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Commentary

Breaking Down Barriers to Reproductive Care for Transgender People

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There are an estimated 1.4 million transgender adults in the United States, representing 0.6% of the population.[1] Transgender and gender diverse (TGD) individuals have gender identities that differ from their recorded sex at birth, and medical/surgical interventions are often pursued to better align these. Gender-affirming medical therapy, including pubertal suppression and initiation of gender-affirming hormone therapy (GAHT), improves quality of life and psychological outcomes.[2,3]

Surgical treatment that includes gonadectomy unquestioningly results in sterilization, but the impact of long-term—GAHT on future reproductive function is still unknown. The World Professional Association for Transgender Health, Endocrine Society, and the American Society for Reproductive Medicine all recommend counseling on the potential risk for fertility impairment and options for fertility preservation (FP) prior to initiating GAHT.[4–6]

Recent advances in assisted reproductive technology (ART) have allowed TGD patients to consider both reproductive and transition goals at initiation and throughout GAHT. Options for FP include oocyte or embryo cryopreservation for transgender men (recorded female at birth, identify as male/masculine) and sperm cryopreservation with semen from ejaculation or testicular sperm extraction for transgender women (recorded male at birth, identify as female/feminine). There are currently no studies addressing fertility potential of gonads treated with pubertal suppression and subsequent GAHT, but the viability of FP options for gonads that have not undergone endogenous puberty is questionable. Ovarian tissue and testicular cryopreservation with in vitro maturation are promising options for prepubescent patients, but testicular cryopreservation is still considered experimental (with no live births to date), and the small numbers of live births after ovarian cryopreservation (no longer experimental as of 2020) were from postpubescent tissue.[7]

Although TGD youth and adults desire to have children and build families, overall prioritization and utilization of FP is low at less than 5%, often due to the desire to move forward with medical transition without delay.[8–14] A cross-sectional survey of transgender youth and parents within a gender clinic showed that the majority of youth are unwilling to delay GAHT for up to 3 months to preserve fertility; 34% would have pursued FP while continuing GAHT if that were an option.[15] Another cross-sectional survey showed that transgender youth ranked having children as lowest among 8 life priorities, because they did not want to delay or stop GAHT.[16] TGD youth may not consider long-term reproductive health implications, and many may wish to have children after transition. A survey of 50 transgender men who had already completed gender-affirming genital surgery reported that 77% had not considered FP at the time of GAHT initiation, but 54% currently reported a desire for children.[11] Additional barriers to FP include cost, invasiveness of procedures, patient perception of mistreatment, discrimination or bias, lack of awareness, and insufficient training of health care providers.[13,16,17]

The literature on FP outcomes in transgender men has previously been limited to case series and observational studies of oocyte or embryo cryopreservation prior to the initiation of GAHT. Although fertility rates after testosterone initiation are largely unknown, the available published data support the continued potential for conception while on this treatment, especially if doses are too low or there is noncompliance. In one survey of transgender men who had a live birth, 80% had been on testosterone and resumed menses within 6 months of cessation, 84% had used their own oocytes for conception, and 32% had conceived while still on testosterone.[18] The duration of testosterone use, however, was short at less than 2 years for over half the participants. Another recent study looked at longer durations of previous testosterone use when describing 7 successful pregnancies among transgender men after in vitro fertilization (IVF).[19] The outcomes of egg retrieval and ovarian stimulation for oocyte cryopreservation were similar

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Abbreviations: ART, assisted reproductive technology; FP, fertility preservation; GAHT, gender-affirming hormone therapy; IVF, in vitro fertilization; TGD, transgender and gender diverse.

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among transgender men who had never been on testosterone versus transgender men who had been on testosterone and cisgender women. The duration of testosterone use had no impact on outcomes, with the longest duration being 17 years; however, all patients had to stop testosterone until the return of menses (an average of 4 months).

Most published literature have reported a recommendation between 1 and 6 months off testosterone for transgender men undergoing fertility treatments.[20,21] Temporary cessation of GAHT may lead to anxiety and increasing gender dysphoria, especially when it leads to resumption of menses and regression of desired secondary sex characteristics. Additionally, the process of ovarian stimulation may take several weeks with multiple injections of gonadotropins that result in elevated estradiol levels as well as serial transvaginal ultrasounds which may be traumatic for transgender men.

In their case report "Successful IVF in a cisgender female carrier using oocytes retrieved from a transgender man maintained on testosterone," Greenwald et al[22] showed for the first time that successful egg retrieval and live birth is possible without interrupting testosterone treatment.[22] They reported the case of a 33-year-old transgender man on subcutaneous testosterone therapy for 10 years who presented with his cisgender female partner for reciprocal IVF, a process that utilizes an embryo from the patient's oocyte and anonymous donor sperm (with intracytoplasmic sperm injection) which is then implanted into the partner's uterus. After the patient undergoes a 14-day course of gonadotropin controlled ovarian stimulation, 20 oocytes are retrieved, 16 are mature, 13 are fertilized with intracytoplasmic sperm injection, and 5 of those progress to blastocyst stage where they are sent for preimplantation genetic testing. Only one embryo is chromosomally normal, suggesting a higher aneuploidy rate of 80% versus the expected 31% for someone that age. That embryo is transferred into the partner's uterus for an uncomplicated pregnancy and a child reportedly healthy at 2 years of age. This is, therefore, also the first report on the health of offspring conceived using an oocyte from an individual on testosterone while the oocyte was harvested.

By showing that a successful live birth is possible after prolonged, uninterrupted testosterone treatment, Greenwald et al[22] paved the way for expanded reproductive options and increased utilization of ART among transgender men.[22] They also highlight many gaps in the knowledge with regards to treatment approach, outcomes, and the impact of testosterone on fertility and egg quality. This patient was likely on a sub-therapeutic dose of testosterone (as evidenced by his breakthrough spotting) and on maximal doses of gonadotropins for ovarian stimulation, suggesting that even higher doses or increased time for controlled ovarian stimulation may be needed for transgender men on therapeutic testosterone regimens that suppress menses.

Although this patient had a successful oocyte yield in response to gonadotropins, the high aneuploidy rate warrants further investigation.[22] Studies on ovarian morphology in response to testosterone exposure are conflicting.[23–25] It has been shown that androgen excess can accelerate the growth of early follicular development and slow the rate of atresia of early antral follicles to give a polycystic ovarian morphology, and the high oocyte yield in response to ovarian stimulation in this case and previous studies supports those findings.[18,23] How the potential impact of testosterone use on ovarian morphology translates to egg quality is unknown and has only begun to be investigated. A study reporting on the outcomes of in vitro maturation of oocytes collected from ovaries exposed to testosterone at the time of gender-affirming surgery showed that the number of cumulus-oocyte complexes retrieved was high, the maturation and survival rates were comparable, and there was no relationship between the duration of testosterone use and the number of observed follicles.[23] The mean duration of testosterone use was only 58 weeks, and the oocyte potency was evaluated by spindle appearance, rather than embryo yield and quality, suggesting that future studies are needed.

There are currently no guidelines for FP or reproductive care of TGD individuals. FP counseling and support services should be standard of care, and many TGD youth and adults report a desire for fertility counseling.[26] It has traditionally been preferable to pursue FP prior to the initiation of GAHT due to the unknown reproductive effects of GAHT, but more patients are presenting at younger ages when parenting wishes are not yet defined and may evolve over time. Fertility counseling, therefore, needs to be an ongoing conversation even after the initiation of GAHT. A lack of clarity regarding risks to reproductive function and fertility-related outcomes while on GAHT makes this counseling more complicated. There are currently very little data with which to counsel transgender men who have already been on testosterone about the success of ovarian stimulation for current or future fertility relative to individuals without high dose testosterone exposure. Additionally, there are no current guidelines for instructing clinicians on how long testosterone needs to be stopped, or if it needs to be stopped at all, prior to ovarian stimulation and no standard stimulation protocols available for patients exposed to testosterone.

Individual centers may not see enough reproductive age patients interested in both GAHT and fertility in order to address these questions with the urgency that is needed. Hence, future studies will require pooling of data across multiple institutions for large prospective analyses on fertility protocols, outcomes, and medical and psychological risks to patients and their offspring. This case report by Greenwald et al[22] brings up important questions with regards to ART in transgender men, and in doing so, highlights the need for more research to break down barriers to reproductive care for this under-studied, vulnerable patient population.[22]

Disclosure

The authors have no multiplicity of interest to disclose.

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