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BRIEF REPORTS

Effects of progesterone on gender affirmation outcomes as part of feminizing hormone therapy

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ABSTRACT

Background: The use of progesterone as a component of feminizing gender-affirming hormone therapy (GAHT) is controversial; however, use in transgender women continues owing to anecdotal reports of benefit.

Objectives: This study aimed to provide quantifiable outcomes data regarding the use of progesterone in transgender women by comparing groups from this population who use feminizing GAHT with and without progesterone.

Methods: This retrospective cohort study captured data from transgender female patients seen at the Summa PRIDE Clinic between September 2019 and December 2021. Data were extracted from chart documentation for patients who were prescribed feminizing GAHT, with and without progesterone, for at least 6 months during the study window. Outcomes included satisfaction with breast development, satisfaction with libido, mental health trends, and weight change at 0, 6, and 9 months from initiation of GAHT.

Results: A total of 88 charts were reviewed (59 in the standard group, 29 in the progesterone group). The progesterone group had statistically significant improvements in satisfaction with breast development at 6 months (53.8% vs. 19.6%; $P = 0.004$) and 9 months (71.4% vs. 20.8%; $P = 0.003$). The progesterone group had more patients at goal testosterone levels < 55 ng/dL at 6 months (47.6% vs. 33%) and 9 months (50% vs. 24.4%), but these were not statistically different. The progesterone group was also more likely to show improved provider-documented mental health at 6 months (70.6% vs. 28.2%; $P = 0.009$); however, the difference was not statistically significant at 9 months. There were no differences between groups for weight change and patient satisfaction with libido.

Conclusion: The addition of progesterone to standard feminizing GAHT was associated with greater satisfaction with breast development and improved patient mental health within 6 months compared with standard GAHT regimens alone in this patient population. Progesterone's impact on libido, testosterone suppression, and weight were nonsignificant.

Background

According to data published by the Williams Institute in 2022, approximately 1.6 million American adolescents and adults ages 13 years and older identify as transgender.[1] The American Psychiatric Association uses the term "gender dysphoria" to describe feelings of discomfort or distress associated with a person's assigned gender at birth, which classifies it as a mental disorder. The World Health Organization and the current 2022 iteration of the ICD-10 uses the term "gender incongruence" to describe a persistent experience of incompatibility between a person's gender identity and societal expectations based on their sex assigned at birth, which does not classify it as a mental disorder, thus decreasing the associated stigma surrounding the phenomenon.[2,3] Although common practice and standards of care guidelines exist for the treatment of gender incongruence, there is a lack of large-scale, randomized, controlled trial evidence to fully characterize the effects of currently available treatment options or to support the use of adjunct agents.

Transgender women and gender nonconforming individuals who desire feminine secondary sex characteristics may choose

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to undergo feminizing gender-affirming hormone therapy (GAHT) to achieve their goals of gender transition. According to a 2010 systematic review and meta-analysis, treating gender incongruence with GAHT leads to a statistically significant improvement in gender dysphoria, psychological symptoms, quality of life, and sexual function.[4] Based on a 2021 survey analysis of 11,914 transgender and nonbinary youth, the group who had access to GAHT showed statistically significantly lower rates of depression and suicidality.[5] Feminizing GAHT will typically lead to variable amounts of breast growth, decreased libido, decreased erectile function, decreased testicle size, softening of skin, decreased or slowed growth of body and facial hair, and body fat redistribution. There are no randomized controlled clinical trials evaluating the safety or efficacy of feminizing or masculinizing hormone regimens in the transgender population; however, there is a wealth of literature on the topic including small-scale trials, case reports, and consensus statements from various medical organizations.

According to published consensus statements and practice guidelines for the treatment of transgender women, a combination of estrogen and an antiandrogen is the most commonly studied and reported regimen of feminizing GAHT.[6-9] The most commonly used antiandrogen is spironolactone; however, other options include finasteride, dutasteride, and gonadotropin hormone-releasing hormone agonists such as goserelin. Cyproterone acetate is available as a first-line agent in countries outside of the United States.[6] Goal serum estradiol levels should remain less than 200 pg/mL, which mimics the midcycle range of estradiol levels during a menstrual cycle, and testosterone levels should be suppressed to less than 55 ng/dL. The addition of progesterone to feminizing GAHT regimens is controversial owing to conflicting case reports and anecdotal evidence that suggest progestins may or may not make any discernable difference in feminization. The role of progesterone in cisgender women is well characterized, with levels surging after ovulation, stimulating breast development by promoting alveologenesis and ductal side branching, as well as its use as a contraceptive and in fertility treatments.[10] Anecdotal evidence exists in transgender communities purporting the benefits of progestins, specifically their effects on increased breast tissue development as opposed to estrogen and antiandrogens alone. According to a study published in 1986, the addition of medroxyprogesterone acetate did not modify estrogen-induced changes in transgender women, specifically weight gain or breast growth.[11] However, this study enrolled only 19 patients with 8 receiving a progestin. Of note, many studies conducted before the 21st century regarding progestin use in transgender women used synthetic injectable medroxyprogesterone, which is no longer used as standard practice owing to its less favorable side effect profile and greater incidence of adverse effects compared with micronized progesterone, which is a bioequivalent progestin used much more frequently today for this indication. In addition, older studies on this topic often focus on formulations of estrogen that are no longer used in GAHT regimens. Currently, the most commonly prescribed formulation is oral 17-beta-estradiol. Of note, synthetic estrogens, such as ethinyl estradiol, are not recommended owing to potential increased risk of adverse events and inability to adjust dose based on serum levels. Based on limited evidence for its use in the breast development of transgender women, progesterone is not currently recommended in practice guidelines for the management of feminizing GAHT.[6-9] In addition to progesterone's purported effects on breast development, it has also been hypothesized that the upregulation of progesterone is associated with the alleviation of psychiatric symptoms including those present in depression, anxiety, and aggressive behaviors.[12]

Current guidelines from the American College of Obstetricians and Gynecologists, the European Society of Endocrinology, and the University of California San Fransisco for the management of feminizing GAHT do not make a strong recommendation for or against progesterone; however, they note that progesterone has been shown to increase breast development in cisgender women and should have the same effects in transgender women based on anecdotal evidence.[6-9] Currently available guidelines report on progesterone's potential adverse effects based on studies of postmenopausal cisgender women using hormone replacement therapy, which include blood clotting, increased risk of breast cancer, and weight gain.[11] Most previous studies on the effects of progesterone have focused primarily on cisgender women, often postmenopausal, which should not be directly applied to transgender women owing to developmental differences in breast tissue and gonadal hormone production, as well as notably different lifetime exposure to estrogen and progesterone from menstrual cycles. In addition, the adverse effect profile of injectable medroxyprogesterone is different from that of micronized progesterone, the most commonly used agent in patients seeking GAHT. Although the evidence surrounding progesterone's effects on breast development, clotting risk, breast cancer risk, and mental health is contradictory or nonexistent in this population, the absolute risk of using progesterone in transgender women is currently thought to be low. Given the available evidence, the general approach of the providers at the Summa PRIDE Clinic is not to proactively add progesterone to a patient's GAHT regimen. However, when patients request it, typically based on information they have found on the Internet, the providers are generally in favor of allowing patients an adequate trial.

Objectives

This study aimed to provide quantifiable outcomes data regarding the use of progesterone in transgender women.

Methods

This retrospective cohort study examined 2 subpopulations composed of transgender women at the Summa PRIDE Clinic in Akron, Ohio, which serves roughly 900 patients and specializes in the care of lesbian, gay, bisexual, and transgender people and other gender and sexual minority groups. The 2 subpopulations compared in this study were transgender women who were prescribed progesterone as part of their GAHT regimens and transgender women who were not prescribed progesterone in their GAHT regimens. Data from patients who established care with a provider of the Summa PRIDE Clinic from September 1, 2019, to December 1, 2021, were pulled and narrowed to patients who were assigned male at birth and prescribed an estrogen product. Patient charts were reviewed and data were extracted during December 2021. Patients were only excluded if

they did not follow up with the clinic while taking GAHT for at least 6 months or if they stopped GAHT within the first 6 months of initiation.

Primary outcomes included patient satisfaction with breast development, satisfaction with libido, mental illness severity trends, and suppression of testosterone levels. Weight change was analyzed as a secondary outcome. Outcomes were assessed at baseline, 6 months, and 9 months on standard GAHT and on progesterone to compare cohorts of patients on nonprogesterone feminizing GAHT and progesterone-containing GAHT regimens. Outcomes regarding satisfaction with breast development and satisfaction with libido were extracted from the narrative of physician chart notes by the same investigator. Three providers were involved in the care of all included patients and they used a structured documentation template that encouraged recording of this information.

Information for each outcome was categorized and documented in REDCap by the lead investigator using prespecified criteria. Patients without documentation for any outcome at any time point were not included in the analysis at that time point. Satisfaction outcomes, including breast development and libido, were categorized as satisfied, neutral, or unsatisfied. Patient mental illness severity was defined as provider-documented diagnosis that could be classified as mild if controlled by one or fewer medications, moderate if controlled by 2 or more medications, severe if uncontrolled on any number of medications resulting in disability or hospitalizations, or not present if the patient had no documented mental illness and no prescribed psychiatric medications. Included mental illnesses observed during data collection were anxiety, depression, bipolar disorder, obsessive compulsive disorder, schizophrenia, and dissociative identity disorder. Gender dysphoria and gender incongruence were not considered mental illnesses for the purposes of this study. At each data collection time point, patient mental health severity was categorized and then compared with the previous assessment to document change as worsening, improved, or unchanged.

Data were imported into IBM (Armonk, NY) SPSSv25.0 software and summarized by study group using appropriate descriptive statistics. Categorical data were compared for distributional equality via Pearson chi-square or Fisher's exact tests depending on cell sample size distribution. Numeric data were compared for rank equality between study groups via Mann-Whitney U tests. Statistical testing was 2 sided with $P < 0.05$ considered statistically significant unless otherwise noted. For outcomes measured at 2 postbaseline study points, a Bonferroni correction was applied and $P < 0.025$ was used to define statistical significance.

Results

A total of 112 patients were screened for inclusion and 88 patients were included in the study. All patients who were excluded were on GAHT for less than 6 months during the study period, discontinued GAHT within the first 6 months, or were lost to follow-up within 6 months of starting GAHT. The standard GAHT group (n = 59) and the standard GAHT plus progesterone group (n = 29) were comparable in all baseline characteristics, which are presented in Table 1. Group demographics were comparable between groups with a median age of 26 years for both groups. Most patients in the standard GAHT group and progesterone group were white (79.7% and 89.7%, respectively). Only one patient was identified that had a history of both renal impairment and liver impairment in the progesterone group.

Statistical analyses of each outcome are presented in Table 2. The group who received progesterone had statistically significant improvements in satisfaction with breast development at 6 months (53.8% vs. 19.6%; $P = 0.004$) and 9 months (71.4% vs. 20.8%; $P = 0.003$). The progesterone group had more patients at goal serum testosterone levels < 55 ng/dL at 6 months (47.6% vs. 33%) and 9 months (50% vs. 24.4%), but these were not statistically different. The progesterone group was also more likely to show improved health care provider-documented mental health at 6 months (70.6% vs. 28.2%; $P = 0.009$); however, this difference was not statistically significant at 9 months. There were no statistically significant differences between the standard GAHT group and the standard GAHT plus progesterone group for weight change or patient satisfaction with libido. Most patients who started

Table 1
Patient characteristics

	Standard GAHT group (n = 59)	Standard GAHT plus progesterone group (n = 29)	*P* value
Age (y), median (IQR)	26 (22–30)	26 (23–30)	0.813
Race, n (%)			0.188
White	47 (79.7)	26 (89.7)	
Black	9 (15.3)	3 (10.3)	
Hispanic	2 (3.4)	0	
Other	1 (1.7)	0	
History of smoking, n (%)	20 (33.9)	15 (51.7)	0.108
History of renal impairment, n (%)	0	1 (3.4)	1
History of liver impairment, n (%)	0	1 (3.4)	1
Baseline weight (kg), median (IQR)	86.9 (73.1–102.5)	83.1 (72.7–122.7)	0.699
Baseline libido, n (%)			0.41
Dissatisfied	2 (6.9)	0	
Neutral	19 (65.5)	8 (61.5)	
Satisfied	8 (27.6)	5 (38.5)	
Baseline mental illness, n (%)			0.692
None	20 (33.9)	10 (34.5)	
Mild	28 (47.5)	11 (37.9)	
Moderate	5 (8.5)	4 (13.8)	
Severe	6 (10.2)	4 (13.8)	

Abbreviations used: GAHT, gender-affirming hormone therapy; IQR, interquartile range.

Table 2
Results

	Standard GAHT group (n = 59 total)	Standard plus progesterone group (n = 29 total)	Difference *P* value
Breast development satisfaction at 6 mo, n (%)	6 mo (n = 56):	6 mo (n = 26):	0.004
Dissatisfied	6 (10.7)	0 (0)	
Neutral	39 (69.6)	12 (46.2)	
Satisfied	11 (19.6)	14 (53.8)	
Breast development satisfaction at 9 mo, n (%)	9 mo (n = 48):	9 mo (n = 14):	0.003
Dissatisfied	4 (8.3)	0 (0)	
Neutral	34 (70.8)	4 (28.6)	
Satisfied	10 (20.8)	10 (71.4)	
Libido satisfaction at 6 mo, n (%)	6 mo (n = 39):	6 mo (n = 19):	0.268
Dissatisfied	6 (15.4)	1 (5.3)	
Neutral	27 (69.2)	12 (63.2)	
Satisfied	6 (15.4)	6 (31.6)	
Libido satisfaction at 9 mo, n (%)	9 mo (n = 35):	9 mo (n = 7):	0.698
Dissatisfied	6 (17.1)	0 (0)	
Neutral	22 (62.9)	5 (71.4)	
Satisfied	7 (20)	2 (28.6)	
Mental illness severity trend at 6 mo, n (%)	6 mo (n = 39):	6 mo (n = 17):	0.009
Worsening	6 (15.4)	0 (0)	
Neutral	22 (56.4)	5 (29.4)	
Improving	11 (28.2)	12 (70.6)	
Mental illness severity trend at 9 mo, n (%)	9 mo (n = 31):	9 mo (n = 12):	0.19
Worsening	4 (12.9)	0 (0)	
Neutral	19 (61.3)	6 (50)	
Improving	8 (25.8)	6 (50)	
Patients at goal testosterone suppression (< 55 ng/mL) at 6 mo n (%)	6 mo (n = 45): 15 (33.3)	6 mo (n = 22): 10 (47.6)	0.265
Patients at goal testosterone suppression (< 55 ng/mL) at 9 mo, n (%)	9 mo (n = 41): 10 (24.4)	9 mo (n = 6): 3 (50)	0.326
Weight (kg) change at 3 mo, median (IQR)	Change at 3 mo (n = 22): 0 (−1.2 to 3.8)	Change at 3 mo (n = 6): −0.25 (−1 to 1.3)	0.649
Weight (kg) change at 6 mo, median (IQR)	Change at 6 mo (n = 24): 0.7 (−2.8 to 3.1)	Change at 6 mo (n = 10): −4.2 (−5.9 to 0.4)	0.095
Weight (kg) change at 9 mo, median (IQR)	Change at 9 mo (n = 31): 0 (−2.6 to 2.7)	Change at 9 mo (n = 5): −8.6 (−22.7 to −0.7)	0.063

Abbreviations used: GAHT, gender-affirming hormone therapy; IQR, interquartile range.

progesterone began after 1-6 months on a standard GAHT regimen (59.3%). The vast majority of patients on progesterone were first prescribed micronized progesterone 100 mg (93.1%); the remainder of patients were prescribed intramuscular medroxyprogesterone. Of those prescribed micronized progesterone, 25 patients took oral micronized progesterone and 2 patients were prescribed oral micronized progesterone to be administered rectally.

Discussion

The results of this study indicate that the addition of progesterone to standard feminizing GAHT regimens is associated with improved satisfaction with breast development and improved mental health within the first 6 months. Progesterone was not shown to make any discernable difference in weight or satisfaction with libido compared with standard GAHT regimens. Progesterone's effects on testosterone suppression may require further study based on the inconclusive findings in this study and the confounding fact that all patients included in this study were also prescribed the antiandrogen spironolactone at varying doses.

Adverse events associated with progesterone were not assessed in this study owing to the small sample size and absence of any documented occurrences. Oral progesterone has been purported as prothrombotic in postmenopausal women; however, no differences in mortality were observed in one large study despite this finding.[13-15] Literatures on the proliferative versus antiproliferative effects of progesterone leading to breast cancer are conflicting and do not provide definite evidence of risk.[6] The clinical significance of previous studies reporting adverse effects of progesterone when used by cisgender premenopausal or postmenopausal women should not generally be extrapolated to all transgender women. No patients included in this study reported any adverse events of progesterone aside from nausea and vomiting when first initiating use. The long-term effects of progesterone use in transgender women have never been studied, and the adverse effects in this population are largely unknown. Further studies are needed to truly weigh the benefits and risks of progesterone for these patients.

Owing to the subjective nature of patient satisfaction with personal gender transition goals, it may be difficult to objectively study the effects of progesterone in transgender women retrospectively. Breast development could be prospectively measured using mass and body measurements in future studies to avoid patient bias when reporting arbitrary satisfaction. Mental health could be prospectively assessed using prespecified criteria and validated patient-completed surveys. Owing to the time constraints of the research project, patient

surveys and consent forms were unable to be completed, and therefore, this study was done retrospectively. Owing to the retrospective chart review aspect of this study, all outcomes were not always explicitly documented in each follow-up chart note; therefore, satisfaction outcomes could not be assessed for all patients at all time points. Satisfaction with libido was talked about the least in provider notes, and therefore, the sample sizes were the smallest in the statistical analysis for this outcome. Most outcomes of this study were subjective in nature and could have led to a placebo effect for patients who believed that adding progesterone to their GAHT regimen would result in further breast development, improved mental health, and increased libido. Many patients at the PRIDE Clinic used telehealth visits during the coronavirus disease 2019 pandemic, which reduced the number of documented patient weights in the targeted time-frame as most patients were not physically present at the clinic. Finally, there was only one patient with documented liver and renal impairment; therefore, it would be difficult to extrapolate these findings to patients with liver or renal impairments.

Conclusion

The addition of progesterone to standard feminizing GAHT regimens was associated with greater satisfaction with breast development and improved patient mental health within the first 6 months than standard GAHT regimens alone in transgender women. Progesterone's impact on libido, testosterone suppression, and weight was nonsignificant. Owing to the subjective nature of the outcomes in this study, these results may not be indicative of the clinical effects of progesterone, but rather the patient's perception of these effects. These results provide preliminary support for some of the anecdotally reported benefits of progesterone in transgender women and emphasize the need for randomized, placebo-controlled trials using objective, validated measurements to further evaluate the role of progesterone in this population.

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