

Fertility Preservation for Transgender Individuals: A Review

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Abstract

Transgender individuals represent a small, albeit growing, patient population that is encountered more frequently in clinical care due to improved insurance coverage and increasing awareness. Gender-affirming treatments, including both gender-affirming hormone therapy and gender-affirming surgery, pose significant risks to fertility potential and outcomes, ranging from potentially impaired fertility rates to full elimination of reproductive potential depending on the type of treatment pursued. However, there are relatively limited data specific to fertility preservation for transgender individuals. Current approaches to treatment are extrapolated from options for fertility preservation after oncologic diagnoses. In this review, we aim to summarize current clinical approaches, fertility preservation options, and patient experiences in fertility preservation for transgender individuals. Several forms of fertility preservation options are available depending on the pubertal status of a transgender individual. Despite the multiple options for fertility preservation, major barriers exist to patient care and there are reports of mixed patient experiences. Further awareness of this clinical situation and understanding of these processes will allow for comprehensive and specialized care for transgender individuals who may otherwise miss opportunities for adequate counseling or treatment options regarding fertility preservation.

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Transgender individuals represent a small but growing patient population in reproductive medicine. Although the number of transgender individuals is not necessarily increasing, the increase in clinical care likely results from improved recognition of transgender individuals and improved insurance coverage. In the United States, Medicare now covers hormonal treatments and does not exclude coverage for surgical gender-affirming therapy. The number of transgender individuals worldwide is underestimated due to limitations of previous population surveys, differences in methodology, and variations in the definition of transgender.¹ A recent meta-analysis attempted to estimate this prevalence and reported rates of 521 transwomen and 256 transmen per 100,000 individuals.² In the United States, a meta-regression of population-based probability samples reported 390 transgender adults per 100,000 individuals.³

Many transgender individuals report recognition of gender identity differing

from sex assigned at birth during pre-pubescence, although the mean age of presentation is 27 to 32 years.^{4,5} There is a growing number of patients presenting for gender-affirming treatment and a trend toward decreasing age at time of presentation.⁶ In the United States, 0.7% of individuals aged 13 to 24 years identify as transgender.⁷ Gender-affirming treatments, including both gender-affirming hormone therapy and surgery, have significant impacts on fertility potential and outcomes. For example, current use of gender-affirming hormone therapy may make fertility outcomes substantially lower whereas gender-affirming surgical treatments may make autologous fertility options impossible.

There are strong arguments for counseling transgender patients about fertility and fertility preservation. Reproductive desire is high among transgender individuals, but the use of reproductive options is surprisingly low. A recent Australian study surveyed 409 transgender and non-binary

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ARTICLE HIGHLIGHTS

- Transgender individuals are at risk for decreased natural and assisted fertility rates.
- Fertility treatment and preservation options should be discussed with transgender individuals regardless of stage of transition, but ideally before gender-affirming hormonal treatment or gonadectomy.
- Relatively few transgender individuals are seen for fertility care due to lack of provider awareness and patient perception of bias.

adults and found that, of participants who were not already parents, 33% hoped to have children in the future.⁸ Nearly all respondents (94.6%) responded that fertility preservation should be offered to all transgender and non-binary people. Public opinion in the United States also shows support for fertility treatment and preservation for transgender individuals. In a 2017 survey, 76.2% of respondents agreed that transgender individuals should be offered assistance to have biological children. However, only 60% of respondents supported fertility preservation in transgender minors or aiding transgender men in carrying a pregnancy.⁹ Other data describes a significantly higher desire for children in transmen compared with transwomen ($P=.016$) before gender-affirming treatment. In contrast, in those who had already started gender-affirming treatment, a current desire to have children was equally present in approximately one-fourth of participants of both genders, whereas the interest in having children in the future was significantly higher in transwomen (69.9%) than in transmen (46.9%; $P=.034$).¹⁰

Support for reproductive options for transgender individuals is formally recognized by multiple national and international organizations. The American Society for Reproductive Medicine states that it opposes restrictions on the use of reproductive technology in transgender individuals.¹¹ The World Professional Association of Transgender Health, American Society for

Reproductive Medicine, and the Endocrine Society recommend that all transgender patients be counseled on the effect of their treatments; both gender-affirming surgeries and hormonal transition, on fertility and offered options for fertility preservation before transition.¹¹⁻¹³ A task force by the European Society of Human Reproductive Endocrinology published an opinion on the ethical principles involved in transgender fertility care and added that physicians caring for this population have moral obligations to invest in follow-up studies, as current data are limited.¹⁴

Nevertheless, many providers may be less familiar with the clinical options available for these patients. A recent survey of providers from nine different countries identified a need for additional information and resources to summarize available options for transgender fertility preservation.¹⁵ There is relatively limited data specific to fertility preservation for transgender individuals and current approaches are extrapolated from options for fertility preservation after oncologic diagnoses. In this review, we summarize current clinical approaches and patient experiences in fertility preservation for transgender individuals.

METHODS

This review summarizes current literature and clinical practices regarding fertility preservation for transgender individuals. The PubMed database was used for literature review. Search terms including *transgender* and *fertility* provided the majority of results. Additional queries included *transgender fertility preservation*, *transgender care*, and *transgender reproduction*. All full manuscripts available in English were reviewed. This paper does not represent a systematic review and as such will not report in full the publications reviewed.

Fertility Preservation Options in Transwomen

Clinical options for fertility preservation in transgender individuals are determined by pubertal status and stage of medical or

TABLE 1. Fertility Preservation Options for Transwomen^a

Fertility preservation method	Stage of transition	Future use
Sperm cryopreservation Completed by self-ejaculation or assisted by vibratory or electrical stimulus	1. Before hormonal transition or gender-affirming surgery 2. After hormonal transition, consider 3-month cessation of estrogen	Cisgender male partner Egg donor and gestational carrier Cisgender female partner IUI or IVF (with partner's oocytes)
Surgical sperm extraction Percutaneous aspiration of sperm from testis (TESE) or epididymis (PESA)	1. Before hormonal transition or gender-affirming surgery 2. After hormonal transition, consider 3-month cessation of estrogen	Cisgender male partner Egg donor and gestational carrier Cisgender female partner IVF with partner's oocytes
TTC ^b Surgical biopsy of testicular tissue	1. Before hormonal transition or gender-affirming surgery 2. After hormonal transition 3. Could be completed at the time of gender-affirming surgery 4. Only option for pre-pubertal transgirls a. Requires IVM of testicular tissue to obtain spermatids	Cisgender male partner Use of egg donor and gestational carrier Cisgender female partner IUI or IVF with partner's oocytes

^aIVM = in vitro maturation; PESA = percutaneous epididymal sperm aspiration; TESE = testicular sperm extraction; TTC = testicular tissue cryopreservation.

^bExperimental worldwide (theoretical, no live births reported).

surgical transition. Options for fertility preservation before gender-affirming hormone therapy or surgery in transwomen include cryopreservation of semen or testicular tissue. Alternatively, a transwoman could pursue embryo creation with use of fresh sperm, before gender-affirming therapy, if in a relationship with a cisgender female pursuing pregnancy or in a relationship planning family creation with use of donor oocytes (Table 1). In post-pubertal transgirls and transwomen, semen may be obtained from either ejaculated specimens or testicular sperm extraction (TESE). Ejaculated specimens may be used for both intrauterine insemination (IUI) and in vitro fertilization (IVF), whereas TESE specimens may be used only for IVF. Clinical pregnancy rates of 23% to 62.1% after IVF with intracytoplasmic sperm injection have been reported in men using semen samples cryopreserved at the time of cancer diagnosis, although these data have not been completed in the transgender population.¹⁶⁻²⁰

In pre-pubertal transgirls, the only option for fertility preservation before initiation of transgender hormonal treatment is

testicular tissue cryopreservation (Table 1). In pre-pubertal cisgender boys, testicular tissue removal for cryopreservation has been reported from age 5 months to 34 years.²¹ Initially, most cryopreservation was completed with use of slow-freeze techniques, although vitrification, which involves a more rapid freezing process to prevent ice crystal formation and associated with improved thaw survival rates, is now being investigated.²² Testicular tissue cryopreservation is still considered experimental; however, there are growing reports of testicular tissue collection with good results in identification of germ cells.^{23,24} Future use of cryopreserved testicular tissue relies on autotransplantation back to the testis,²⁵ scrotum,²⁶ or ectopic subdermal locations.²⁷ Animal studies confirm complete spermatogenesis after re-implantation with adequate competence to achieve both fertilization and live birth.²⁸ However, little is known about the functionality of human sperm generated from these auto-transplanted tissues and there have been no reported live births from this method.²²

The effect of gender-affirming hormone therapy, primarily estrogen supplementation, on testicular morphology has been described in multiple publications with different results. This information is applicable to transwomen who started gender-affirming hormone therapy after pubertal completion and should not be applied to transwomen who underwent gender-affirming hormone therapy at Tanner stage 2-3. In the largest sample to date, Schneider et al²⁹ examined 108 subjects taking anti-androgens and different dosages of estrogen supplementation before gender affirmation surgery. Patients who discontinued gender-affirming hormone therapy before surgery had a higher mean testicular weight, which correlated well with the level of spermatogenesis and testosterone levels, compared with subjects who continued gender-affirming hormone therapy until surgery. The timing of hormonal discontinuation did not directly correlate with testicular histology, as 24% of patients showed complete spermatogenesis, 24% showed meiotic arrest, and 35.2% showed spermatogonial arrest.³⁰

The anti-androgenic effects on spermatogenesis have been extrapolated from the cisgender male contraceptive literature. The suppression of spermatogenesis seen after use of gonadotropin suppression has been shown to be reversible after 3 months without therapy.³¹ The effect of estrogen supplementation on the testis is variable and dependent on the level and length of treatment. In a single cisgender male studied, lower doses of estrogen supplementation (20 µg/d) had no effect on sperm motility or density, whereas higher doses of estrogen supplementation (60 µg/d) decreased sperm motility in a few days and total counts in a few weeks.³² After discontinuation of estrogen supplementation, motility returned to baseline faster than sperm density.

Options for fertility preservation in transwomen who have already started gender-affirming hormone therapy include discontinuation of hormonal medication and sperm banking (Table 1). A small retrospective study showed progressively lower

total motile sperm counts in transgender women who banked semen samples before hormonal treatment (63.2 M), after 3 to 6 months of hormonal discontinuation (39.1 M), and during continued hormonal treatment (0.2 M) ($P < .01$).³³ Ejaculated sample quality may allow for spontaneous conception or intrauterine insemination. Poor semen quality may still be an option for use in IVF with intracytoplasmic sperm injection.

Transwomen who have completed genital reconstruction have irreversible sterility and no fertility preservation options are currently available at this stage of care. Future options for uterine transplantation may be applicable to this group of patients. The use of deceased donors may be preferred, as both a uterine and vaginal transplant would ideally be completed. Multiple factors, including anatomic and hormonal differences in transwomen, must be investigated before this option is realistically possible.^{34,35}

Fertility Preservation Options in Transmen

Options for fertility preservation for transmen before gender-affirming hormone therapy or surgery include oocyte cryopreservation, embryo cryopreservation, or ovarian tissue cryopreservation. Both oocyte and embryo cryopreservation require a controlled ovarian stimulation (COS) with repeated assessment by transvaginal ultrasound, which may be uncomfortable or emotionally distressing for these patients. Aside from considerations related to patient comfort during the COS process, stimulation protocols used in transmen before gender-affirming hormone therapy are similar to those used for infertility or other indications for fertility preservation.

Transmen who have already begun gender-affirming hormone therapy may still pursue oocyte or embryo cryopreservation (Table 2). There are few published studies related specifically to this method of COS after high dose testosterone use. Conceptually, a longer duration of testosterone cessation may allow return of intrinsic gonadotropin-ovarian stimulation and recruitment of a

TABLE 2. Fertility Preservation Options for Transmen^a

Fertility preservation method	Stage of transition	Future use
Oocyte cryopreservation Live birth rates similar to embryo cryopreservation	1. Before hormonal transition or gender-affirming surgery 2. After hormonal transition, consider 3-month cessation of testosterone	Cisgender male partner Partner sperm and use of gestational carrier Cisgender female partner Donor sperm, implantation into partner's uterus or gestational carrier
Embryo cryopreservation Requires uses of donor sperm or presence of male partner	1. Before hormonal transition or gender-affirming surgery 2. After hormonal transition, consider 3 month cessation of testosterone	Cisgender male partner Partner sperm and use of gestational carrier Cisgender female partner Donor sperm, implantation into partner's uterus or gestational carrier
OTC ^b Surgical removal of ovarian tissue	1. Before hormonal transition or gender-affirming surgery 2. After hormonal transition 3. Could be completed at the time of gender-affirming surgery 4. Option for pre-pubertal transboys 5. Will require auto transplant of ovarian tissue back to the body	Cisgender male partner Auto transplant for IVF development followed by IVF with partner sperm Cisgender female partner Auto transplant of ovarian tissue for IVF development followed by IVF with donor sperm.
IVM ^c Removal of immature oocytes at time of OTC	1. Before hormonal transition or gender-affirming surgery 2. After hormonal transition 3. Could be completed at the time of gender-affirming surgery 4. Option for pre-pubertal transboys	Cisgender male partner Fertilization of oocytes post-IVM with partner sperm and use of gestational carrier Cisgender female partner Fertilization of oocytes post-IVM with donor sperm and implantation into partner's uterus or gestational carrier

^aIVF = in vitro fertilization; IVM = in vitro maturation; OTC = ovarian tissue cryopreservation.^bExperimental in the United States.^cExperimental worldwide.

resting follicle pool more robust than that present while on testosterone. One previous review recommends cessation of testosterone for 3 months before stimulation.³⁶ Another required return of menses, which took 3 to 6 months from time of testosterone cessation. In this group, an antagonist protocol using follicle stimulating hormone and letrozole was used to minimize the increased estradiol levels expected with ovarian stimulation.³⁷ Oocytes obtained after a stimulation cycle may be cryopreserved as oocytes or fertilized with sperm provided by cisgender male partner or donor sperm. Transmen with a cisgender male partner can elect to

have embryos undergo a planned implantation in a gestational carrier. Transmen with a cisgender female partner may use cryopreserved oocytes and donor sperm for embryo creation with transfer of the embryo to their female partner (Table 2). Before hysterectomy, transmen may consider autologous embryo transfer, although this option may contribute to significant gender dysphoria, and may likely be undesirable for most transmen.

Ovarian tissue may be cryopreserved at any time, but is ideally completed at the time of gender-affirmation surgery. In addition to storing ovarian tissue for future use

and re-implantation, ovarian tissue may also be a source of immature oocytes amenable to in vitro maturation. Studies have examined ovarian tissue and cumulus-oocyte-complexes from patients undergoing gender-reaffirming surgery, including hysterectomy and bilateral salpingo-oophorectomy. All patients had previous testosterone use for at least 1 year, as recommended by the Endocrine Society before gender-reaffirming surgery.³⁸ De Roo et al³⁹ examined ovarian tissue from 40 patients collected at the time of gender-affirmation surgery. Ovarian cortices from each patient showed a mean number of 90 follicles with most being primordial (68.5%), and fewer intermediate follicles (20.62%) and primary follicles (10.74%). This distribution of follicle type was similar to previously reported values in age-matched fertile women, suggesting no impact of testosterone on ovarian architecture and specifically no transition to polycystic ovary morphology, as previously thought.⁴⁰⁻⁴² Although there is no demonstrated effect of testosterone on follicle distribution, high-dose testosterone has been associated with ovarian stromal hyperplasia and stromal leuteinization.⁴¹ Evaluation of serum hormone levels including anti-Müllerian hormone, follicle-stimulating hormone, and testosterone levels showed no correlation with the number or type of follicles identified and did not differ by length of testosterone treatment.³⁹

Ovarian tissue cryopreservation is an established option for fertility preservation in Europe but is still considered experimental in the United States.⁴³ Ovarian tissue cryopreservation is the only option for prepubertal transboys and currently requires transplantation for future use (Table 2). More than 130 live births have been reported in cis women using ovarian tissue cryopreservation.^{44,45} The role of ovarian tissue transplantation in transmen remains unclear as the fertility potential of this tissue would require cessation of testosterone treatment and auto transplantation of ovarian tissue back to the body for in vivo follicular development, which may not be an option for most transmen.

Alternatively, ovarian tissue as a source of immature oocyte collection and in vitro maturation (IVM) offers another option for fertility preservation in transmen. IVM facilitates the development of an oocyte from the immature, germinal vesicle stage to the metaphase II stage, amenable to fertilization. Lierman et al⁴⁶ collected a total of 680 cumulus-oocyte-complexes from 16 transmen after testosterone treatment at the time of gender-affirmation surgery. After 48 hours, 38% of the cumulus-oocyte-complexes were mature and found to have a normal spindle structure, suggesting no morphologic effect of prolonged testosterone treatment on oocytes.^{39,46} In transmen with a male partner, ovarian tissue may be used for IVM with fertilization of mature oocytes by partner sperm and use of a gestational carrier. In transmen with a female partner, ovarian tissue may be used for IVM with fertilization of mature oocytes by donor sperm and embryo transfer to partner's uterus (Table 2).

There are reports of transmen who pursue pregnancy either due to infertility of a partner or personal desire to carry a child. In a survey of transmen who became pregnant and delivered, 61% (n=25) discontinued testosterone before pregnancy and 80% (n=20) reported return of menses within 6 months of testosterone discontinuation.⁴⁷ Transmen who have completed both gender-affirming hormone therapy and surgery, with hysterectomy and oophorectomy, have irreversible sterility.

Transgender Experience and Barriers to Care

Despite recommendations for counseling on fertility preservation for transgender individuals, a relatively small percentage of patients are successful in pursuing fertility preservation procedures. A recent study reported on a sample of 105 transgender adolescents starting gender-affirming hormone therapy who were referred for fertility preservation counseling. Of these 105 adolescents, 13 (12.4%) were seen for initial consultation and 5 completed cryopreservation of gametes (four sperm and one oocyte).⁴⁸ Similar results were described in another study

where most adolescent participants cited plans for adoption (45%) or denied a desire for future children (21%).⁴⁹ However, in a survey study of 50 transmen who had previously completed gender-affirmation surgery, 77% had not considered fertility preservation at the time of gender-affirming hormone initiation. At the time of the survey, 54% reported a desire for children and transmen with children reported a significantly higher quality of life.⁵⁰

Barriers to pursuing fertility preservation include cost, invasiveness of procedures, and patient perception of mistreatment or bias.⁴⁸ A Korean survey study found that transgender patients were most likely to discontinue hormonal transition therapy due to cost.⁵¹ In the United States, many transgender individuals are uninsured or underinsured for both gender-affirming treatments and basic preventive care.⁵² However, recent changes in Medicare coverage cover gender-affirming hormonal therapies and no longer exclude gender-affirming surgical coverage. Although there are limited available data on the cost of fertility preservation for transgender individuals, extrapolating the cost burden for other medical needs specific to the transgender population, the high costs of fertility preservation may limit significantly their ability to complete desired interventions depending on geographic location and local payment structures. In a study by Abern et al,⁵³ nearly half of transmen in a study from the United States reported not pursuing fertility preservation due to cost.

In addition to financial barriers, patients report hesitancy to pursue fertility preservation due to invasive and distressing procedures. The process of ovarian stimulation in transgender men, specifically, may trigger gender dysphoria as a reminder of their sex assigned at birth, an identification they had tried to distance themselves from.³⁷ Similar concerns exist for transwomen, as sperm collection may also contribute to gender dysphoria and a reminder of their sex assigned at birth.

Transgender individuals who have pursued assisted reproduction report mixed experiences. In a 2015 qualitative study, James-Abra et al⁵⁴ interviewed 11 individuals about

their reproductive experiences. Two respondents reported positive experiences due in part to provider knowledge and use of gender neutral terms, such as parent rather than mother or father. However, most participants reported negative experiences of clinical documentation limiting their ability to adequately self-identify and provider's cis- or heteronormative assumptions. Only one participant reported refusal of services.⁵⁴

Outcomes after fertility treatments for transgender individuals are limited. There are few reports on children of transgender parents and most are focused largely on sexual identification and orientation, which are not impacted by having a transgender parent.⁵⁵ The level of interpersonal, specifically marital, conflict and age of the child at parental transition were noted to have the greatest impact on childhood psychological distress.^{55,56} In one of the few studies to assess childhood development, children of transmen were found to be "normal and happy, demonstrating secure attachment."⁵⁷

CONCLUSION

Transgender individuals who pursue gender-affirming hormone therapy or surgery are at risk for fertility compromise and should be offered options for fertility preservation or treatment. Options for fertility preservation vary by stage of transgender transition. Few studies have evaluated fertility outcomes in this patient population and more work is needed to fully understand and optimize the patient experience, treatment approach, and fertility outcomes.

Abbreviations and Acronyms: IVF = in vitro fertilization

Potential Competing Interests: The authors report no competing interests.

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