Fertility preservation in transgender men without discontinuation of testosterone

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Objective: To report two cases of fertility preservation in two transgender men without an extended period of higher dose testosterone cessation.
Design: Chart abstraction was completed for two cases of oocyte preservation in transgender men without stopping testosterone gender-affirming therapy before controlled ovarian stimulation (COS).
Setting: A university-affiliated fertility clinic in San Francisco, California.
Patient(s): Two 27-year-old transgender men on higher dose testosterone undergoing oocyte cryopreservation.
Intervention(s): Not applicable.
Main Outcome Measure(s): Both patients had been on 6 and 20 months of testosterone therapy, respectively, and continued throughout COS. A random start antagonist plus letrozole protocol was used for the patient in case 1, with a leuprolide acetate trigger. A luteal start antagonist protocol was applied to the patient in case 2 with a leuprolide acetate trigger.
Result(s): In case 1, a total of 35 oocytes were retrieved, with a total of 23 metaphase II (MII) oocytes cryopreserved. An additional 7 MII oocytes were obtained after in vitro maturation for a total of 30 MII oocytes that were vitrified. In case 2, 14 oocytes were retrieved, and 9 mature oocytes (MII) were vitrified.
Conclusion(s): Transgender men have historically been advised to discontinue testosterone before COS, a process that may be distressing for many individuals. This is the first published case report demonstrating the proof of concept of COS without cessation of high-dose testosterone therapy in two transgender men. Future studies with larger sample sizes should be performed to confirm these findings. (Fertil Steril Rep® 2022;3:153–6. ©2022 by American Society for Reproductive Medicine.)
Key Words: Fertility preservation, transgender, ovarian stimulation, testosterone, oocyte preservation

The World Professional Association for Transgender Health, Endocrine Society, and American Society of Reproduction all recommend counseling transgender men on Assisted Reproductive Technologies (ART) and fertility preservation (FP) before initiation of gender-affirming treatment (GAT) (1). For postpubertal transgender men who present after initiating GAT with testosterone therapy, data on best practices for FP are limited because our current understanding of the long-term impact of testosterone therapy on reproduction is poorly understood and largely speculative.

The current practice, due to lack of data on controlled ovarian stimulation (COS) and oocyte outcomes while continuing high-dose testosterone therapy, is to temporarily suspend testosterone treatment for an arbitrary length of time, usually between 1 and 6 months or until the resumption of menses (2–4). However, COS involves significant "female" hormone exposure with associated physical symptoms, frequent monitoring with transvaginal ultrasound, and transvaginal aspiration of oocytes under sedation. While these procedures alone can be traumatic to some transgender men, the physical changes associated with discontinuation of testosterone and female hormonal stimulation can be significantly dysphoric and a possible barrier to those seeking FP (4, 5).

One published case report demonstrated successful COS with leuprolide acetate injection for final maturation of the oocytes in a 20-year-old transgender man who had been on testosterone therapy for 18 months (6). At the time of retrieval, the patient was on 25 mg of weekly intramuscular testosterone, and a total of 22

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metaphase II oocytes were cryopreserved (6). According to standard guidelines for the management of masculinizing hormone therapy, typical dosing of intramuscular/subcutaneous testosterone cypionate for transgender men is 50 mg/week, with a maximum dosage of 100 mg/week (7). Lower dosages of testosterone, starting as low as 20 mg/week intramuscularly/subcutaneously, are recommended for genderqueer and nonbinary individuals (7).

In our clinic, patients presenting on testosterone therapy at the time that they decide to proceed with COS are informed of the unknown effects of testosterone on the ability of the ovary to respond to gonadotropin stimulation, oocyte quality, the ability of these oocytes to fertilize, live birth rates, and potential long-term epigenetic effects on offspring. Patients are recommended to withhold testosterone treatment for 1–3 months before initiation of COS. Despite this counseling, patients still may elect to proceed with COS without cessation of testosterone therapy.

We report herein two cases of oocyte preservation in transgender men who elected to undergo COS for FP without cessation of GAT with higher dosages of testosterone cypionate therapy day.

CASE REPORT

With each patient's written informed consent, we conducted a retrospective chart review of two patients who underwent ART for FP without cessation of GAT with testosterone from 2020 to 2021. All data was obtained from chart review and reported without any patient identifiers. Institutional review board exemption from our institution was obtained for this study.

Case 1

A 27-year-old transgender man who had been taking weekly testosterone injections since April of 2019 was referred for FP counseling in May of 2020 in preparation for a gender-affirming hysterectomy and bilateral salpingo-oophorectomy. He was nulliparous and had been amenorrheic since May of 2019. Before starting testosterone, he had regular 28-day cycles. He endorsed a remote history of oral contraceptive pills used for birth control. His medical history was notable for diabetes and hypertension. He had undergone bilateral mastectomy. He was taking subcutaneous testosterone cypionate 80 mg weekly. On examination, his vital signs were normal, and his body mass index was 25.06 kg/m^2. A transvaginal ultrasound showed an anteverted uterus (volume, 33 cm^3), an endometrial stripe of 5.3 mm with normal ovaries bilaterally, and an antral follicle count (AFC) of 36. His serum testosterone level at the time of presentation was 1,273 ng/dL, and his serum antimüllerian hormone level was 11.9 ng/mL. The options for FP were reviewed in detail, and the patient expressed interest in oocyte cryopreservation.

He decided to proceed with FP in January 2021 and continued testosterone (80 mg subcutaneously) throughout the process. Given the presence of amenorrhea, a random start protocol was initiated with subcutaneous follitropin alfa (150 IU; Gonal-F, Merck Canada) and subcutaneous menotropins (150 IU; Menopur, Ferring Canada). Letrozole (5 mg orally; Femara) was given daily throughout the stimulation to maintain low estradiol (E2) levels for the purpose of minimizing the potential dysphoria associated with elevated levels and potential withdrawal bleeding on completion of the cycle. On stimulation day 4, his dosage of menotropins was decreased to 75 IU subcutaneously. Daily subcutaneous ganirelix acetate (0.25 mg; Orgalutran, Merck) was initiated on stimulation day 8 until the day of trigger. Because of a robust response, his follitropin alfa (Gonal-F, Merck Canada) dose was decreased to 75 IU subcutaneously on stimulation day 9. At this time, the patient's E2 was noted to be 1,381 pg/mL, and he endorses symptoms of abdominal bloating. Given his desire to maintain physiologically low levels of estrogen, letrozole was increased to 7.5 mg orally on stimulation day 11.

Follicle tracking was performed by transvaginal ultrasound without difficulty. When the lead follicle reached 20 mm, with most follicles in the 13–20 mm range, a subcutaneous leuprolide acetate trigger (4 mg [0.8 mL]) was given. Laboratory values before the trigger included luteinizing hormone (LH) levels of 5.97 IU/L and E2 levels of 1371 pg/mL. Post-trigger laboratory findings revealed an appropriate response to the agonist trigger with LH levels of 67.23 IU/L and progesterone levels (p4) of 12.3 nmol/L. The endometrium achieved a thickness of 8.6 mm. There were a total of 35 oocytes retrieved, with a total of 23 MII oocytes cryopreserved on the day of retrieval. An additional 7 oocytes progressed to MII 1-day postretrieval with in vitro maturation for a total of 30 MII oocytes that were vitrified. The patient reported no major side effects related to the ovarian stimulation aside from mild abdominal cramping and bloating.

Case 2

A 27-year-old transgender man who has been taking weekly testosterone injections since August of 2020 presented in September 2020 for FP counseling. He was nulliparous with regular 28-day menses even before the initiation of testosterone therapy. He denied previous hormonal contraceptive pill use. He was healthy and was preparing to undergo a bilateral mastectomy. He was taking testosterone cypionate (60 mg subcutaneously weekly) with plans to increase his dose on completion of ART (to 80 mg subcutaneously weekly). On examination, his vital signs were normal, and his body mass index was 29.05 kg/m^2. A transvaginal ultrasound showed an anteverted uterus (volume, 35 cm^3), an endometrial stripe of 3.8 mm with normal ovaries bilaterally, and an AFC of 9. His serum T level at the time of presentation was 410 ng/dL, and his antimüllerian hormone level was 2.67 ng/mL. The options for FP were reviewed in detail, and the patient expressed interest in oocyte cryopreservation.

In February of 2021, with the continuation of his weekly testosterone, he started follitropin alfa (300 IU; Gonal-F, Merck Canada) and menotropins (150 IU; Menopur, Ferring Canada) subcutaneously after completion of a baseline ultrasound and confirmation of entrance to the luteal phase. The patient was counseled on the use of letrozole (5 mg orally; Femara) to maintain low E2 levels for the purpose of minimizing the potential dysphoria associated, but he declined. Daily

ganirelix acetate (0.25 mg; Orgalutran, Merck) was injected starting on stimulation day 5 until the day of final oocyte maturation. Follicle tracking was performed by transvaginal ultrasound without difficulty. When the lead follicle reached 22 mm with the majority in the 13–18 mm range on stimulation day 9, a leuprolide acetate subcutaneous trigger (4 mg [0.8 mL]) was given. On the day of trigger, his max E2 level was 1,749 pg/mL and LH level was 2.11 IU/L. One day after the trigger, his laboratory values included an LH level of 19.09 IU/L and a progesterone level of 3.3 nmol/L. Given the low-normal levels in response to agonist trigger, a chorionic gonadotropin (5,000 IU subcutaneously; Pregnyl, Merck Canada) booster was given that evening and he proceeded with an oocyte retrieval 36 hours after the agonist trigger. The endometrium achieved a thickness of 8.8 mm. There were a total of 14 oocytes retrieved, and 9 MII oocytes were vitrified. The remainder of the oocytes were germinal vesicles, and postretrieval in vitro maturation was unsuccessful. The patient tolerated the process well and reported no major side effects of ovarian stimulation aside from mild abdominal bloating.

DISCUSSION

This is the first case report demonstrating the proof of concept of COS for FP in transgender men without cessation of typical to high-dose testosterone therapy. In our current case report, the patients in the described cases were on 6–20 months of testosterone before undergoing oocyte cryopreservation. The dosages described in these two cases are higher than the level observed in the previously described case study (6).

Many parallels can be made to FP for transgender men and oncofertility patients. To increase the chance for success in oncofertility, COS is typically performed with high doses of gonadotropins to maximize the number of oocytes retrieved and stored (8). In our clinic, a similar approach is often used with transgender men in an attempt to reduce the burden and potential gender dysphoria associated with multiple rounds of COS. Interestingly, studies evaluating ovarian histological changes after testosterone exposure in birth-assigned females have reported an ovarian phenotype similar to polycystic ovary syndrome–polycystic follicles with increased AFC with increased collagenization of the tunica albuginea, stromal hyperplasia, and luteinization of stromal cells (9–11). Patients with this ovarian morphology, particularly with a high AFC, as seen in patient 1 of our series, are known to be at higher risk for ovarian hyperstimulation syndrome (12). To balance the desire of maximizing success with as few COS cycles as possible and the risk of OHSS, we routinely implement antagonist protocols with leuprolide acetate trigger to reduce the risk of OHSS in this theoretically high-risk patient population (12). Prior research has shown that in TM populations with testosterone exposure, antagonist-based protocols are a feasible means of ovarian stimulation (13).

It is notable that the patient in case 1, who was receiving higher doses of testosterone at the time of COS and had evidence of higher systemic testosterone levels, had a particularly robust response to agonist trigger in comparison to the patient in case 2 of our study. In the previously described case report of one transgender male undergoing COS without cessation of lower dose testosterone, the authors noted a blunted response to agonist trigger and brought into question the ability of the pituitary to mount a physiologic response after prolonged testosterone exposure (6).

As COS is associated with exposure to supraphysiological levels of estrogen, a significant concern exists regarding the safety of the procedure in patients with hormone-sensitive cancers (14, 15). As such, the use of letrozole in conjunction with classic COS protocols has been advocated to avoid unnecessary and potentially harmful effects associated with the rise in estrogen levels on cancer (16, 17). The COS with letrozole was associated with significantly decreased peak estradiol levels without any negative impact on the number of mature oocytes collected (18). We use a similar approach with transmasculine individuals in our clinic, routinely counseling patients on the potential benefits of letrozole. While letrozole does, to an extent, limit our ability to track follicular growth, it decreases the individual's exposure to estrogen and the potentially dysphoria-inducing symptoms, including posttreatment withdrawal bleeding. The patient in case 2 opted to not proceed with letrozole therapy as he had recently started testosterone therapy and was not yet amenorrheic. Prior studies have shown there is a dose-dependent amenorrheic response to testosterone and, while >90% of transmasculine people on testosterone achieve amenorrhea by 6 months, menses can persist for up to a year or longer (19, 20).

While COS has historically been a viable option for many transgender men, it is not without major limitations. Little is known regarding the long-term impact of testosterone exposure on embryo quality, fertilization, pregnancy outcomes, and long-term outcomes from offspring. A study by Lierman et al. (21) from 2017 assessed the developmental competence of testosterone-exposed oocytes in transgender men. In this study of 16 transgender men, the authors found that the spindle structure analysis, a qualitative marker for oocyte functionality, and chromosomal alignment after vitrification appeared normal (21).

To the author's knowledge, no relevant animal studies or case reports of pregnancies using androgen-exposed oocytes without cessation of testosterone during COS have been described, and our current understanding of the long-term impact of testosterone exposure on reproductive outcomes is largely speculative. In a cross-sectional study of 41 transgender men who became pregnant and delivered after transition, 5 transgender men became unintentionally pregnant while amenorrhoeic on testosterone (3). While the detailed length of time on testosterone was not described for these 5 individuals, data from this study as a whole argues that transgender men on testosterone can retain fertility and become pregnant (3).

Two recent studies report outcomes of transgender men with a history of testosterone use after temporary discontinuation of testosterone before COS. Adeleye et al. (13) reported on COS outcomes in a cohort of 13 transgender men, 7 with a history of testosterone use for a median of 46 months. Notably, 3 transgender men with prior testosterone use presented for further family planning, with 2 desiring transfer

of embryos with donor insemination into cisgender female partners and 1 desiring autologous transfer of embryos inseminated with cisgender male partner's sperm. All 3 couples became successfully pregnant. Leung et al. (22) reported on ART outcomes in 26 transgender men, 61% of whom had been on testosterone from 3 months to 17 years. Seven couples desiring pregnancy were described; all 7 ultimately became pregnant with deliveries of healthy children. While small and retrospective in nature, both of these studies suggest that follicular development and oocyte quality do not seem to be significantly impacted by prior testosterone use (13, 22).

CONCLUSION

We present two cases of transgender men undergoing COS without cessation of testosterone GAT. Both patients in the reported cases had adequate responses to COS while continuing 60–80 mg of testosterone therapy. Additionally, our patient on 20 months of testosterone had a robust response to an agonist-only trigger. This case report adds to the small body of literature exploring the necessity of stopping testosterone therapy before the initiation of ART in transgender men. Continuation of testosterone may improve the experience of transgender men and decrease gender dysphoria exacerbation that has previously been described with COS. Additional outcomes, including fertilization rates, embryo quality, pregnancy and live birth rates, and long-term outcomes for offspring, should be further investigated.

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