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FERTILITY PRESERVATION

Oocyte cryopreservation among transmasculine youth: a case series

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Introduction

Approximately 150,000 youth (ages 13–17) in the USA identify as transgender [1]. Transgender people frequently experience gender dysphoria, which refers to the affective distress that stems from incongruence between an individual's assigned sex at birth and their gender identity [2]. Many transgender people seek gender-affirming hormone therapy (i.e., testosterone or estrogen) or surgery as a means to decrease gender dysphoria by bringing their bodies and gender identities into alignment. While these interventions are effective in reducing gender dysphoria and improving psychosocial functioning [3], many of the surgical procedures are sterilizing, and the long-term effects of gender-affirming hormones on reproductive function are unknown.

There are data to suggest that a large proportion of adult transgender men and women desire children, and many transgender men would consider oocyte cryopreservation to preserve their fertility [4–6]. Accordingly, national and international organizations, including the World Professional Association for Transgender Health [7], American Society for Reproductive Medicine (ASRM) [8], and Endocrine Society [9] have put forth guidelines recommending that transgender individuals are counseled about fertility preservation options prior to initiating gender-affirming treatments, including hormone therapy. However, the ASRM also cautions practitioners to counsel patients about the paucity of data on long-term effects of gender-affirming hormones on fertility and the limited outcome studies on fertility preservation in transgender individuals.

Since 2007, when the first multidisciplinary gender clinic was established within a pediatric institution [10], the number of such pediatric subspecialty programs has grown significantly [11]. We are thus seeing an increasing number of adolescents presenting for gender-affirming hormone therapy [12], with the most recent Endocrine Society guidelines suggesting that hormone therapy can be started in patients younger than 16 years old in the proper setting [9]. The shifting paradigm toward treating transgender adolescents with gender-affirming hormones at earlier ages has created a clinical dilemma for fertility specialists, who may not be historically trained to provide fertility care for adolescents. While there is abundant literature on oocyte cryopreservation for fertility preservation in adult women, data on the experiences and success of oocyte cryopreservation specifically in the adolescent population are limited to case reports and case series [13–19].

Fertility counseling for transgender adolescents is especially difficult as we have little data about the impact of possibly decades-long gender-affirming hormone therapy on reproduction. This conundrum is particularly pertinent to transmasculine (i.e., female-to-male) adolescents, as the process of oocyte cryopreservation is expensive, time-consuming, and physically invasive. The physical invasiveness of oocyte harvesting may uniquely impact transgender adolescents as gender dysphoria is often accompanied by severe discomfort with body parts that are incongruent with gender identity. Reproductive organs are particularly gendered aspects of the body, and some transgender adolescents have expressed discomfort with the idea of using their own body parts for reproduction [20]. Even among transmasculine adults, oocyte cryopreservation is sometime associated with worsening gender dysphoria [21]. In part due to concerns that oocyte harvesting may adversely impact mental

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health [22] and worsen gender dysphoria [21], there has been growing interest in exploring the possibility of cryopreserving androgen-exposed ovarian tissue at the time of gender-affirming hysterectomy/oophorectomy to preserve fertility [23, 24]; however, there are conflicting data in the literature about the effect of prolonged testosterone exposure on the ovaries [24–31]. Additionally, this approach is currently considered experimental as a method of fertility preservation. Thus, oocyte cryopreservation remains the only established option for preserving fertility among transgender adolescents who, like most adolescents, typically are not in the position to pursue embryo cryopreservation.

The purpose of this case series is to (1) report the feasibility of ovarian stimulation and oocyte cryopreservation in five transgender male adolescents prior to their initiating testosterone treatment, (2) address unique counseling considerations for this population, and (3) highlight distinct management considerations for fertility specialists when caring for transgender adolescents.

Materials and methods

Participants in this retrospective case series are five adolescent transgender patients (ages 18 and younger) who underwent oocyte cryopreservation prior to gender-affirming hormone treatment at two large academic institutions. As this is a retrospective case report of de-identified patients, ethical approval and individual consent to publish were not required for this case series by any of the authors' distinct Institutional Review Boards. Data were collected from five cases of postmenarchal transgender males (birth-assigned females) who underwent oocyte cryopreservation between 14 and 18 years of age. None of the individuals had begun gender-affirming hormone therapy or been on puberty blockers prior to beginning the process of oocyte cryopreservation. All reported regular menses and had no significant medical history. Prior to oocyte retrieval, screening was performed per FDA regulations so that the embryos created from the cryopreserved oocytes could be transferred into a gestational carrier, if needed, in the future.

Three of the five patients described in this series were referred from the same pediatric subspecialty gender program where they received in depth fertility counseling from medical and mental health providers specializing in pediatric transgender care, as well as a specialized pediatric fertility preservation advanced practice nurse, prior to referral for fertility preservation as previously described [32].

Ovarian stimulation, retrieval, and cryopreservation

Details of the ovarian stimulation cycles are presented in Table 1. Either recombinant follicle stimulating hormone (rFSH) alone (Follistim, Merck & Co, Inc.,) or a combination of rFSH and human menopausal gonadotropin (hMG, Menopur, Ferring Pharmaceuticals) was administered to stimulate follicular development. Abdominal or vaginal ultrasound was utilized in conjunction with serum estradiol levels to monitor ovarian response. Each individual was administered a gonadotropin releasing hormone (GnRH) antagonist (Ganirelix Acetate, Merck & Co, Inc. or Cetrotide, EMD Serono) to prevent premature ovulation. All were triggered using a 250-mcg injection of choriogonadotropin alfa (Ovidrel, EMD Serono) to induce final oocyte maturation.

Transvaginal oocyte retrieval was performed under ultrasound guidance, with conscious sedation, 36 h after the trigger injection was administered. Following retrieval, all cumulus-oocyte-complexes (COCs) were recovered in Multipurpose Handling Medium (MHM; Irvine Scientific, USA) supplemented with 3 mg/ml human serum albumin (HSA; Irvine Scientific, USA), and maintained in 500 μl Quinn's Advantage

Table 1 Oocyte cryopreservation cycle outcomes

Patient characteristics and cycle details	Case 1	Case 2	Case 3	Case 4	Case 5
Age at presentation (years)	14	18	18	16	16
AMH (ng/mL)	6.5	5.9	5.9	3.6	4.3
Starting gonadotropin dose (IU)	150 rFSH 75 hMG	150 rFSH	150 rFSH	150 rFSH	100 rFSH 75 hMG
Total gonadotropin dose (IU)	2675	1150	2050	3300	1725
Duration of stimulation (days)	9	9	10	11	9
Estradiol level on day of trigger (pg/mL)	1446	3246	1016	2215	2475
Modality of ultrasound monitoring	Abdominal	Vaginal	Vaginal	Vaginal	Vaginal
Total number of oocytes retrieved	11	19	13	20	28
Number of mature oocytes cryopreserved	8	14	13	11	25

AMH antimullerian hormone, *rFSH* recombinant follicle stimulating hormone, *hMG* human menopausal gonadotropin

fertilization medium (SAGE, USA) under oil at 37 °C in an atmosphere containing 6.0% CO_2, 5% O_2, and 91% N_2 for 2 h. Cumulus cells were then denuded enzymatically with hyaluronidase (80 IU/ml; SAGE, USA) to assess nuclear maturity. Mature oocytes were vitrified using a commercial vitrification kit (Irvine Scientific, USA) with the Cryolock device (Irvine Scientific, USA), as described by Kuwayama et al. [33].

Results

All of the patients completed ovarian stimulation and oocyte retrieval without adverse side effects or complications. The mean dose of gonadotropin used was 2180 IU (range 1150–3300), and the mean duration of stimulation was 9.6 days (range 9–11). The mean number of oocytes retrieved was 18.2 (range 11–28), of which a mean of 14.2 oocytes (range 8–25) were mature and cryopreserved (Table 1). All individuals initiated testosterone within 3 months of completing oocyte cryopreservation. Two individuals have since undergone bilateral subcutaneous mastectomies and a third is preparing for this procedure.

Discussion

Oocyte cryopreservation for fertility preservation appears feasible and safe in transgender adolescents with proper counseling. Recent studies suggest that fertility preservation counseling occurs regularly in pediatric gender clinics housed within institutions with formal pediatric fertility preservation programs; however, utilization of fertility preservation services is quite low [34, 35]. Youth in the aforementioned studies identified cost, invasiveness of procedures, desire not to delay medical transition, and plans to adopt children or no desire to have children in the future as reasons for declining fertility preservation [34, 35]. Recent studies suggest that a subset of transgender adolescents (24–36%) express desire for biological parenthood [20, 36] and may benefit from fertility preservation technologies; thus, fertility specialists should be prepared to counsel and care for this vulnerable population with unique fertility needs.

Unfortunately, many unanswered questions remain regarding proper fertility care for transgender adolescents. There is sparse data on the effect of long-term testosterone use on future reproductive function, and no data, to the authors' knowledge, on the fertility consequences of starting testosterone in adolescence or for adolescents who had puberty halted with GnRH agonists prior to starting testosterone. In addition, the quality and efficacy of mature oocytes retrieved in adolescence (prior to any exposure to potentially gonadotoxic treatment) has also recently been questioned [37, 38]. Of the existing case reports and series on oocyte cryopreservation in adolescence, only one reports the long-term outcome where a cancer survivor returned to use oocytes frozen at 17 years of age, and had a live birth using a gestational carrier [18]. Similar to our series reported here, a case series of fertility preservation in teenage girls with sickle cell anemia noted higher than expected gonadotropin requirements for stimulation, given young age and reassuring ovarian reserve testing [15]. This brings to the forefront the need for studies that compare the competence and quality of oocytes cryopreserved in adolescence prior to any testosterone treatment versus oocytes harvested from transgender adults on long-term testosterone therapy. Even if testosterone is discovered to have minimal effect on future fertility, it is possible that young transmasculine patients may still prefer to undergo oocyte cryopreservation before starting testosterone, to prevent the need to temporarily cease testosterone therapy and administer gender incongruent hormones in the future, once they have progressed in their gender transitions. Alternatively, it may be more palatable for some individuals to receive gender incongruent hormones for oocyte harvesting after experiencing the irreversible physical changes of a testosterone-mediated puberty. Indeed, some adult transgender men who discontinued testosterone to pursue fertility preservation reported worsening dysphoria in the context of resuming menses, while others felt it was less distressing than anticipated [21].

From a psychosocial standpoint, there have not been any studies that have systematically examined whether transgender adolescents undergoing ovarian stimulation experience any distress, and we unfortunately do not have that data in the patients described in this series. However, a recently published case study suggests that the oocyte cryopreservation process may be physically and emotionally demanding even for transgender adolescents who strongly desire fertility preservation, have had time to prepare for the fertility preservation process, and report satisfaction with their experience [32]. There also have not been any studies exploring decisional regret related to pursuing (or not pursuing) fertility preservation among transgender adolescents. Because the concept of fertility preservation for transgender people is only recently gaining popularity, we do not yet have accurate estimates of patients returning to utilize cryopreserved gametes and the associated live birth rates. To date, there have been two documented cases of adult transgender men undergoing oocyte cryopreservation *before* initiating gender-affirming hormone therapy who have returned to use preserved gametes, with each case resulting in twin live births [39].

Fertility counseling considerations for transgender adolescents

Fertility-related decision-making is complicated for transgender youth, in part because they must consider their fertility desires and parenting intentions during a developmental

period in which reproductive health decision-making is non-normative. Adolescents may not have the cognitive capacity to fully understand the long-term consequences of their present decisions or fully anticipate what they would desire as an actualized adult [40]. In fact, more than a quarter of transgender 14- to 17-year-olds surveyed indicated they "did not know" whether they wanted biological children [20], and the majority of transgender adolescents in another study recognized that their desires for biological parenthood may change in the future [36]. Furthermore, ethical issues in adolescent fertility preservation in general, including concerns related to assent and consent, parental or provider pressure, and cost and insurance coverage, all apply to the transgender patient [41].

Unique to transgender adolescents is the need to weigh the individual benefits of fertility preservation against the potential risk for worsening gender dysphoria by delaying gender-affirming hormone treatment and pursuing a potentially distressing, invasive oocyte harvesting procedure. Making reproductive decisions during adolescence is complicated by each youth's desires for physical transition and the immediacy of these transition needs. In addition, each individual has a different relationship with their body and reproductive anatomy—the thought of using gender incongruent body parts and gametes for reproduction may be very distressing for some, whereas for others, the relative distress may be manageable. Similar, each individual will have varying priorities when it comes to their reproductive options—having biologically related children may be very important to one individual and not at all important to another. The relative importance of biological parenthood should be considered alongside the relative risk of exacerbating gender dysphoria and explored during the fertility counseling process. It is also important to recognize that youth may not want to parent. Indeed, in a recent study, some transgender adolescents expressed frustration that medical providers and parents routinely spoke to them with the expectation that they would want to parent in the future [20]. Thus, fertility preservation should be discussed as an *option* for transgender youth who desire it. It may also be helpful to explore how an adolescent might feel should they change their mind and desire biological parenthood in the future and learn at that time that they are infertile.

Furthermore, transgender adolescents also may be making decisions that have long-term implications on reproductive health in the context of limited romantic or sexual experience [32]. This may complicate counseling around how to utilize cryopreserved oocytes in the future if the likely anatomy of co-parent is unknown. Transgender young men attracted to cisgender women have the option to use donor sperm to fertilize cryopreserved oocytes and have their partner carry a pregnancy to term. However, in this situation, it will not be possible for both parents to be biologically related to their child, the implications for which will vary based on personal values. Alternatively, transgender young men attracted to cisgender men will have the option to use partner sperm to form an embryo that is biologically related to both parents. In this situation, youth will have to understand the cost of having a gestational carrier, which can be as much as $250,000 in the USA [42].

Conclusions

Centers offering fertility preservation to transgender adolescents should have a multidisciplinary team, including Pediatric Endocrinologists, Reproductive Endocrinologists, and Mental Health Professionals, all experienced in the care of transgender youth. Transabdominal monitoring of ovarian stimulation should be offered to patients who may be uncomfortable with transvaginal ultrasonography. Facilities should ensure that there are no restrictions as to the minimum age in which anesthesia can be performed. Finally, parental consent, with assent of the adolescent, should be obtained in advance of the retrieval, to prevent any problems the day of the procedure if someone other than a legal guardian escorts the patient. As demonstrated by the cases above, the process of ovarian stimulation and oocyte cryopreservation can be safely performed in transgender adolescents, but there is still much research to be done about the necessity of fertility preservation in this population, and the quality of oocytes obtained both before and after testosterone exposure.

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