European Journal of Plastic Surgery (2019) 42:267–272
https://doi.org/10.1007/s00238-018-1491-3

ORIGINAL PAPER

Effects of hormone therapy in patients who underwent male-to-female gender confirmation surgery

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Received: 24 October 2018 / Accepted: 12 December 2018 / Published online: 7 January 2019

Abstract

Background An estimated 1.4 million transgender individuals currently reside in the USA and this patient population is increasing on an annual basis (Am J Public Health 107: 1–8, 2017). Along with this census increase, there has also been an increasing number of gender confirmation surgeries being performed in the USA (American Society of Plastic Surgeons, 2016). Our primary objective was to study the effects of hormonal therapy on testicular volumetrics on transgender patients who underwent male-to-female (MtF) bottom gender confirmation surgery.

Methods Retrospective review of patients who underwent MtF bottom gender confirmation surgery. Based on World Professional Association for Transgender Health (WPATH) guidelines a minimum of 1 year of hormonal therapy was required in order to be included. Two groups were analyzed based on their hormone therapy regimen (estrogen and estrogen/progesterone). Demographics, comorbidities, body mass index (BMI), medications (and length of use), testicular volumetrics (weight, length of spermatic cord, volume), and post-operative complications (dehiscence, seroma, hematoma, infection, return to the OR) were analyzed.

Results A total of 54 patients were analyzed. The mean age of the sample population was 37.7 (± 13.3) years old. The mean difference in BMI before and after hormonal treatment was − 0.14 (± 1.7) in the estrogen only group and + 0.3 (± 1.7) in the estrogen/progesterone (combined) group ($p = 0.396$). The mean weight of surgical specimens in the estrogen only and in the combined group was 30.2 (± 14.9) and 24.1 (± 8.7), respectively ($p = 0.033$). The spermatic chord length for patients in the estrogen group was 5.4 cm (± 1.7), and 4.5 cm (± 1.6) for patients in the combined group ($p = 0.009$). Of all the patients, 18 presented with minor wound dehiscence of labia majora. Analysis of complications regarding to the type of hormonal therapy they received showed no difference among patients in the estrogen only and the combined group ($p = 0.859$).

Conclusion Hormone therapy is an integral aspect of a multidisciplinary approach to transgender medicine and surgery. Further studies are required to elucidate systemic effects in detail and evaluate outcomes in a post-operative setting.

Level of Evidence: Level III, risk /prognostic study.

Keywords Transgender · Hormone therapy · Orchiectomy · Gender confirmation surgery

Introduction

In the USA, based on data gathered from nation surveys, the population of transgender patients is currently estimated to be 390 per 100,000 adults [1]. However, this number is believed to be quite an underestimate due to inaccuracies of census surveys (i.e., recording birth gender, inconsistent identification with the term "transgender," and correlating sexual orientation to gender identity) [1]. With this rise in census among this patient population, an increasing number of insurers have come to consider gender-related surgeries medically necessary [1–3]. The American Society of Plastic Surgeons reported 3256 gender confirmation surgeries (1759 male-to-female,

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1497 female-to-male) were performed in the USA in 2016 [2]. This was reported to be a nearly 20% increase from the year before [2].

Based on WPATH guidelines, prior to gender confirmation surgery, the initiation of medical transition begins with hormone therapy [4–7]. The goal of hormone therapy is to induce secondary sex characteristics while in conjunction suppressing native biologic secondary sex characteristics of the patient [4–7]. According to the clinical practice guidelines set forth by the American Endocrine Society in 2017, a multidisciplinary evaluation to confirm the diagnosis of gender dysphoria and address any medical or mental health issues is recommended prior to initiation of hormone therapy [8]. In adolescent transwomen, GnRH analogs (leuprolide acetate, goreselin) may be started in early puberty to stop pubertal progression and delay the physical changes of the normal pubertal rise in testosterone until the patient is ready for feminizing hormone therapy [8]. The feminizing hormone regimen components are similar in adolescents as well as in adults who start therapy after completing their birth sex puberty and may include one or more of the following agents: estrogen (oral, sublingual, intramuscular, subcutaneous, transdermal), progesterone (oral, intramuscular, transdermal, topical, subcutaneous injection/implant), and an oral anti-androgen agent (spironolactone, finasteride, cyproterone acetate) [4–8].

Our primary goal is to evaluate and analyze the overall effects of hormonal therapy on testicular pathology and volumetrics in transgender patients who underwent MtF gender confirmation surgery. Our secondary goal was to analyze the association between hormonal therapy and surgical outcomes.

Methods

After appropriate Institutional Review Board approval by the research committee, a retrospective review that evaluated transgender patients at the Mayo Clinic in Rochester who underwent MtF bottom gender confirmation surgery were recorded and analyzed. The criteria for exclusion included patients with a history of hormonal therapy without gender confirmation surgery, inadequate documentation, and incorrect patient identification based on ICD-9 codes. The Mayo Clinic Advanced Cohort Explorer Databases were accessed, studied, and organized into a HIPAA compliant Excel spreadsheet for further analysis. All patients' charts were audited by two reviewers to control for inter-reviewer variability. The categorical variables of interest were age, BMI, comorbidities (diabetes mellitus, hypertension, hyperlipidemia, and obstructive sleep apnea), type of hormone therapy (estrogen only or combined with progestin), and post-operative complications (hematoma, seroma, local wound infection, or wound dehiscence and return to the operating room). The continuous variables included hormone therapy length of use and testicular volumetrics (weight, volume, length of spermatic cord). In addition, age, BMI, and follow-up time were analyzed.

To assess the hormonal effects on the weight of the patients, the difference in BMI before the start of hormonal therapy and at the date of surgery was calculated. To evaluate the gonadal effects of hormonal therapy, the weight and volume of testes, and the spermatic chord length of the surgical specimens were recorded. Total follow-up was calculated from the clinic visit when the hormonal treatment started to the last clinic visit, and the post-operative follow-up time was calculated from the date of surgery until the last clinic visit. Post-operative complications including hematoma, seroma, surgical site infection, wound dehiscence, deep vein thrombosis (DVT), and return to the operating room were collected and analyzed.

Patients were analyzed in two groups based on the type of hormonal therapy they received pre-operatively (estrogen therapy alone vs. estrogen and progesterone therapy). Continuous data was evaluated by the Shapiro-Wilk test for normal distributions. Data with normal distribution was reported as means with standard deviation and comparisons were performed with the *t* test. Data with no normal distribution was presented as medians with interquartile ranges for the 25th to 75th percentile, and comparisons were performed with the Mann-Whitney-Wilcoxon test. Categorical data was presented as a percentage and analyzed using the chi-square test, and for small samples the Fisher's exact test was used. Spearman's rank correlation coefficient was calculated to analyze the relation between BMI at the time of surgery and the different surgical specimen metrics. A value of $p < 0.05$ was considered significant.

Results

Between February 2017 and April 2018, a total of 54 patients were identified. Mean age was 37.7 (± 13.3) years. Four (7.4%) patients had diabetes mellitus, 4 (7.4%) hyperlipidemia, and 2 (3.7%) had obstructive sleep apnea syndrome. All patients received pre-operative hormonal treatment for a for a minimum of 365 days before surgery, with 26 (48.1%) patients receiving only estrogen replacement therapy, and 28 (51.9%) patients receiving combined (estrogen + progesterone) therapy. General characteristics of the patients are detailed in Table 1.

Characteristics of the groups

Characteristics of each hormonal treatment group are summarized in Table 2. All patients began feminizing hormone therapy after Tanner Stage 5 of their birth sex

Table 1 Patient's characteristics

Variable	Number (%)
Patients included	54 (100)
Follow-up, months	17.5 ± 11
Age	37.7 ± 13.3
BMI	25.9 ± 5.1
BMI ≥ 25	31 (57.4)
Comorbidities	
Hyperlipidemia	4 (7.4)
DM	4 (7.4)
OSA	2 (3.7)
Hormonal treatment	
Estrogen only	26 (48.1)
Estrogen + progestin	28 (51.9)

BMI, body mass index; *DM*, diabetes mellitus; *OSA*, obstructive sleep apnea syndrome

puberty. The mean age of patients with estrogen only therapy was 35.6 (± 12.7) years and with combined therapy was 39.5 (± 13.8) years, ($p = 0.256$).

Comorbidities were similar between the estrogen only and the combine group, diabetes mellitus in 3 (11.5%) and 1 (3.6%) patients, ($p = 0.342$); hyperlipidemia 3 (11.5%) and 1 (3.6%) patients, ($p = 0.342$); and OSA 1 (3.9%) and 1 (3.6%, $p = 1.000$), respectively. Mean duration of the hormonal treatment was 420 days (± 34) for patients in the estrogen only group, and 425 days (± 41) for patients in the combined group, ($p = 0.597$).

Hormonal effects

Hormonal effects in BMI and surgical specimens and complications for each group are summarized in Table 3. The mean BMI before hormonal therapy was higher in patients with estrogen only therapy (26.4 ± 5.3) than in patients with combined therapy (25.2 ± 5.3, $p = 0.120$). At the date of surgery, the mean BMI in patients with estrogen only therapy slightly decreased to 26.3 (± 5.2), and it increased to 25.5 (± 5.1) in patients with combined treatment ($p = 0.533$). The mean difference in BMI from the start date of hormonal treatment until surgery was negative (− 0.14, ± 1.7) in the estrogen only group and positive (+ 0.3, ± 1.7) in the combined group ($p = 0.396$).

The mean weight of testicular tissue in the estrogen only and in the combined group was 30.2 (± 14.9) and 24.1 (± 8.7), respectively ($p = 0.033$). Additionally, the spermatic chord length for patients in the estrogen group was 5.4 cm (± 1.7) and 4.5 cm (± 1.6) for patients in the combined group ($p = 0.009$).Volume of the specimen in the estrogen only group was 37.2 cm^3 (± 20.1) and 36.9 cm^3 (± 13.8) in the combined group ($p = 0.681$). The mean BMI of the patients was positively correlated only with the mean weight of the testes ($r = 0.217$, $p = 0.023$). No correlation between BMI and volume of the testes ($r = 0.062$, $p = 0.518$), and length of spermatic chord ($r = 0.118$, $p = 0.225$) was found (Table 4).

Per our institutional protocol, all patients are followed for a minimum of 6 months. Of all the patients, 14 (25.9%) presented with minor wound dehiscence of the labia majora and 2 (3.7%) with hematoma which did not required surgical intervention. There were no seroma, surgical site infections, or DVT reported. Analysis of complications regarding to the type of hormonal therapy they received showed that 8 (30.1%) patients presented with a complication in the estrogen only group and 8 (28.6%) patients in the combined group ($p = 0.859$). These included 8 (30.1%) minor wound dehiscence in the estrogen only group; six (21.45%) minor group dehiscence, and 2 (7.1%) hematomas in the combined group. Overall, there was no significant difference in complication rates between the two groups. Finally, patients who developed a complication were more likely to have gained weight from the time they started hormonal treatment to the date of surgery ($p = 0.002$) than patients who did not develop any complication. Differences in BMI at the start date of hormonal treatment or at the time of surgery, however, were not statistically significant (Table 5).

Table 2 Hormonal treatment groups

Variable	Estrogen only group	Combined group	*p*
Patients	26 (100)	28 (100)	
Age, years	35.6 ± 12.7	39.5 ± 13.8	0.256
Comorbidities			
HLD	3 (11.5)	1 (3.6)	0.342
DM	3 (11.5)	1 (3.6)	0.342
OSA	1 (3.9)	1 (3.6)	1.000
Duration of treatment, days	420 ± 34	425 ± 41	0.597

BMI, body mass index; *HLD*, hyperlipidemia; *DM*, diabetes mellitus; *OSA*, obstructive sleep apnea syndrome

Table 3 Effects of hormonal therapy

Variable	Estrogen only group	Combined group	*p*
Patients	26 (100)	28 (100)	
BMI			
Pre-treatment	26.4 ± 5.3	25.2 ± 5.3	0.336
At surgery	26.3 ± 5.2	25.5 ± 5.1	0.533
Difference, BMI points	− 0.14 ± 1.7	+ 0.3 ± 1.7	0.396
Specimen			
Weight, grams	30.2 ± 14.9	24.1 ± 8.7	0.033
Volume, cm^3	37.2 ± 20.1	36.9 ± 13.8	0.681
SC length, cm	5.4 ± 1.7	4.5 ± 1.6	0.009
Post-operative complication	8 (30.1)	8 (28.6)	0.859
Wound dehiscence	8 (30.7)	6 (21.4)	0.433
Hematoma	0 (0)	2 (7.1)	0.491
Seroma	0 (0)	0 (0)	–
DVT	0 (0)	0 (0)	–
Post-operative FU, months	6.6 ± 5.11	3.4 ± 2.3	0.014

BMI, body mass index; *DVT*, deep vein thrombosis, *FU*, follow-up

Discussion

Although there are several guidelines on clinical care of transgender patients from various international organizations, there is a lack of direct evidence based on longitudinal studies and most practice standards are based on expert opinion or interpretation of findings from other research study populations [9–11]. However, the most recent clinical practice guideline (2017) published by the American Endocrine Society bases many of its recommendations on a systematic review of current literature on transgender patients [8]. The authors recommend hormone therapy in patients who have entered the pubertal phase (typically Tanner stage 2) and recommend against puberty blocking in pre-pubertal children [7]. The guidelines recommend suppressing pubertal hormones with gonadotropin-releasing hormone (GnRH) analogs [8]. The evidence supporting this recommendation stems from a prospective follow-up study completed in the Netherlands that evaluated mental health outcomes in 55 transgender patients at three different times (prior to starting pubertal suppression therapy, initiation of pubertal suppression therapy, 1 year after gender confirmation surgery) [8, 12, 13]. The study found that the overall level of depression decreased significantly at the initiation of pubertal suppression therapy. However, gender-dysphoria did not resolve until gender confirmation surgery [8, 12, 13]. In addition, GnRH analog therapy can be reversed fairly quickly with cessation of treatment [8].

The guidelines also recommend initiating sex hormone treatment (estradiol in transfeminine patients, testosterone esters in transmale patients) in a staged manner (gradually increasing dosage every 6 months) due to the greater risk of irreversibility [6, 8, 12]. Sex hormone therapy, whether estrogen or testosterone, is associated with an increased adverse outcomes [6, 8, 12]. There is a moderate risk of developing coronary artery disease, cerebrovascular disease, hypertension, hypertriglyceridemia, cholelithiasis, severe liver dysfunction, and breast cancer [6, 8, 12]. Estrogen, specifically, has a very high risk of thromboembolic disease; whereas, testosterone has a very high risk of erythrocytosis [6, 8, 12]. Although the authors do comment on overall effects of hormone therapy leading to

Table 4 BMI correlation with surgical specimens

Variable	Correlation coefficient*	*p* value
BMI and weight	0.217	0.023
BMI and volume	0.062	0.518
BMI and SC length	0.118	0.225

BMI, body mass index; *SC*, spermatic cord

*Spearman's rank correlation coefficient

Table 5 BMI and complications analysis

Variable	Complications	No complications	*p*
Patients	38 (70.4%)	16 (29.6%)	
BMI			
Start[¥]	26.3 ± 5.4	25.5 ± 5.3	0.519
Surgery[μ]	27.3 ± 4.9	25.2 ± 5.1	0.181
Difference[β]	+ 0.97 ± 1.6	− 0.28 ± 1.5	0.002

BMI, body mass index

[¥] BMI when the patient started hormonal treatment

[μ] BMI at surgery date

[β] Difference between BMI at start hormonal treatment date and at surgery date

decreased testicular volume and ejaculate volume, there is no quantification of this phenomena [6, 8]. Based on our literature review, and to the best of our knowledge, our study is the first report testicular volumetrics changes within testicular tissue.

Beckwith et al. report in their population of 200 transgender patients, 95% of patients were prescribed hormone therapy by their primary care provider at the mean age of 31.8 years [13]. Interestingly, the authors note that there is a significant likelihood of unmonitored hormone therapy prior to the documented initiation date [14]. This finding is supported by several previous studies, with an estimated prevalence of medically unmonitored hormone use as high as 60% within the USA and Canada [4, 14–20]. This largely due to the significant difficulty of accessing appropriate medical care in the context of greater socioeconomic barriers [14–21]. Although we did not specifically evaluate for unmonitored hormone therapy in our patient population, we cannot assume our study population does not fall prey to this confounder.

Of note, to the best of our knowledge, all of our specimens were from patients who started hormone feminization therapy after their testes were completely developed. Hence, the changes observed in the testicular tissue at the time of orchiectomy may not demonstrate the true effects of hormone therapy. The effects of hormone therapy on testes in very early development may be quite different. However, the feasibility of such a study would be quite minimal due to inaccuracies of volumetric measurements outside of directly obtaining specimens.

Our results demonstrate a statistically significant lower specimen weight in patients who received estrogen and progesterone therapy compared to estrogen therapy alone. Based on our review, there is no current literature proposing an explanation for this finding. However, based on review of our data, we noted that patients who received estrogen and progesterone therapy were likely to have a higher BMI compared to patients who received estrogen therapy alone. Although this finding was not statistically significant, it would have reached statistical significance with a small increase in our sample size. Interestingly, patients who had a higher BMI were more likely to experience post-operative complications (i.e., minor wound dehiscence). There was no correlation between testicular volumetrics and BMI.

There are several known limitations to our study. The findings of this study may not be entirely generalizable to other healthcare institutions due the retrospective, single-institution nature of the study, and relatively small sample size. Although we did evaluate testicular pathology, our data was limited to permanent sections with limited analysis. In addition, true testicular volumetrics were only assessed at the time of the orchiectomy and there was no data recorded prior to this surgical intervention.

Conclusion

Transgender medicine is a complex multidisciplinary effort. Hormone therapy is a foundational element to this evolving clinical process and more rigorous hormonal therapy guidelines should be implemented in order to decrease undesirable side effects, decrease complications, and improve our current outcomes.

Funding None.

Compliance with ethical standards

Conflict of interest Trishul Kapoor, MD; Joseph Banuelos, BA; Todd B. Nippoldt, MD; Pedro Ciudad, MD; Jorys Martinez-Jorge, MD; Oscar J. Manrique, MD do not have any conflict of interest.

Informed consent Informed consent waiver was obtained from the institutional board review for this retrospective study and the study was deemed to be of minimal risk.

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