Emily Wiesenthal, BA, Kristy Cho, MD, FRCSC, Jeffrey Roberts, MD, FRCSC, Caitlin Dunne, MD, FRCSC

Fertility options for transgender and gender-diverse people

Comprehensive fertility counseling is critical to the equitable provision of care to transgender and gender-diverse patients and should be the standard of care.

ABSTRACT: While transgender and gender-diverse individuals desire parenthood at similar rates as cisgender people, research suggests that many do not receive adequate fertility counseling. Because some medical and surgical gender-affirming therapies may affect the ability to reproduce, comprehensive fertility counseling before the initiation of such therapies is critical to the care of gender-diverse patients. Community physicians can inform transgender, gender-diverse, and nonbinary patients about their fertility preservation options, including sperm, egg, or embryo freezing. When ready to start a family, transgender and gender-diverse patients may choose from a wide spectrum of fertility treatments, including insemination, in vitro fertilization, and third-party reproduction with a gestational carrier, donor sperm, or donor eggs. Health care providers can improve fertility care for transgender and gender-diverse people by becoming familiar with their reproductive health; inquiring about their gender identity, pronouns, and preferred terms for body parts, and revising clinic forms to include that information; and understanding the potential barriers to care these individuals face, including the cost of care, the risk of elevated dysphoria, limited access to fertility centres in rural communities, and the fear and lived experience of discrimination.

Ms Wiesenthal is a medical student in the Faculty of Medicine, University of British Columbia. Dr Cho is a reproductive endocrinology and infertility subspecialty fellow in the Division of Reproductive Endocrinology and Infertility at UBC. Dr Roberts is a clinical associate professor in the Division of Reproductive Endocrinology and Infertility at UBC, and a co-director, Pacific Centre for Reproductive Medicine. Dr Dunne is a clinical associate professor in the Division of Reproductive Endocrinology and Infertility at UBC and a co-director at the Pacific Centre for Reproductive Medicine.

This article has been peer reviewed.

The decision to start a family is important, irrespective of one's gender identity. Transgender and gender-diverse (TGD) people express interest in parenthood at similar rates as cisgender persons.[1] It is estimated that between 1% and 3% of the Canadian population identifies as transgender or gender-diverse, and 40% to 54% of TGD people desire to be parents.[1,2] Overall, a small but important proportion of the Canadian population (0.3% to 0.6%) chooses to undergo gender-affirming medical interventions.[2] Since some medical and surgical gender-affirming therapies can reduce fertility or lead to permanent sterility, it is essential that health care providers counsel TGD people about the options for fertility preservation before the initiation of such therapies.[3] However, physicians may not be equipped to meet this need. A 2018 survey of TGD men in the United States found that more than half of the respondents had not discussed fertility desires with their health care providers.[4] We review the existing reproductive options for TGD people and emphasize the need for health care professionals to broach fertility planning with their TGD patients.

Background

"Gender identity" is used to describe a person's sense of their gender as male, female, both, neither, or anywhere else along the gender spectrum.[5] Many diverse, culturally specific terms are used by individuals to describe their gender identities. "Transgender," which may be abbreviated as "trans," is an umbrella term for people whose gender identity does not align with the sex they were assigned at birth.[6] "Nonbinary" is an umbrella term for those whose gender identity is not exclusively male or female.[7] Terms such as "gender nonconforming," "gender-diverse," "gender-fluid," and "gender-neutral" are also commonly used to describe gender identities or gender expressions that fall outside the gender binary.[6] "Cisgender" is used to describe people whose gender identity aligns with the sex they were assigned at birth.[5]

"Dysphoria" refers to the discomfort or distress that some TGD and nonbinary people experience as a result of the discrepancy between their gender identity and their sex assigned at birth. "Gender dysphoria" is a medical diagnosis that must be persistent and well documented in order to initiate gender-affirming hormonal and/or surgical therapies in BC.[8-10]

The application of gender-affirming therapies is highly individualized for each person. In an interview in which he shared his experience with fertility treatments, Trystan Reese, a trans man, explained that "often people think about transition for trans people as being like a one and done thing. . . like it's a map."[11] Reese noted instead, that such interventions serve more as a "menu of options" that include hormones, surgery, binding, packing, tucking, padding, hair removal, and other forms of social transition, which TGD people may or may not choose to pursue at different points throughout their lifetime.[11]

Parenthood and pregnancy have been routinely framed within the context of cisgender, heteronormative family structures. Patients whose gender and sexual identities fall outside this framing have historically been discriminated against and denied access to assisted reproductive technologies, and have even had their competency as parents called into question.[2] While the right to access fertility services regardless of gender identity is now widely recognized, there is still much work to be done by the medical community to establish equity in fertility care. More research is needed to better understand the effects of gender-affirming hormone therapy on fertility and to optimize fertility treatment outcomes for TGD patients.[2]

In this review, treatment options are presented in two broad scenarios:

- Fertility preservation for TGD adults who wish to have a biological child *in the future*.
- Fertility treatments for TGD adults who are *currently ready* to start a family.

Fertility preservation

For TGD adults with ovaries, options for fertility preservation include egg freezing, embryo freezing, and ovarian tissue freezing **[Table]**.[12] The most common fertility preservation option for TGD adults with testicles is sperm freezing.

Egg freezing

TGD people with ovaries can undergo ovarian stimulation for egg retrieval and freezing. Even those who have received androgen therapy will respond to ovarian stimulation, although a temporary cessation of testosterone is recommended.[12] In the past, protocols required a minimum of 3 to 6 months to allow for the return of menses before egg freezing, which is an unacceptable prerequisite for most patients.[13] However, a recent foundational case report by our group demonstrated a normal egg yield after only 7 days of being testosterone-free before initiating ovarian stimulation, and a total of only 24 days off testosterone to complete the entire treatment.[13]

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The process of egg freezing for TGD men is largely the same as for cisgender women. Daily subcutaneous injections of exogenous gonadotropins are administered to stimulate ovarian multifollicular growth over a period of approximately 2 weeks. Ultrasounds are performed regularly throughout the stimulation (normally via transvaginal approach, but transabdominal is possible) to monitor follicle growth. Eggs are removed by transvaginal aspiration in a minimally invasive procedure, usually under conscious sedation; however, some fertility clinics can offer a general anesthetic. Mature eggs are frozen in liquid nitrogen in a process called vitrification, or "flash-freezing." Research suggests that they can be stored for long periods without decreasing in quality.[14] The average cost of an egg freezing cycle can vary by fertility clinic but usually costs around $8000 for the procedure, $3000 to $5000 for medications, and $500 annually for ongoing storage.

All people with ovaries are born with a finite number of eggs, which diminish over the next 5 decades. Therefore, cisgender women and gender-diverse people with ovaries are subject to the same decline in egg quality and quantity throughout their lives.[15] The optimal time to freeze eggs is before age 35 when they are still at, or near, their best reproductive potential.[16] Although egg freezing can be performed until age 44, it is often not recommended after age 40 due to substantially lower efficiency and cost-effectiveness.[16] For example, in a person 34 years or younger, 10 frozen eggs confer about a 60% chance of one child in the future. Those same 10 eggs from a person age 41 to 42 years have an estimated live birth rate of 20%.[17] Furthermore, in people with lower ovarian reserve, it is sometimes not possible to obtain 10 eggs in one cycle. A reproductive endocrinologist will perform ovarian reserve testing, such as serum anti-Müllerian hormone and antral follicle count by ultrasound, prior to egg freezing. Finally, it is important to inform patients that no number of frozen eggs can guarantee a live birth in the future.

Embryo freezing

On the day of egg retrieval, individuals have the option of freezing their eggs unfertilized or inseminating them and culturing embryos for freezing (vitrification). The latter requires that the individual choose sperm, from either a donor or a partner, to be available at the time of egg retrieval. Freezing embryos instead of eggs has some advantages, such as providing more clarity about how the eggs may fertilize and grow into good-quality blastocysts. Embryos also have a higher vitrification-warming survival rate of 95% to 98% or higher compared to 80% for eggs.[17,18] Finally, embryos at the blastocyst stage can undergo preimplantation genetic testing for aneuploidy, whereas eggs cannot. The principal disadvantages of preserving embryos are the lack of flexibility to change one's mind about the sperm source in the future and the dual consent required to use the embryos if a partner's sperm was used.

Ovarian tissue freezing

Ovarian tissue freezing, wherein ovarian tissue is collected (often during oophorectomy), cryopreserved, and retransplanted in the future, has resulted in a reported 130 live births in cisgender women to date worldwide.[7,12,19,20] The "experimental" label was removed from

this promising therapy in 2019.[21] However, the American Society for Reproductive Medicine states that ovarian tissue freezing should be offered only to carefully selected patients, given the limited data on its safety, efficacy, and reproductive outcomes.[21] Currently, this procedure is not widely performed in Canada and is rarely used relative to standard egg freezing.

Sperm freezing

In TGD people with sperm, the use of gender-affirming estrogen therapy can suppress gonadotropin levels via negative feedback to the hypothalamus and pituitary. Reduced or absent follicle-stimulating hormone and luteinizing hormone levels result in lower stimulation of the Sertoli (sperm-producing) and Leydig (testosterone-producing) cells, which leads to lower serum and intratesticular testosterone levels and absent spermatogenesis.[22] The extent of luteinizing hormone and follicle-stimulating hormone suppression may be dose dependent. One retrospective cohort study of TGD patients with sperm reported that there was a trend toward worsening semen parameters in those

TABLE. Family building options for transgender and gender-diverse individuals.*

Any partner	Patient				
	Patient with ovaries and a uterus	Patient with ovaries and without a uterus†	Patient with a uterus and without ovaries†	Patient with sperm	Patient without ovaries, a uterus, or sperm†
Any partner with ovaries and a uterus	• IUI‡ with donor sperm (for the patient and/or partner) • IVF§ using patient's or a partner's eggs with donor sperm (patient and/or partner may carry pregnancy)	• IUI with donor sperm (for a partner) • IVF using patient's or a partner's eggs with donor sperm (partner to carry pregnancy)	• IUI with donor sperm (for a partner) • IVF using a partner's eggs with donor sperm (patient or partner to carry pregnancy)	• Intercourse • Home insemination with patient's sperm • IUI with patient's sperm (for a partner) • IVF with patient's sperm (a partner to carry the pregnancy)	• IUI with donor sperm (for a partner) • IVF with donor sperm (a partner to carry the pregnancy)
Any partner with ovaries and without a uterus†	• IUI with donor sperm for the patient • IVF using patient's or a partner's eggs with donor sperm (patient to carry the pregnancy)	• IVF using patient's or a partner's eggs with donor sperm (gestational carrier carries pregnancy)	• IVF using a partner's eggs with donor sperm (patient to carry pregnancy)	• IVF using a partner's eggs with patient's sperm (gestational carrier carries pregnancy)	• IVF using a partner's eggs with donor sperm (gestational carrier carries pregnancy)
Any partner with a uterus and without ovaries†	• IUI with donor sperm (for patient) • IVF using patient eggs with donor sperm (patient or partner to carry pregnancy)	• IVF using a patient's eggs with donor sperm (partner to carry pregnancy)	• IVF using donor eggs with donor sperm (patient or partner to carry pregnancy)	• IVF using donor eggs with patient's sperm (partner to carry pregnancy)	• IVF using donor eggs with donor sperm (partner to carry pregnancy)
Any partner with sperm	• Intercourse • Home insemination with partner's sperm • IUI with partner's sperm (for the patient) • IVF with a partner's sperm (patient to carry the pregnancy)	• IVF using patient's eggs with a partner's sperm (gestational carrier carries pregnancy)	• IVF using donor eggs with partner's sperm (patient to carry pregnancy)	• IVF using donor eggs with patient's and/or a partner's sperm (gestational carrier carries pregnancy)	• IVF using donor eggs with a partner's sperm (gestational carrier carries pregnancy)
No partner or a partner without ovaries, a uterus, sperm†	• IUI with donor sperm (for the patient) • IVF with donor sperm (patient to carry the pregnancy)	• IVF using patient's eggs with donor sperm (gestational carrier carries pregnancy)	• IVF using donor eggs with donor sperm (patient to carry pregnancy)	• IVF using donor eggs with patient's sperm (gestational carrier carries pregnancy)	• IVF using donor eggs with donor sperm (gestational carrier carries pregnancy)
Fertility preservation for the patient	• Egg/embryo freezing • Ovarian tissue freezing**	• Egg/embryo freezing • Ovarian tissue freezing	• No options are currently available	• Sperm/embryo freezing • Testicular tissue freezing (experimental)	• No options are currently available

* In addition, all people have the option of adoption and step-parenthood.

† Without/lack of a uterus/sperm/ovaries refers to the biological absence of an organ, a desire not to use the organ, or the impaired reproductive function of the organ.

‡ IUI = intrauterine insemination

§ IVF = in vitro fertilization

** Ovarian tissue freezing is performed only in specialized fertility clinics. See the discussion under the section "Fertility preservation."

who had previous exposure to estrogen compared to those who were estrogen-naive.[23] The subjects who were using exogenous estrogen at the time of the study had a higher prevalence of abnormal semen analysis results, and three of the seven current users had no sperm at all (azoospermic).[23] Stopping estrogen therapy is recommended to assess for the recovery of sperm parameters before trying to conceive.

To obtain a sperm sample for freezing in those who have already begun estrogen therapy, it is unclear how long hormones should be stopped before normal spermatogenesis resumes.[1,24] The resumption of sperm production after the cessation of exogenous estrogen can be extrapolated from testosterone contraception trials.[25] The recovery of sperm concentration to more than 20 million/mL required a median time off testosterone of 3.4 months.[25] However, it took up to 24 months for 100% of individuals to attain spermatogenesis.[25] In practice, the patient might be advised to perform a routine semen analysis at an outpatient laboratory to screen for the presence and concentration of sperm. Once spermatogenesis has returned, the patient can seek sperm freezing at a fertility clinic. The cost is estimated at approximately $400 and $800 annually for storage, but this may vary by clinic.

Some patients do not tolerate the extended cessation of estrogen therapy required to achieve completely normal levels of spermatogenesis (> 39 million sperm per sample).[26] These patients can be counseled to bank a semen sample before the complete restoration of spermatogenesis. In vitro fertilization with intracytoplasmic sperm injection (IVF/ICSI) requires low numbers of sperm, which renders the freezing of samples with even very low numbers of sperm (thousands or tens of thousands of sperm per sample) a feasible option. For fresh sperm samples, extremely low numbers of sperm (tens or hundreds) can be sufficient for IVF/ICSI because the sample is not subject to the freeze–thaw process, through which, on average, the amount of viable sperm is reduced by 50%.[27] To obtain enough sperm for the less costly and less invasive procedure of intrauterine insemination, several samples with normal concentration (> 15 million sperm/mL) should be banked.

Prepubertal patients

In the pediatric population, reversible gonadotropin-releasing hormone agonist analogs are often prescribed as a means of suppressing puberty and the development of secondary sexual characteristics until patients are ready to begin hormone therapy.[22] The desire for fertility preservation appears to be lower among TGD youth than among TGD adults based on a review that reported an estimated 24% to 36% of TGD youth wanted biologically related children.[1] However, it has been reported that far fewer TGD youth access fertility preservation counseling than are interested, and only a small number ultimately choose to pursue preservation treatment before gender-affirming therapies.[28] However, a 2018 survey of TGD adolescents and young adults reported that nearly half agreed that their feelings about fertility might change in the future.[29] Prepubertal options for fertility preservation are limited to ovarian tissue and testicular tissue freezing.[1] The long-term effect of pubertal suppression on fertility is unknown.[1] Testicular tissue freezing remains experimental, and no reported live births have resulted from this method.[12]

Fertility treatments

The fertility options for TGD individuals are largely the same as those available to cisgender individuals **[Table]**.[3] However, efforts should be made to limit the exacerbation of gender dysphoria during fertility treatment.[5] Furthermore, patients should be advised that the current practice is based on expert opinion, small case studies, and extrapolations from cisgender populations.[1]

Patients with ovaries

Testosterone therapy potentially affects ovarian architecture and function.[30] One study of TGD individuals undergoing oophorectomy who had a history of long-term testosterone therapy found a histologic trend toward polycystic ovarian morphology (increased ovarian volume and numerous ovarian follicles).[31] However, another study reported no change in the distribution of ovarian follicles.[32] There are conflicting findings on the effect of exogenous testosterone on ovarian reserve. Anti-Müllerian hormone is produced by the granulosa cells in small ovarian follicles and has been validated as an accurate measure of ovarian reserve, regardless of cycle timing.[33] Research suggests that anti-Müllerian hormone levels are significantly lower after the initiation of testosterone therapy in TGD individuals.[34] However, a 2016 study of adolescent TGD patients reported no change in anti-Müllerian hormone levels with hormone therapy.[35] It seems plausible that testosterone therapy would not interfere with the measurement of ovarian reserve, as anti-Müllerian hormone is only slightly lower in long-term users of oral contraceptive pills.[36]

In light of the paucity of safety data, the World Professional Association for Transgender Health and the American Society for Reproductive Medicine presume a loss of fertility with the use of hormone therapy and recommend reviewing the options for fertility preservation prior to the initiation of any hormonal or surgical gender-affirming care.[2] While high-quality evidence is needed,[23,30] it is reassuring to note that several case reports and cohort studies have shown promising in vitro fertilization and egg freezing outcomes even after years of hormone therapy.[11,12,22]

TGD patients with ovaries who wish to have someone else carry the pregnancy can undergo ovarian stimulation and egg retrieval for the purposes of in vitro fertilization. A 2019 retrospective cohort study that compared assisted reproductive technology outcomes in TGD individuals with ovaries and outcomes in cisgender women found similar ovarian stimulation outcomes between the two groups.[37] Most of the TGD patients were undergoing testosterone therapy at the time of presentation, with a mean time of 44 months on testosterone and an average of 4 months cessation before beginning ovarian stimulation. There was no significant difference between TGD and cisgender patients in terms of the number of eggs retrieved, which suggests that even long periods of testosterone therapy do not have negative effects on ovarian stimulation.[37]

For many patients, the requirement to stop or delay testosterone therapy is a major deterrent to proceeding with ovarian stimulation.[37] In the largest study of its kind, a review of 53 patients found that less than 50% of the cohort

who originally presented for fertility consultation ultimately proceeded with treatment.[37] The cessation of gender-affirming hormones is one of several aspects of the fertility process that may amplify patients' experience of gender dysphoria.[19] For TGD individuals, the administration of exogenous gonadotropins needed for ovarian stimulation and its subsequent increase in endogenous estrogen production may be a "highly feminizing" and distressing experience.[19] Egg retrieval and repeated transvaginal ultrasound assessment may also lead to discomfort. It is important to discuss these considerations with patients. Strategies to help reduce patient dysphoria during this process include the addition of an aromatase inhibitor (estrogen blocker) during ovarian stimulation and the use of transabdominal rather than vaginal ultrasonography when possible.[19]

Patients with a uterus

TGD people with a uterus can carry a pregnancy as long as testosterone is not used during gestation because it could lead to virilization of a female fetus.[19] Some TGD patients with a uterus and ovaries may choose to stop hormonal therapy and resume spontaneous ovulation to conceive by intercourse, home insemination, or intrauterine insemination.

If the intent is to conceive with embryo transfer from in vitro fertilization, the return of spontaneous menses is not a prerequisite. Even if the patient does not stop hormone therapy long enough to attain a menstrual cycle, exogenous estrogen and progesterone can be administered to induce endometrial growth and receptivity. This is common practice for postmenopausal cisgender women who achieve pregnancy with donor eggs. Pregnancy has been reported in TGD individuals who were previously exposed to exogenous testosterone, but the available studies are small and observational.[19,30,38] After giving birth, some TGD people may choose to chestfeed their infants (even if they have had prior chest masculinization surgery).[39] Of note, testosterone abstinence is recommended during this time because the elevated serum testosterone level can suppress lactation.[40] Obstetrical care providers should use gender-inclusive language to discuss pregnancy, childbirth, and lactation, and should be aware of the potentially undesired physical changes associated with these experiences.

Patients with sperm

For TGD people with sperm, fertility options include intercourse, home insemination, intrauterine insemination, or in vitro fertilization. People with sperm can choose to fertilize a partner's eggs or donor eggs and use a partner's uterus or gestational carrier to gestate the pregnancy **[Table]**. Although IVF/ICSI is often successful, even with extremely low sperm counts, there are limited data describing IVF outcomes with sperm from TGD individuals.[24]

While high-quality evidence is needed, it is reassuring to note that several case reports and cohort studies have shown promising in vitro fertilization and egg freezing outcomes even after years of hormone therapy.

Masturbation as a means of sperm collection for fertility treatments may prove distressing to TGD patients. The requirement to temporarily stop or delay gender-affirming therapy may also worsen dysphoria. In order to minimize this stress, alternative options for sperm collection include penile vibratory stimulation, transrectal electroejaculation, or surgical sperm retrieval.[28] Some of these minimally invasive options may require local or general anesthesia.

Fertility after gender-affirming surgery

Some TGD people choose to access surgical gender-affirming therapies as part of their transition process. Surgical interventions such as hysterectomy and/or gonadectomy may result in permanent sterility unless gonadal tissue, sperm, or eggs are frozen ahead of time. There are currently no fertility preservation options available for patients who have completed these procedures **[Table]**.[12] For TGD men who undergo hysterectomy without oophorectomy, egg retrieval for in vitro fertilization or egg freezing can still be performed.

Barriers to care

In addition to the risk of elevated dysphoria during the fertility process, TGD individuals experience many systemic barriers in accessing fertility care. As societal inequities contribute to TGD people being disproportionately affected by poverty, homelessness, and unemployment, cost is routinely cited as a major barrier to accessing fertility treatments.[9,12] There is no provincially funded medical coverage for fertility preservation, in vitro fertilization, or insemination in BC, and the financial burden of treatment may prove particularly onerous for young people.[19] Infrequent fertility inquiry and counseling by providers, inadequate provider knowledge of TGD reproductive health, limited access to fertility centres in rural communities, and the fear and lived experience of discrimination are also significant barriers.[7,28,38]

Providers can improve fertility care for their TGD patients by inquiring about their gender identity, pronouns, and preferred terms for body parts, and by revising clinic forms to include this information.[41] Providers should be familiar with TGD reproductive health and the potential barriers to care.[19] Fertility counseling regarding egg/sperm preservation and reproductive options should be the standard of care for all TGD patients.[24] Reproductive counseling can be delivered by the primary care physician or referred to a specialist in endocrinology, urology, obstetrics-gynecology, or infertility.

Summary

Comprehensive fertility counseling is critical to the equitable provision of care to TGD patients. While TGD individuals desire parenthood at similar rates as cisgender individuals, research suggests most fail to receive fertility counseling from any health care providers.[4,24] Because some medical and surgical gender-affirming treatment may negatively impact future fertility, it is critical to address the options for fertility preservation and family-building options before initiating such therapies.[3] ■

Competing interests

None declared.

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Additional resources

ASRM Today–Transgender care: A patient's view with Trystan Reese [podcast] http://asrmtoday.org/asrm-today-transgender-care-a-patients-view-with-trystan-reese

Inappropriate questions: "How did you get pregnant?" [podcast] www.cbc.ca/radio/iqpodcast/how-did-you-get-pregnant-1.5622930

Trans-inclusive abortion services [PDF] www.optionsforsexualhealth.org/wp-content/uploads/2019/07/FQPN18-Manual-EN-BC-web.pdf

Gender inclusive language [PDF] www.phsa.ca/transcarebc/Documents/HealthProf/Gender_Inclusive_Language_Clinical.pdf

Gender-affirming care for trans, Two-Spirit, and gender diverse patients in BC: A primary care toolkit [PDF] www.phsa.ca/transcarebc/Documents/HealthProf/Primary-Care-Toolkit.pdf

Sexual & reproductive health: Information about sexual health and reproductive planning for trans and gender diverse people [web resource] www.phsa.ca/transcarebc/care-support/access-care/sexual-hlth

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