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Authors

Adeleye, Amanda
Stark, Brett
Jalalian, Liza
et al.

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SHORT REPORT

Evidence of Spermatogenesis in the Presence of Hypothalamic Suppression and Low Testosterone in an Adolescent Transgender Female: A Case Report

Amanda J. Adeleye,[†] Brett A. Stark,[†,*] Liza Jalalian, Evelyn Mok-Lin, and James F. Smith

Abstract

Objective: To report a novel case of semen cryopreservation after testicular sperm extraction in an adolescent transgender female without cessation of gonadotropin-releasing hormone (GnRH) agonist therapy and feminizing hormone therapy.

Methods: This is a case report of a 16-year-old transgender female using leuprolide acetate for 4 years and estradiol for 3 years requesting semen cryopreservation at the time of gender-affirming orchiectomy. She desired to proceed without cessation of gender affirming hormone therapy. The patient's consent was obtained for written publication.

Results: The patient underwent testicular sperm extraction followed by orchiectomy. The sample was processed and cryopreserved in a 1:1 Test Yolk Buffer. Multiple early and late spermatids were identified as well as spermatagonium in the TESE specimen.

Conclusion(s): Advanced spermatogenesis may occur in the presence of a GnRH agonist. Cessation of GnRH agonist therapy may not be essential for semen cryopreservation in adolescent transgender females.

Keywords: estradiol; fertility preservation; GnRH agonist; semen cryopreservation; testicular sperm extraction; transgender

Introduction

Transgender and gender expansive (TGE) adolescents have a stated gender identity that differs from their sex assigned at birth.[1] TGE people may present to medical care at a variety of ages to initiate medical treatment for the purpose of gender affirmation. The World Professional Association for Transgender Health, Endocrine Society, and American Society of Reproduction all recommend counseling TGE individuals on fertility preservation (FP) before initiation of gender-affirming treatment (GAT).[2]

As TGE adolescents are presenting at increasingly younger ages, a portion of these individuals may not complete puberty before initiation of GAT. This early presentation can be an obstacle to FP for TGE individuals who have not yet developed mature gametes. The current dogma is that spermatogenesis begins in early puberty, but physical manifestations of puberty vary greatly among boys at the time of spermarche. It is presumed that spermatogenesis is dependent upon some hypothalamic activity, gonadotropin secretion, and the production of testosterone.[3] Histological studies of cadaver specimens or testicular biopsies for medically indicated cryopreservation have demonstrated that there may be a prepubescent expansion of the types

Division of Reproductive Endocrinology and Infertility, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California San Francisco, San Francisco, California, USA.
[†]Cofirst author.

*Address correspondence to: Brett A. Stark, MD, MPH, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California San Francisco, 499 Illinois St, San Francisco, CA 94158, USA, E-mail: brett.stark@ucsf.edu

A and B spermatagonial stem cells, but to date, data do not support more advanced spermatogenesis in early childhood.[4,5]

This report describes the case of a transgender female who presented for gender-affirming surgery and consequent testicular sperm extraction after years of pubertal suppression without cessation of a gonadotropin-releasing hormone (GnRH) agonist and feminizing hormone treatment (FHT) in early puberty (Tanner 2).

Materials and Methods

Our patient is a 16-year-old transgender female who presented to the department of urology and was evaluated by a reproductive urologist in consultation for gender-affirming surgery. Her history is notable for initiation of pubertal suppression with a GnRH agonist (leuprolide acetate 7.5 mg IM monthly) at age 12 years, which was later changed to a leuprolide acetate dose of 11.75 mg IM every 3 months by the patient's request for convenience. Her physical examination at the time was consistent with Tanner stage 2. One year later, at age 13 years, she initiated FHT that consisted of estradiol patches with titration to her current dose of transdermal estradiol 0.1 mg twice weekly. There were no periods of discontinuation of hormonal treatment. After living her identified gender for 10 years, she made the decision with her family to pursue gender-affirming surgical treatment at age 16 years.

Her growth curve was noted to slow in the year before surgical intervention. At age 14 years she was at the 46th percentile for height and 42nd percentile for weight on the CDC growth chart for females. Three months before surgical intervention, at age 15 years, her height was at the 34th percentile for her age and 36th percentile for weight on the CDC growth chart for females with a BMI of 18.95 kg/m^2.

Laboratory results collected 6 months before presentation demonstrated adequate hypothalamic suppression with an FSH < 0.7 mIU/mL (reference range for pubertal cisgender boys: 1.0–12.0 mIU/mL), luteinizing hormone (LH) 0.3 mIU/mL (reference range for pubertal cisgender boys: 0.6–12.1 mIU/mL), and a total testosterone of 8 ng/dL (reference range for pubertal cisgender boys: 158–826 ng/dL). Serum estradiol on 0.1 mg of twice weekly transdermal estradiol was 124 pg/mL (reference range for pubertal cisgender boys: 3–34 pg/mL). At the time of initial evaluation at University of California, San Francisco, she was 16 years of age and remained at tanner stage 2. A preoperative evaluation of semen parameters and analysis of urine for the presence of spermaturia were offered but declined due to patient discomfort. She underwent an uncomplicated testicular sperm extraction followed by bilateral orchiectomy and creation of a neovagina. In accordance with the patient and her parent's wishes, all testicular tissue was inspected to determine whether any sperm could be retrieved. All data was obtained from chart review and reported without any patient identifiers. IRB exemption from our institution was obtained for this study.

Results

After digestion and dilution in a 1:1 Test Yolk Buffer, inspection of the patient's testicular sample demonstrated no evidence of mature spermatozoa. However, multiple early and late spermatids were identified as well as spermatogonium (Fig. 1). This specimen was cryopreserved.

Discussion

With the recommendation to consider FP before the start of GAT, there is a growing number of adolescents on pubertal suppressive agents presenting for discussion of FP.[6,7] This presents a unique challenge for peripubertal girls for whom it has been presumed that there is no spermatogenic activity. Pubertal suppression with a GnRH agonist has been well documented as reversible in non-TGE populations, allowing reactivation of pubertal development and secondary sexual characteristics consistent with natal sex upon cessation of treatment.[8–10] In cisgender adolescent males with precocious puberty, sperm can be found in the urine within 0.7–3 years after GnRH agonist cessation.[11] In adolescent transgender females, data on sperm production after prolonged GnRH agonist therapy are limited to one case series of two patients, only one of whom had evidence of spermatogenesis 3 months after cessation of GnRH agonist therapy.[12] Our patient had a physical examination and laboratory values consistent with sufficient hypothalamic suppression. This case report demonstrates the first evidence of early spermatogenesis in an adolescent transgender female despite hypothalamic suppression with GnRH agonist therapy.

Spermatogenesis in the absence of male levels of testosterone or LH stimulation is contrary to the classical teaching of spermatogenesis. Without testosterone, formation of the blood–testis barrier is compromised, germ cells do not progress through meiosis, and mature sperm are thought to be unable to be released from Sertoli cells.[13] Notably, spermatogenesis starts

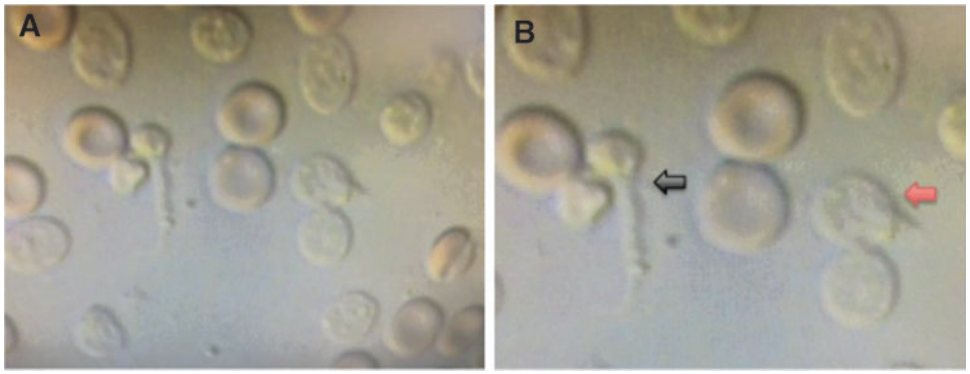

FIG. 1. Evidence of spermatogenesis in the presence of GnRH agonist suppression. 10× light microscopy of TESE specimen **(A)** 10× **(B)** Late spermatid (*left arrow*) early spermatid (*right arrow*). GnRH, gonadotropin-releasing hormone; TESE, testicular sperm extraction.

before puberty and spermarche, the beginning of mature sperm production, often precedes the ability to ejaculate. Sperm may be detected in urine samples from cisgender boys generally occurring around age 12 or 13 years.[14] Our patient had demonstrated early signs of puberty, which was the impetus for initiating GnRH agonist therapy, suggesting that she may have had sufficient enough hypothalamic pituitary activation to initiate spermatogenesis. However, her initial pubertal signs were remote from surgical intervention that occurred 4 years later, and any spermatocytes produced in early puberty would not be present years later.

The potential for spermatogenesis in the absence of testosterone or gonadotropin stimulation raises the possibility of FP without discontinuation of GnRH agonist or gender-affirming therapy. This discontinuation has previously been shown to be a significant barrier to pursuing FP due to the potential progression in undesired masculine secondary sex characteristics and the associated exacerbation in gender dysphoria.[15] Other methods of FP for peripubertal transgender girls, such as electroejaculation with a transrectal probe[16] and surgical retrieval of sperm,[17] may also be feasible without discontinuation of GnRH agonist or gender-affirming therapy. Pursing FP without hormonal discontinuation could greatly improve the quality of life for those who find discontinuation intolerable.

There are multiple limitations to this study. First, this study is a single case report. Although this report is hypothesis generating, it is not widely applicable. Data from other transgender girls with a similar experience would be key to understanding the likelihood of sperm retrieval from early pubertal transgender girls. In addition, this was a clinical case and the finding of maturing spermatids was unexpected. Therefore, additional histological evaluation to discern germ cells versus postmeiotic maturing spermatocytes was not completed. Given the distinct morphological appearance of spermatids, our visual data support that this transgender girl did produce spermatids in an atypical hormonal milieu. In addition, gonadotropin and sex steroid levels were collected remote from surgical extraction of testicular tissue. It is conceivable that she may have had incomplete pituitary suppression. However, given her gender dysphoria, she maintained her hormonal regimen up until surgery, and the combined use of a GnRH agonist and exogenous estradiol would be expected to exert significant gonadotropin suppression. Finally, this cryopreserved specimen has not been assessed for fertility potential.

For transgender girls who have not yet reached spermarche, testicular tissue cryopreservation may become a viable option in the future. However, successful maturation of spermatogonial stem cells in testicular tissue has not yet been demonstrated in humans.[18] Families who choose this option are relying on future research to progress rapidly in their lifetime before using cryopreserved tissue, hence this may be a temporally and financially implausible option for most.[18,19]

This case report suggests that cessation of GnRH agonist therapy may not be essential for FP in adolescent transgender females. Further research is needed to determine the impact of GnRH agonist therapy on spermatogenesis in adolescent transgender females.

Among transgender adolescents who pursue FP, information about the semen quality and eventual reproductive capability of these specimens will be critical.

Author Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

FHT = feminizing hormone treatment
FP = fertility preservation
GAT = gender-affirming treatment
GnRH = gonadotropin-releasing hormone
LH = luteinizing hormone
TESE = testicular sperm extraction
TGE = transgender and gender expansive