Fertility Preservation Outcomes in Adolescent and Young Adult Feminizing Transgender Patients

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abstract

BACKGROUND: Fertility preservation enables patients undergoing gonadotoxic therapies to retain the potential for biological children and now has broader implications in the care of transgender individuals. Multiple medical societies recommend counseling on fertility preservation before initiating therapy for gender dysphoria; however, outcome data pre- and posttreatment are limited in feminizing transgender adolescents and young adults.

METHODS: The University of Pittsburgh Institutional Research Board approved this study. Data were collected retrospectively on transgender patients seeking fertility preservation between 2015 and 2018, including age at initial consultation and semen analysis parameters.

RESULTS: Eleven feminizing transgender patients accepted a referral for fertility preservation during this time; consultation occurred at median age 19 (range 16–24 years). Ten patients attempted and completed at least 1 semen collection. Eight patients cryopreserved semen before initiating treatment. Of those patients, all exhibited low morphology with otherwise normal median semen analysis parameters. In 1 patient who discontinued leuprolide acetate to attempt fertility preservation, transient azoospermia of 5 months' duration was demonstrated with subsequent recovery of spermatogenesis. In a patient who had previously been treated with spironolactone and estradiol, semen analysis revealed persistent azoospermia for the 4 months leading up to orchiectomy after discontinuation of both medications.

CONCLUSIONS: Semen cryopreservation is a viable method of fertility preservation in adolescent and young adult transgender individuals and can be considered in patients who have already initiated therapy for gender dysphoria. Further research is needed to determine the optimal length of time these therapies should be discontinued to facilitate successful semen cryopreservation.

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Dr Barnard collected the data, conducted the initial analysis, and drafted the initial manuscript; Dr Rothenberg assisted in data analysis and reviewed the manuscript for important intellectual content; Drs Dhar, Menke, Witchel, and Montano were instrumental in acquiring the data and selecting patients for inclusion as well as critically reviewing and revising the manuscript; Dr Orwig conceptualized the study and reviewed and revised the manuscript; Dr Valli-Pulaski conceptualized and designed the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Most adult feminizing transgender individuals on gender-affirming therapy have abnormal semen parameters; however, studies show that parameters months after discontinuing treatment were similar to those of individuals not on therapy. Literature is sparse on this topic, particularly in adolescents.

WHAT THIS STUDY ADDS: This study features adolescents and young adults not previously studied in this context. Consecutive semen analyses were collected from 2 patients after discontinuing therapy for gender dysphoria to determine how cessation may change sperm quantity and quality.

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In the pediatric population, fertility preservation techniques were initially used to enable patients undergoing gonadotoxic cancer therapies to retain the option to have biological children after treatment. Fertility preservation techniques have now expanded their application to the preservation of fertility for transgender and gender-nonconforming individuals undergoing therapy for gender dysphoria. As early as Tanner Stage II, pubertal suppression with gonadotropin-releasing hormone (GnRH) agonists can be used to halt further development of secondary sex characteristics.[1] The effects of GnRH agonist therapy are reversible, allowing for the return of spermatogenesis after discontinuation.[2] Other androgen-lowering medication commonly employed in this population includes spironolactone.[1] For natal males, gender-affirming therapy primarily consists of estradiol. Although there is a lack of high-quality longitudinal data, there is concern that estradiol could induce irreversible damage to germ cells in the testes.[3] For this reason, the World Professional Association for Transgender Health, the Endocrine Society, and the American Society for Reproductive Medicine recommend counseling regarding fertility preservation before initiating a GnRH agonist or gender-affirming therapy.[4–6]

Although limited, recent studies have shed light on the reproductive insight and desires of transgender adolescents and young adults (AYAs) considering GnRH agonist and gender-affirming therapy. Most youth use online sources for information regarding the effects of these therapies on fertility, although 56% of the youth in 1 study also reported hearing about these issues from a physician.[7] An online survey revealed that transgender youth are interested in many types of family building, including adoption and having biological children.[8] However, other surveys have noted lower rates of interest in biological children in youth who identify as transgender, but notably, approximately half of them also questioned whether their feelings on having genetic children may change in the future.[7] Interestingly, in companion surveys of the parents of transgender youth and young adults, only 1 in 5 wished their children would have biological offspring; these numbers are lower when compared with the pediatric cancer population.[7]

Limited data are available on the use of fertility preservation services in the transgender AYA population. Surveys show that counseling on reproductive options and fertility preservation is variable depending on the patient population surveyed, ranging from 20.5% to 98%.[8–10] In 1 study focusing on referral patterns, only ∼13% of transgender AYAs were ultimately referred for fertility preservation, with a disproportionate number of referrals going to those of male natal sex.[10] With respect to use, a study of 105 transgender AYAs showed that only 13 opted for consultation on fertility preservation options, with 4 completing semen cryopreservation and 1 completing oocyte cryopreservation.[4] In regard to semen cryopreservation outcomes in the transgender AYA population, reports are limited to a single case series that describes the outcome of semen cryopreservation in 2 AYA transgender females.[9] No studies in the AYA population address semen cryopreservation after initiation of GnRH agonist and/or gender-affirming therapy. We aimed to report fertility preservation outcomes in the AYA population of feminizing transgender patients undergoing semen cryopreservation at our institution.

METHODS

Study Population

AYA transgender patients at our institution are seen predominantly by adolescent medicine or pediatric endocrinology providers. Each patient receives counseling on fertility preservation options before initiation of GnRH agonist and/or gender-affirming hormone therapy. All feminizing transgender AYA patients who expressed interest were referred for fertility preservation. Those referred between January 1, 2015, and September 30, 2018, were included in the study. Institutional review board approval was obtained from the University of Pittsburgh (PRO17060610).

Outcome Measures

Chart abstraction included patient age at fertility preservation consultation, age at semen cryopreservation, and semen analysis parameters. Any history of GnRH agonist and/or gender-affirming therapy was obtained as well as whether these therapies were discontinued before semen analysis. Semen parameters collected included volume of ejaculate, sperm concentration, motility, and morphology (modified Kruger criteria). Statistical analysis was performed by using Stata version 15.1 (Stata Corp, College Station, TX).

RESULTS

Patient Characteristics

All patients participating in fertility preservation were of non-Hispanic, white race. The median age at which patients first experienced gender dysphoria was 12 (range 6–14), with initial presentation for evaluation of gender dysphoria at age 17 (range 15–24; Table 1).

Eleven feminizing transgender patients accepted a fertility preservation referral from adolescent medicine or pediatric endocrinology

TABLE 1 Demographics for AYA Feminizing Transgender Patients

Previous Therapy, *n*	Age of Initial Gender Dysphoria	Age at Initial Gender Dysphoria Consultation	Age at Fertility Preservation Consultation
No previous therapy			
1	7	17	17
2	14	15	16
3	13	20	21
4	12	20	20
5	12	24	24
6	6	15	16
7	Unknown	Unknown	23
Previous therapy			
1	13	17	18
2	Unknown	18	19

for semen cryopreservation. Referrals from these providers resulted in telephone fertility preservation consultation with a member of the fertility preservation team at median age 19.5 (range 16–24). One patient accepted a referral due to strong parental preference but ultimately declined to proceed with fertility preservation. A total of 10 (90.9%) patients completed at least 1 collection. The median interval from referral to collection was 17 days (range 1–30 days). Results of the semen analysis were discussed via telephone with a reproductive endocrinology and infertility provider.

Patients With No Previous GnRH Agonist or Gender-Affirming Therapy

Eight of the 10 patients who participated in fertility preservation (80.0%) had no previous history of GnRH agonist and/or gender-affirming therapy. All patients were able to complete a collection (Table 2). Semen analysis parameters were overall within normal limits with the exception of abnormal morphology; median morphology was 6.0% normal forms (modified Kruger criteria, normal range >13.0%). After semen cryopreservation, all patients in the study proceeded with initiation of GnRH agonist therapy, and 4 patients concurrently started estradiol therapy. One patient opted to discard their collection for personal reasons ∼4 months after collection.

Patients With Previous History of GnRH Agonist or Gender-Affirming Therapy

Two patients had previously initiated treatment of gender dysphoria on presentation for semen cryopreservation (Table 3). The first patient had been treated with leuprolide acetate (15 mg intramuscular injection every 28 days) for 6 months before semen collection. At the recommendation of the pediatric endocrinologist, this medication was stopped before attempting semen cryopreservation. Three months after the last dose, semen analysis was attempted and showed 12 total sperm, with only 2 being motile. Two months later (5 months after the last leuprolide acetate dose), semen cryopreservation was again attempted and revealed semen analysis parameters that were within normal limits, with the exception of low morphology (9%).

The second patient had previously been on a regimen of spironolactone and estradiol for 26 months. Before fertility preservation, she was using 100 mg of spironolactone daily and a weekly transdermal estradiol patch delivering 75 μg per day. Although the patient was able to collect a specimen on all attempts, semen analysis revealed persistent azoospermia 2, 3, and 4 months after discontinuation of both medications. The patient ultimately was unsuccessful in fertility preservation efforts before completing scheduled gender-confirmation surgery with orchiectomy.

DISCUSSION

Semen cryopreservation is a feasible method of fertility preservation in

TABLE 2 Semen Analysis Parameters for Patients With No Previous GnRH Agonist or Gender-Affirming Therapy (*n* = 8)

Semen Analysis Parameters	Median	Range	Normal Reference
Volume, mL	3.0	0.75–6.1	>1.4
Density, million	21.0	2–80	>14.9
Motility, %	54.0	16.6–74	>39
Morphology,[a] %	6.0	3–10	>13
No. vials cryopreserved	10	4–25	N/A
No. collections	2	1–3	N/A

N/A, not applicable.

[a] Modified Kruger criteria.

TABLE 3 Semen Analysis Parameters After Discontinuation of Therapy for Gender Dysphoria

Patient	Gender-Affirming Therapy						Semen Parameters				
	Leuprolide Acetate, mg per 28 d	Spironolactone, mg per d	Estradiol, μg per d	Age of Initiation, y	Duration of Therapy, mo	Duration of Therapy Discontinuation, mo	Volume, mL	Density (per mL), Sperm	Motility, %	Morphology, %	No. Sperm Cryopreserved
1	15	N/A	N/A	17.5	6	3	1	12	16.6	N/A	12
						5	2	73 million	56	9	146 million
2	N/A	100	75	18	26	2	2.5	0	N/A	N/A	0
						3	1.5	0	N/A	N/A	0
						4	1.7	0	N/A	N/A	0

N/A, not applicable.

AYA feminizing transgender patients. For those individuals with no previous treatment of gender dysphoria, the process can be completed quickly, with collections occurring every 2 to 3 days to preserve several samples before initiating GnRH agonist or gender-affirming therapy. We found that patients with previous use of a GnRH agonist may require discontinuation for several months to allow for resumption of spermatogenesis. Further studies are needed to determine the length of time required for spermatogenesis to resume (if at all) after exposure to estradiol and/or spironolactone. The 1 individual taking these medications before collection in our study was azoospermic up to 4 months after discontinuation and opted to proceed with a scheduled orchiectomy. This information is critical to address as part of a multidisciplinary fertility discussion with youth and their guardians so that an informed decision can be made regarding fertility preservation use.

Limited studies in the adult population evaluating feminizing transgender patients pursuing semen cryopreservation for fertility preservation also reveal abnormal semen analysis parameters. In 1 report of 7 adult patients who completed semen cryopreservation while on gender-affirming therapy, 3 (42.9%) were azoospermic.[11] These individuals were taking estradiol and spironolactone, and 2 of the 3 were also on the 5-α-reductase inhibitor finasteride.[11] However, the other 4 adults who continued on gender-affirming therapy with estradiol and spironolactone during semen cryopreservation were able to successfully cryopreserve sperm, with 1 having completely normal semen analysis parameters.[11] In a retrospective study of patients discontinuing gender-affirming therapy to pursue fertility preservation, all individuals had normal semen analysis parameters an average of 4.7 months after discontinuation of gender-affirming therapy.[12] To date, no prospective studies have been published describing the time course of resumption of spermatogenesis after discontinuation of GnRH agonist or gender-affirming therapy in patients who are azoospermic while on treatment.

For many transgender patients, the potential need to discontinue GnRH agonist or gender-affirming therapy to allow for resumption of spermatogenesis may be a significant barrier to pursuing fertility preservation because cessation of therapy may result in exacerbation of gender dysphoria and progression of undesired male secondary sex characteristics.[9] For individuals for whom this risk is not acceptable or if azoospermia is noted on semen analysis, there are several alternate options, including electroejaculation, testicular sperm extraction, and testicular tissue cryopreservation. For feminizing youth who are uncomfortable with or unable to masturbate, electroejaculation with a transrectal probe can produce semen for cryopreservation.[13] Testicular sperm extraction is a surgical procedure that can be used for AYA feminizing transgender individuals with azoospermia, similar to its use in the infertility population or in patients with cancer for fertility preservation.[14] The option of testicular tissue cryopreservation, either as a fertility preservation procedure or in conjunction with gender-confirming surgery, offers an alternative experimental method.[15,16] This therapy is currently offered under research protocols for prepubertal boys undergoing other forms of gonadotoxic therapy, and its low-risk safety profile makes it an attractive option despite the limitations regarding future tissue use.[17] Although data on efficacy are lacking in the transgender population,

accessing the myriad fertility preservation options available to the infertility and cancer populations affords health care providers the ability to individualize treatment and minimize gender dysphoria in transgender AYA patients undergoing fertility preservation.

For the patients in our study who had no previous therapy, isolated low sperm morphology was noted in all samples. Morphologic assessment of sperm is the most subjective aspect of the semen analysis, even within a high-volume fertility clinic.[18] Additionally, there are no established semen analysis parameters for the AYA population. Comparison of the semen analysis parameters of youth (age $\leq$20) with malignancy to adults (age $>$20) with malignancy did not report any significant difference in values.[19] Other studies looking at semen analysis results in the population of young patients with cancer do not include morphology as a parameter studied.[20,21] A small study of adult transgender women referred for semen cryopreservation before starting gender-affirming therapy also noted sperm abnormalities with low morphology (7.98%) and total motile sperm concentration (8.7×10^6/mL).[22] Studies have also shown greater use of tight undergarments and tucking, whereby the penis and testicles are maintained in an inguinal position close to the body, in feminizing transgender adults, although it is unclear if these behaviors contribute to altered semen parameters.[23] Because counseling for semen cryopreservation does address sperm use in future fertility treatments, those with low morphology or other abnormal semen analysis parameters should have a particular focus on the potential need for advanced reproductive technologies, such as in vitro fertilization, to achieve future pregnancy.

Strengths of our study include the first published data on outcomes, including semen analysis parameters, in the transgender AYA population. Our study is unique in that it includes both individuals who are naïve to GnRH agonist and/or gender-affirming therapy as well as 2 individuals who were already on treatment for gender dysphoria. We are limited by a small sample size and the retrospective nature of this study. Lifestyle factors, including medication or illicit drug use and behaviors such as tucking, were unable to be accounted for unless noted in the medical record. We also did not have any patients present for semen cryopreservation who were unable to ejaculate to produce a specimen. It is possible that patients who are unable or uncomfortable with masturbation are self-selecting out of fertility preservation discussions once they understand the process, and it is important to explore other options, such as electroejaculation, testicular sperm extraction, or testicular tissue cryopreservation, for these patients to preserve fertility if they desire.

CONCLUSIONS

Semen cryopreservation can be used as a method of fertility preservation in the transgender AYA population. It would be optimal to have normative data with which to guide AYA transgender patients to avoid collection attempts resulting in azoospermia. Our experience suggests that further research is needed to determine the length of time needed for spermatogenesis to resume after discontinuation of GnRH agonist treatment. Further study is also needed to ascertain the long-term effects of gender-affirming therapy and prognosis for the return of spermatogenesis in transgender AYAs who present with azoospermia. Finally, additional studies are needed to assess if some AYA patients may be able to cryopreserve sperm without discontinuation of gender-affirming therapy.

ABBREVIATIONS

AYA: adolescent and young adult
GnRH: gonadotropin-releasing hormone

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