesis	8.2 (7)	4.2 (1)	7.9 (3)	15.8 (3)	.16
Hypospermatogenesis	20.0 (17)	25.0 (6)	10.5 (4)	31.6 (6)	.16
Maturation arrest	28.2 (24)	37.5 (9)	31.6 (12)	15.8 (3)	.18
Sertoli cell phenotype	20.0 (17)	25.0 (6)	15.8 (6)	21.1 (4)	.92
Leydig cell phenotype	16.5 (14)	25.0 (6)	13.1 (5)	5.2 (1)	.19
Hyalinization	28.2 (24)	25.0 (6)	34.2 (13)	21.1 (4)	.71
Scarring/fibrosis	20.0 (17)	25.0 (6)	21.1 (8)	10.5 (2)	.95
Atrophy	25.9 (22)	20.1 (5)	26.3 (10)	21.1 (4)	.85

Note: Data are presented as mean ± SD or percent (number). GAHT = gender-affirming hormone therapy.

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pathology parameters with the exception of the following: when patients were categorized as either ≤40 years of age (n = 48) vs. >40 years of age (n = 37), patients who were older were more likely to have hyalinization (43.2% vs. 16.7%, *P* = .01) as well as atrophy (40.5% vs. 14.6%, *P* = .007).

DISCUSSION

In this retrospective study, we compared the effects of the duration of GAHT on the testicular parameters and found that, among patients who were on GAHT for 0–36 months, 37–60 months, and >60 months, there were no significant differences in these pathologic indices for up to 7 years of GAHT use. Similar findings were reported in the literature in the setting of GAHT use (16–18). Although our results were not significant, it is possible that we did not find

significant results because the sample size was not large enough to detect such differences; still, we want to highlight that 28.2% of our patients had persistent spermatogenesis in our study. Moreover, 8.2% of our patients had normal, active spermatogenesis despite GAHT use with a median duration of 4 years. These results are especially important for understanding the effects of GAHT use on spermatogenesis and should prompt us to study this further.

Although there were no statistically significant associations between any pathology parameters among the three GAHT categories, age >40 years was associated with hyalinization and atrophy. This was not surprising, because age was a known risk factor affecting male fertility (19). But it was an important finding that implied that age should be a consideration during discussions about fertility preservation.

Regarding this study's strengths, we believe that our study enhances the current body of literature, because it has one of the biggest cohorts on literature review (9). Additionally, it augments the gynecologic literature with this type of study, which previously was showcased primarily in the urologic literature. Because there was only one provider who performed orchiectomies in the transgender patient population at our institution, we were confident that we captured the characteristics of this particular cohort. All data points were defined a priori. In addition, we collected data on the types of agents and formulations of GAHT, both of which have not been studied in previous studies. Lastly, our pathology slides from the orchiectomy specimens were reviewed by a small group of pathologists specializing in gonadal evaluations. Review of these reports was completed at the start of the study and helped us define our data points.

The limitations of our study included those inherent to its descriptive retrospective design. We completed an a priori power analysis and determined that we may be limited in the number of patients per category; therefore, we proceeded with a descriptive study. Moreover, we did not complete a post hoc analysis because we did not have an appropriately sized control group within our cohort, which would have ideally been a sizable group of patients on no GAHT, because we followed WPATH guidelines in which orchiectomy was only performed on transgender patients who had been using hormones for at least 1 year before surgery, unless medically contraindicated (5.3% of our patients). Other limitations were the lack of a standardized definition of active vs. hypospermatogenesis and lack of identification of immature or mature spermatozoa within the testicular pathology reports. The reported pathologic findings were subjectively defined and could have been influenced by interobserver variability. Importantly, the testicular parameters were considered markers for fertility, but they were not considered the gold standard for assessing testicular health, and therefore, we can only extrapolate our findings.

CONCLUSION

Although this study may have been underpowered, we did observe that approximately 30% of patients on GAHT had some gonadal potential and that the duration of therapy did not appear to negatively affect histologic markers. However, given that <10% of all patients had active spermatogenesis, it may be important to consider early counseling and discussion with transgender patients about their fertility goals before using GAHT, because we do not know enough about the effects of gender-affirming treatments.

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