Reproductive Health

Background/Introduction

All humans, including transgender individuals, have the reproductive right to decide whether to have children (United Nations Population Fund, 2014). Gender- affirming hormonal treatments and surgical interventions that alter reproductive anatomy or function may limit future reproductive options to varying degrees (Hembree et al., 2017; Nahata et al., 2019). It is thus critical to discuss infertility risk and fertility preservation (FP) options with transgender individuals and their families prior to initiating any of these treatments and to continue these conversations on an ongoing basis thereafter (Hembree et al., 2017). Established FP options, such as embryo, oocyte, and sperm cryopreservation, may be available for postpubertal transgender individuals (Nahata et al., 2019). Research protocols for ovarian and testicular tissue cryopreservation have also been developed and studied (Borgström et al., 2020; Nahata et al., 2019; Rodriguez-Wallberg et al., 2019). Whereas the use of embryos, mature oocytes, and sperm have all proven to be efficacious when employed within clinical treatments, cryopreserved gonadal tissues would require either future retransplantation aimed at obtaining fully functional gametes or the application of laboratory methods for culture, which are still under development in basic science research settings. Of note, recent American Society for Reproductive Medicine guidelines have lifted the experimental label on ovarian tissue cryopreservation, but evidence remains limited in prepubertal children (Practice Committee of the American Society for Reproductive Medicine, 2019).

Some research suggests transgender and gender diverse (TGD) people may be less likely to desire genetically related children or children at all when compared with cisgender peers (Defreyne et al., 2020; Russell et al., 2016; von Doussa et al., 2015). Yet, several other studies have shown that many TGD individuals 1) desire genetically related children; 2) regret missed opportunities for FP; and 3) are willing to delay or interrupt hormone therapy to preserve fertility and/or conceive (Armuand, Dhejne, et al., 2017; Auer et al., 2018; De Sutter et al., 2002; Defreyne et al., 2020; Tornello & Bos, 2017).

Many barriers to FP have been reported, such as cost, urgency to start treatment, inability to make future-oriented decisions, and inadequate provider knowledge/provider biases that affect offering FP (Baram et al., 2019; Defreyne et al., 2020). Additionally, transgender individuals may have worsening dysphoria due to various steps in the FP process that are inseparably connected with the gender assigned at birth (Armuand, Dhejne, et al., 2017; Baram et al., 2019). An interdisciplinary team approach, where both medical and mental health providers collaborate with gender-affirming fertility specialists, can help overcome some of these barriers (Tishelman et al., 2019). In addition to fertility considerations, efforts to ensure equitable high-quality care for all forms of family building throughout the full reproductive continuum must be maintained. This includes perinatal care, pregnancy, delivery, and postpartum, as well as contraceptive options to prevent unplanned pregnancies, and pregnancy termination if sanctioned (Bonnington et al., 2020b; Cipres et al., 2017; Krempasky et al., 2020; Light et al., 2018; H Moseson, L Fix, et al., 2020). TGD people who wish to carry a pregnancy should undergo standard of care preconception care and prenatal counseling and should receive counseling about breast/chest feeding in environments supportive of people with diverse gender identities and experiences (MacDonald et al., 2016; Obedin-Maliver & Makadon, 2016).

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Summary of Recommendations

Statement 1: We recommend that health care providers who are treating TGD people and prescribing or referring patients for hormone therapies/surgeries should advise their patients about:

A. known effects of hormone therapies/surgery on future fertility;
B. potential effects of therapies that are not well studied and are of unknown reversibility;
C. fertility preservation (FP) options (both established and experimental);
D. psychosocial implications of infertility.

Statement 2: We recommend that clinicians refer TGD individuals interested in fertility preservation to providers with expertise in fertility preservation for further discussion.

Statement 3: We recommend that transgender care teams partner with local reproductive specialists and facilities to provide specific and timely information and fertility preservation services prior to offering medical and surgical interventions that may impact fertility.

Statement 4: We recommend that clinicians counsel pre- or early pubertal TGD youth seeking gender-affirming therapy and their families that established fertility preservation options are limited.

Statement 5: We recommend that TGD people with a uterus who wish to carry a pregnancy should undergo preconception care, prenatal counseling regarding use and cessation of gender-affirming hormones, pregnancy care, labor and delivery, chest/breast feeding supportive services, and post-partum support according to local standards of care in a gender-affirming way.

Statement 6: We recommend that medical providers discuss contraception methods with TGD people who engage in sexual activity that can result in pregnancy.

Statement 7: We recommend that providers who offer pregnancy termination services ensure procedural options are gender-affirming and serve transgender people and those of diverse genders.

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All these statements have been recommended based on the large amount of background literature that supports a favorable risk-benefit ratio to providing reproductive health counseling to patients and families. We recognize that, in some cases, evidence is limited and/or reproductive services may not be accessible or desirable.

Statement 1:
We recommend that health care providers who are treating TGD individuals and prescribing or referring patients for hormone therapies/surgeries should advise their patients about:

A. known effects of hormone therapies/surgeries on future fertility;
B. potential effects of therapies that are not well studied and are of unknown reversibility;.

C. fertility preservation (FP) options (both established and experimental;.
D. psychosocial implications of infertility.

Individuals assigned female at birth

Gender-affirming hormone therapy may negatively impact future reproductive capacity (Hembree et al., 2017). Based on current evidence in transgender men and gender diverse people assigned female at birth, these risks are as follows:

Gonadotropin-releasing hormone agonists (GnRHas) may be used for pubertal suppression to prevent further pubertal progression until adolescents are ready for masculinizing treatment. GnRHas may also be used for menstrual suppression. GnRHas impact the maturation of gametes but do not cause permanent damage to gonadal function. Thus, if GnRHas are discontinued, oocyte maturation would be expected to resume.

There are few studies detailing the effects of testosterone therapy on reproductive function in transgender men (Moravek et al., 2020). Restoration of normal ovarian function with oocyte maturation after testosterone interruption has been demonstrated in transgender men who have achieved natural conception. A retrospective study on oocyte cryopreservation showed no differences in total number of oocytes retrieved or in the number of mature oocytes between transgender men and age- and BMI-matched cisgender women (Adeleye, Cedars, et al., 2019; Adeleye, Reid, et al., 2019). The first results have recently been published evaluating live birth rates after controlled ovarian stimulation in transgender men compared with cisgender women (Leung et al., 2019). Testosterone was discontinued prior to ovarian stimulation. Overall, the results concerning the influence of testosterone on reproductive organs and their function appear to be reassuring. However, there have been no prospective studies to date evaluating the effect of long-term hormone therapy on fertility (*i.e.*, started in adolescence) or in those treated with GnRHas in early puberty followed by testosterone therapy. Consideration should be given to the fact that the required medications and procedures for cryopreserving oocytes (a pelvic examination, vaginal ultrasound monitoring, and oocyte retrievals) may lead to increasing gender dysphoria in transgender men (Armuand, Dhejne, et al., 2017).
Surgical interventions among transgender men will have obvious implications for reproductive capacity. If patients desire a hysterectomy, there is the option of preserving the ovaries to retain the possibility of having a genetically related child. Alternatively, if the ovaries are removed either separately or concurrently with the hysterectomy, there may also be the option of concurrent ovarian tissue cryopreservation at the time of oophorectomy. Although this procedure is no longer considered experimental, many transgender men may desire *in vitro* maturation of primordial follicles, which is still investigational. Studies evaluating oocyte function have shown oocytes isolated from transgender men with testosterone exposure at the time of oophorectomy can be matured *in vitro* to develop normal metaphase II meiotic spindle structure (De Roo et al., 2017; Lierman et al., 2017).

Individuals assigned male at birth

Based on current evidence in transgender women and gender diverse people assigned male at birth, the influence of medical treatment is as follows:

GnRHas inhibit spermatogenesis. Data suggest that discontinuation of treatment results in a re-initiation of spermatogenesis, though this may take at least 3 months and most likely longer (Bertelloni et al., 2000). Furthermore, the psychological burden of re-exposure to testosterone should be considered.

Anti-androgens and estrogens result in an impaired sperm production (de Nie et al., 2020; Jindarak et al., 2018; Kent et al., 2018). Spermatogenesis might resume after discontinuation of prolonged treatment with anti-androgens and estrogens, but data are limited (Adeleye, Reid, et al., 2019; Alford et al., 2020; Schneider et al., 2017). Testicular volumes diminish under the influence of gender-affirming hormone treatment (Matoso et al., 2018). Semen quality in transgender women may also be negatively affected by specific life-style factors, such as a low frequency of masturbation, wearing the genitals tight against the body (e.g. with use of tight undergarments for tucking) (Jung & Schuppe, 2007; Mieusset et al., 1987; Mieusset et al., 1985).

Statement 2:
We recommend that clinicians refer TGD individuals interested in fertility preservation to providers with expertise in fertility preservation for further discussion.

Research shows many transgender adults desire biological children (De Sutter et al., 2002; Defreyne et al., 2020; Wierckx, Van Caenegem, et al., 2012), yet FP rates remain widely variable, particularly in youth (< 5%-40%) (Brik et al., 2019; Chen et al., 2017; Chiniara et al., 2019; Nahata et al., 2017; Segev-Becker et al., 2020). In a recent survey, many youth acknowledged their feelings about having a biological child might change in the future (Strang et al., 2017). Sterilization is a violation of human rights (Ethics Committee of the American Society for Reproductive Medicine, 2015; European Court of Human Rights, 2021; Meyer III et al., 2002), and due to advances in social attitudes, fertility medicine, and affirmative transgender healthcare, biological parenthood during transition is a viable option for transgender people. Due to the influence clinical opinion may have on transgender or non-binary people's FP and on parenting decisions, FP options should be explored by health care providers alongside options such as fostering, adoption, coparenting, and other parenting alternatives (Bartholomaeus & Riggs, 2019). Transgender patients who have been offered this type of discussion and have been given the choice to undergo procedures for FP have reported the experience to be an overall positive one (Armuand, Dhejne, et al., 2017; De Sutter et al., 2002; James-Abra et al., 2015).

In other patient populations, fertility referrals and formal fertility programs have been shown to increase FP rates and improve patient satisfaction (Kelvin et al., 2016; Klosky, Anderson, et al., 2017; Klosky, Wang, et al., 2017; Shnorhavorian et al., 2012) Physicians' attitudes have been investigated, and recent studies indicate both an awareness and a desire to provide fertility-related information to children and their families. However, barriers have also been identified, including lack of knowledge, comfort, and resources (Armuand, Nilsson, et al., 2017; Frederick et al., 2018).Thus, the need for appropriate training of health care providers has been highlighted, with emphasis placed on fertility counseling and offering FP options to all at-risk individuals in an unbiased way (Armuand, Nilsson, et al., 2017). Parents' recommendations have also been shown to significantly influence FP rates in adolescent and young adult males with cancer (Klosky, Flynn, et al., 2017). These findings can help inform best practices for fertility counseling and FP referrals for transgender individuals.

Statement 3:
We recommend that transgender care teams partner with local reproductive specialists and facilities to provide specific and timely information and fertility preservation services prior to offering medical and surgical interventions that may impact fertility.

Cryopreservation of sperm and oocytes are established FP techniques and can be offered to pubertal, late pubertal, and adult birth assigned males and birth assigned females, respectively, preferably prior to the initiation of gender-affirming hormone (GAH) treatment (Hembree et al., 2017; Practice Committee of the American Society for Reproductive Medicine, 2019). Cryopreservation of embryos can be offered to adult (post-pubertal) TGD people who wish to have a child and have an available partner. The future use of cryopreserved gametes is also dependent on the gametes and reproductive organs of the future partner (Fischer, 2021; Maxwell et al., 2017)

Although semen parameters have been shown to be compromised when FP is performed after initiation of GAH medication (Adeleye, Reid, et al., 2019), one small study showed that when the treatment was discontinued, semen parameters were comparable to those in TGD patients who had never undergone GAH treatment. With regard to ovarian stimulation, oocyte vitrification yield, and subsequent use of the oocytes in in-vitro fertilization (IVF), there is no reason to anticipate a different outcome in assisted reproductive technology (ART) treatments for TGD patients than that obtained in cisgender patients undergoing ART—other than individual confounding factors related to (in)fertility—when gametes are banked prior to any medical treatment (Adeleye, Cedars, et al., 2019). The use of oocytes in ART treatment resulted in similarly successful outcomes in TGD compared with controlled, matched cisgender patients (Adeleye, Cedars, et al., 2019; Leung et al., 2019; Maxwell et al., 2017). Although these are established options, few pubertal, late pubertal or adult TGD people undergo FP (Nahata et al., 2017), and many experience challenges while undergoing FP interventions. Not only is the cost of these methods a barrier, but these procedures are often physically and emotionally uncomfortable, and many express concerns about postponing the transitioning process (Chen et al., 2017; De Sutter et al., 2002; Nahata et al., 2017; Wierckx, Stuyver, et al., 2012). Especially for the birth assigned females, the invasiveness of endovaginal ultrasound follow-up of the ovarian stimulation and oocyte retrieval procedures (and associated psychological distress) have been cited as a barrier (Armuand, Dhejne, et al., 2017; Chen et al., 2017). There is also the concern that young adults going through transitioning may not have a clear vision of parenting and are therefore likely to decline the opportunity to use FP at that time— while as adults, they may have different opinions about parenthood (Cauffman & Steinberg, 2000). The reduction of gender dysphoria during transitioning could also influence the decision-making process surrounding FP (Nahata et al., 2017). Based on research showing TGD youths' fertility perspectives may change over time (Nahata et al., 2020; Strang et al., 2017), FP options should be discussed on an ongoing basis.

Statement 4:

We recommend that clinicians counsel pre- or early TGD youth seeking gender- affirming therapy and their families that established fertility preservation options are limited.

For prepubertal and early pubertal children, FP options are limited to the storage of gonadal tissue. Although this option is available for TGD children in the same way that it is available for cisgender prepubertal and early pubertal oncological patients, there is no literature describing the utilization of this approach in the transgender population. Ovarian tissue autotransplantation has resulted in over 130 live births in cisgender women. Most of these patients conceived naturally without ART (Donnez & Dolmans, 2015; Jadoul et al., 2017), and the majority stored their ovarian tissue either as adults or during puberty. Although the recent American Society for Reproductive Medicine guideline has lifted the experimental label from ovarian tissue cryopreservation (Practice Committee of the American Society for Reproductive Medicine,

2019), there are very few case reports describing a successful pregnancy in a woman following the transplantation of ovarian tissue cryopreserved before puberty. Demeestere *et al.* (Demeestere et al., 2015) described the case of a successful pregnancy following transplantation of tissue procured at the age of 14, and recently Matthews *et al.* (Matthews et al., 2018) described the case of a girl diagnosed with thalassemia who had ovarian tissue stored at the age of 9 and transplantation 14 years late. She subsequently conceived through IVF and delivered a healthy baby.

Currently, the only future clinical application for storing ovarian tissue is autotransplantation, which might be undesirable in a transgender man (due to the potentially undesirable effects of estrogen). A laboratory procedure that would make it possible to mature oocytes *in vitro* starting with ovarian tissue would be the ideal future application of stored ovarian tissue for transgender people, but this technique is currently only being investigated and optimized in basic science research settings (Ladanyi et al., 2017; Rodriguez-Wallberg. & Oktay, 2010).

Procurement of testicular tissue in prepubertal boys has been documented as a low-risk procedure (Ming et al., 2018). Some authors have also described this approach as a theoretical option in transgender people (De Roo et al., 2016; Martinez et al., 2017; Nahata et al., 2018). However, there are no reports in the literature describing the clinical or investigational utilization of this FP option for transgender patients. Moreover, the viability of the clinical application of autotransplantation of testicular tissue remains unknown in humans, and *in vitro* maturation techniques are still in the realm of basic science research. Thus, specialists involved in FP for prepubertal boys consider this technique experimental (Picton et al., 2015). The possibility of storing gonadal tissue should be discussed prior to any genital surgery that would result in sterilization, although the probability of being able to use this tissue must be clearly addressed.

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Statement 5:
We recommend that TGD people with a uterus who wish to carry a pregnancy should undergo preconception care and prenatal counseling regarding the use and cessation of gender-affirming hormones, pregnancy care, labor and delivery, and chest/breast feeding supportive services, and postpartum support according to local standards of care in a gender-affirming way.

Most transgender men and gender diverse people assigned female at birth retain their uterus and ovaries and thus can conceive and carry a pregnancy even after long-term testosterone use (Light et al., 2014). Many transgender men desire children (Light et al., 2018; Wierckx, Van Caenegem, et al., 2012) and are willing to carry a pregnancy (Moseson et al., 2021). ART has expanded the opportunity for many transgender men to conceive and fulfill their family planning wishes (De Roo et al., 2017; Ellis et al., 2015; Maxwell et al., 2017). Some transgender men report psychological isolation, dysphoria related to the gravid uterus and chest changes, and depression (Charter, 2018; Ellis et al., 2015; Hoffkling et al., 2017; Obedin-Maliver & Makadon, 2016). Conversely, other studies have reported some positive experiences during pregnancy as well (Fischer, 2021; Light et al., 2014). Mental health providers should be involved to provide support and counseling should be provided addressing when to stop and when to resume gender-affirming hormones, what options are available for the mode of delivery and for chest/breast feeding (Hoffkling et al., 2017). Finally, system-level and interpersonal-level interventions should be implemented to ensure person-centered reproductive health care for all people (Hahn et al., 2019; Hoffkling et al., 2017; H. Moseson et al., 2020; Snowden JM, 2018).

Given the potential harmful effects of testosterone on the developing embryo, discontinuing testosterone or masculinizing hormone therapy prior to conception and during the entire pregnancy is recommended. However, the optimal time for both the discontinuation of testosterone prior to pregnancy and its resumption after pregnancy is unknown. Since stopping gender-affirming hormones may cause distress and exacerbate dysphoria in transgender men, when and how to stop this therapy should be discussed during prenatal counseling (Hahn et al., 2019). Because information about the duration of testosterone exposure and the risk of teratogenicity is lacking, testosterone use should be discontinued prior to attempting pregnancy and/or before stopping contraception. Moreover, there is limited information regarding health outcomes of infants born to transgender men. Small case series attempting to evaluate this question have revealed no adverse physical or psychosocial differences between infants born to transgender men and infants in the general population (Chiland et al., 2013).

Chest/Breast Feeding

In the limited studies evaluating lactation and chest/breast feeding, the majority of transgender men who chose to chest/breast feed postpartum were successful, with research suggesting induction of lactation is in part dependent on preconception counseling and experienced lactation nursing support (MacDonald et al., 2016; Wolfe-Roubatis & Spatz, 2015). Specifically, transgender men and TGD people who use testosterone should be informed 1) although quantities are small, testosterone does pass through chest/breast milk, and 2) the impact on the developing neonate/child is unknown, suggesting gender-affirming testosterone use is not recommended during lactation but may be resumed after discontinuation of chest/breast feeding (Glaser et al., 2009). Transgender men should be made aware that some patients who carry a pregnancy may experience undesired chest growth and/or lactation even after chest reconstruction and should therefore be supported if they desire to suppress lactation (MacDonald et al., 2016).

There is limited information concerning lactation in transgender women, but many also express the desire to chest/breast feed. While there is a case report of a transgender woman successfully lactating and chest/breast feeding her infant after hormonal support using a combination of estrogen, progesterone, domperidone, and breast pumping (Reisman & Goldstein, 2018), the nutritional and immunological profile of chest/breast milk under these conditions has not been studied. Therefore, patients need to be informed about the risks and benefits of this approach to child feeding (Reisman & Goldstein, 2018).

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Statement 6:
We recommend that medical providers discuss contraception methods with TGD people who engage in sexual activity that can result in pregnancy.

Many transgender individuals may retain reproductive capacity, and they personally (if they retain a uterus, ovaries, and tubes) or their sexual partners (for sperm producing individuals) may experience unplanned pregnancies (James et al., 2016; Light et al., 2014; H Moseson, L Fix, et al., 2020). Therefore, intentional family planning counseling, including contraception and abortion conducted in gender-expansive ways is needed (Klein et al., 2018; Obedin-Maliver, 2015; Stroumsa & Wu, 2018). TGD people may not use contraception due to an erroneous assumption that testosterone is a reliable form of contraception (Abern & Maguire, 2018; Ingraham et al., 2018; K. Jones et al., 2017; Potter et al., 2015). However, based on current understanding, testosterone should not be considered a reliable form of contraception because of its incomplete suppression of the hypothalamic-pituitary-adrenal axis (Krempasky et al.,

2020). Furthermore, pregnancies have occurred while individuals are amenorrheic due to testosterone use, which may outlast active periods of administration (Light et al., 2014). Pregnancy can also occur after long-term testosterone use (at least up to 10 years) though the effect on oocytes and baseline fertility is still unknown (Light et al., 2014).

TGD people assigned female sex at birth may use a variety of contraceptive methods (Abern & Maguire, 2018; Bentsianov et al., 2018; Bonnington et al., 2020a; Chrisler et al., 2016; Cipres et al., 2017; K. Jones et al., 2017; Krempasky et al., 2020; Light et al., 2018).These methods may be used explicitly for pregnancy prevention, menstrual suppression, abnormal bleeding, or other gynecological needs (Bonnington et al., 2020a; Chrisler et al., 2016; Krempasky et al., 2020; Schwartz et al., 2019) . Contraceptive research gaps within this population are profound. No studies have examined how the use of exogenous androgens (*e.g.,* testosterone) may modify the efficacy or safety profile of hormonal contraceptive methods (*e.g.,* combined estrogen and progestin hormonal contraceptives, progestin only based contraceptives) or non-hormonal and barrier contraceptive methods (*e.g.,* internal and external condoms, non-hormonal intrauterine devices, diaphragms, sponges, *etc.*).

Gender diverse individuals who currently have a penis and testicles may engage in sexual activity with individuals who have a uterus, ovaries, and tubes of any gender. Gender diverse people who have a penis and testicles can produce sperm even while on gender-affirming hormones (*i.e.,* estrogen), and although semen parameters are diminished among those who are currently using or who have previously used gender- affirming hormones, azoospermia is not complete and sperm inactivity is not totally suppressed (Adeleye, Reid, et al., 2019; Jindarak et al., 2018; Kent et al., 2018). Therefore, contraception needs to be considered if pregnancy is to be avoided in penis-in-vagina sexual activity between a person with a uterus, ovaries, and tubes and one with a penis and testicles, irrespective of the use of gender-affirming hormones by either partner. Currently, contraceptive methods available for use by the sperm-producing partner are primarily mechanical barriers (*i.e.,* external condoms, internal condoms), permanent sterilization (*i.e.,* vasectomy), and gender-affirming surgery (*e.g.,* orchiectomy, which also results in sterilization). Gender expansive contraceptive counseling that considers sperm producing, egg producing, and gestating partners (as relevant) is recommended.

Statement 7:

We recommend that providers who offer pregnancy termination services should ensure procedural approaches are gender-affirming and serve transgender people and those of diverse genders.

Unplanned pregnancies and abortions have been reported among transgender individuals (Abern & Maguire, 2018; Light et al., 2014; Light et al., 2018; H Moseson, L Fix, et al., 2020) and documented through surveys of abortion-providing facilities (R. K. Jones et al., 2020). However, the population-based epidemiology of abortion provision and the experiences and preferences of TGD individuals undergoing abortion still represents a critical gap in research (Fix et al., 2020; H Moseson, L Fix, et al., 2020; H Moseson, MR Lunn, et al., 2020). Nonetheless, given that pregnancy capacity exists among many TGD people and pregnancies may not always be planned or desired, access to safe, legal, and gender-affirming pregnancy medical and surgical termination services is necessary.

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