**Transgender Care and Gender Affirmation Surgery**

Alexander Kotlyar MD[1], Cecile Ferrando MD MPH[2], Pasquale Patrizio, M.D., MBE[1]

1. Section of Reproductive Endocrinology and Infertility, Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale School of Medicine, New Haven CT.
2. Center for Urogynecology and Pelvic Reconstructive Surgery, Obstetrics, Gynecology & Women's Health Institute, Cleveland Clinic, Cleveland OH.

Introduction:

Transgender care/issues have been a fixture of numerous cultures throughout history. However, it has only came into prominence in the western world into the 1940s with the pioneering work of Harry Benjamin (1). The standard of care was set with the establishment of guidelines from the World Professional Association for Transgender Health (WPATH). Now in its seventh version, these guidelines outline the steps needed to provide individuals with gender dysphoria with both the medical, surgical, and mental health tools to undergo their desired gender transition. However, while transgender care has become increasingly widespread, numerous cultural and medical barriers still exist.

In many cultures, gender roles are firmly set in which certain masculine and feminine roles are expected of a male and female, respectively. Any digression from these expected roles can result in social isolation and stigma (2). However, there is regional variation with more acceptance in certain countries and less acceptance in others (3). Recently, western countries have passed legislation recognizing a third gender with Germany being the first country in Europe to do so. Several Asian countries such as India have subsequently followed suit (4, 5). Table 1 describes important terminology used to better understand transgender individuals and their care.

| Table 1: Classification of Transgender Definitions | |
|---|---|
| Transgender | A broad term encompassing patients whose gender expression, behavior, and/or identity which differs from the gender given at birth. |
| Gender identity | A patient's inherent sense of being either male, female, or a non-binary gender. |
| Sexual orientation | The gender that an individual is sexually or emotionally attracted to. |
| Gender expression | The manner in which patients express gender e.g. clothing, habits, behaviors, grooming. |
| Gender variance/nonconformity | Behavior that does not fit with what is considered typical for an assigned gender. |
| Genderqueer | An individual who either identifies as both genders or neither. |
| Cisgender | A patient who identifies with the gender assigned at birth. |
| Transsexual | An individual who identifies themselves with the other sex and seeks gender-affirmation treatment to either feminize or masculinize their body. |
| Crossdresser | An individual who wears clothing of the opposite sex but does not identify as that opposite sex. |
| Bigendered | Identification of gender as alternatively male or female, no gender, or neither male nor female. |
| Intersex | Individuals who have congenital variations of their reproductive organs that are consistent with standard male and female anatomy e.g. newborns with ambiguous genitalia. |
| Transgender man (Female-to-Male) | A person who was identified as a female at birth, but who presently identifies themselves as male* |
| Transgender woman (Male-to-Female) | A person who was identified as a male at birth, but who presently identifies themselves as female* |
| * This term is often used after an individual has initiated some form of gender affirming therapy. | |

Approach to Clinical Care:

a. Primary Care:

The essential first-line to provide adequate care to transgender individuals is in the primary care-setting. One of the initial steps in providing this is to establish the diagnosis of gender dysphoria. This is defined according to the diagnostic and statistical manual of mental disorders, fifth edition (DMS-5) as "distress that might be present in the context of incongruence between sex assignment at birth and gender identity" (6). Furthermore, primary care-providers should be able to recognize and assess basic mental health concerns and eligibility for hormone therapy and or surgery. A primary care provider is also essential in maintaining transgender patient's preventative care and metabolic well-being while they are undergoing their gender-affirming transition. This will provide the basis for efficient and continuous basic healthcare for the transgender population (7).

b. Endocrine Therapy:

Following judicious assessment and referral by their primary care provider, many transgender patients will choose to pursue hormone therapy. Numerous recent review articles outline the standard transitional hormonal regimens used (8, 9).

The initial step in hormonal therapy for transgender patients is to suppress endogenous reproductive hormone production. This is typically done with GnRH agonists such as leuprolide acetate or with GnRH antagonists. If such GnRH analogues are not available for financial reasons or due to side-effect intolerance, agents with anti-androgenic actions can be used such as Cyproterone acetate (not available in USA), Spironolactone, or certain Progestins. For adolescents that meet the criteria for gender dysphoria, the treatment is typically initiated after girls and boys first start to demonstrate the physical changes of puberty. It must be emphasized that such treatment should be started in coordination with a multidisciplinary team of medical (endocrinologist) and mental health professionals (8).

Once adequate suppression of endogenous hormones is achieved, hormone supplementation is started. In the case of transgender women, feminizing hormones are given in the form of estrogen tablets or transdermal patches. 17β-estradiol (17β-E2) is preferred over ethinyl estradiol or conjugated estrogens since 17β-E2 plasma levels can be assessed using commercial assays. In addition, 17β-E2 has a smaller risk of thromboembolism than synthetic estrogens like ethinyl estradiol.

It must be noted that transgender women are at risk of increased mortality while on hormonal therapy. In a retrospective cohort study from the Netherlands, 966 transgender females and 365 transgender males were followed for at least one year. For the transgender women in this study, all-cause mortality was 51% higher than in the general population. The greatest causes of death were suicide, acquired immunodeficiency syndrome (AIDS), cardiovascular disease (CVD), and drug abuse (10). Therefore, any provider handling these patients must discuss these risks and provide comprehensive informed consent.

Hormonal therapy for transgender men is centered around testosterone therapy. This is given as either a transdermal gel or a long-acting depot injection (enanthate or cypionate). As with estrogen therapy, blood levels are used to monitor patients to ensure that levels are within the physiologic range for the intended gender.

c. Reproduction:

Removal of the gonads (ovaries or testes) causes a permanent inability to have genetically-linked children and, similarly, long-term hormonal treatment can have a deleterious effect on fertility. GnRH agonists can halt the maturation of germ cells thereby abrogating fertility. Testosterone therapy can not only prevent ovulation, but also alter ovarian histology. Furthermore, gender-affirming surgery can include hysterectomy (14%) for transgender men and orchiectomy (11%) for transgender women which render these patients permanently sterile (11).

Numerous studies have shown that over half of all transgender patients desire children (12). As a consequence, WPATH, the American Society for Reproductive Medicine (ASRM), and the European Society of Human Reproduction and Embryology (ESHRE) recommend offering referrals to reproductive endocrinologists for comprehensive discussions concerning gamete (and thus future fertility) preservation options for any transgender patient. Oocyte cryopreservation and sperm cryopreservation with possible embryo production via in-vitro fertilization are currently available options. Transgender men desiring oocyte or embryo cryopreservation will undergo controlled ovarian hyperstimulation with exogenous gonadotropins and then oocyte retrieval and/or in-vitro fertilization. It must be noted that significant distress and worsening of gender dysphoria may be experienced by some transgender men caused by cessation of testosterone therapy and by pelvic examination/ultrasounds to monitor the ovarian response and for accomplishing oocyte retrieval for cryopreservation (13). Therefore, provider sensitivity to this and coordination with a mental health provider throughout this process is crucial. Of note, there is not univocal agreement on the length of time (? few weeks-to 2 months) in stopping testosterone replacement before starting controlled ovarian stimulation.

Ovarian tissue cryopreservation, which could be offered at the same time of gender conforming surgery, is an option rarely offered to transgender men since would require ovarian tissue to be re-implanted into the patient for future attempts at conceiving. However, the possible futuristic opportunity to grow oocytes in vitro from culture of ovarian cortex, should leave this option open if there are no other solutions. While encouraging in-vitro results have been obtained with maturation of follicles to metaphase II, researchers have yet to proceed to the stage of IVF/ICSI for a transgender male with an intact uterus (11).

Sperm cryopreservation can be expeditiously done in transgender women who have not yet undergone orchiectomy. A specimen can be obtained via masturbation or via testicular sperm extraction. Although sperm cryopreservation is ideal prior to the start of estrogen hormone therapy, there is evidence that semen parameters may be adequate for intrauterine insemination or spontaneous conception following several months of discontinuation of hormone therapy.

A new frontier that has been recently explored is that of uterine transplantation. Theoretically, this surgery could be offered to transwomen providing the opportunity to carry their own pregnancies. Over 42 uterine transplants have been done to date, but only in cisgender women (15). Numerous concerns remain over the adequacy of the pelvic blood supply in transgender women, placement of a uterus in a non-gynecoid pelvis, and the supplementation of hormones needed to sustain pregnancy. Despite these barriers, uterus transplantation in transgender women may be ethically permissible based on justice and equality (16).

d. Surgical Management:

Surgical management is a key part of gender-affirming treatment for a sub-population of transgender patients. Based on the results of the 2015 United States Transgender Survey (USTS), of 27,715 respondents, 25% had undergone gender-affirming surgical therapy in some form. Genital reconstruction surgery is often the last step in the transition for patient undergoing gender transition(17). The WPATH guidelines layout discrete criteria to undergo such surgery which are in addition to the need for 12 months of continuous hormonal therapy (3).

Transgender men may undergo mastectomy as the first surgical step in their transition. Subsequent surgery may then involve hysterectomy, oophorectomy, vaginectomy and phallic construction. The latter involves phalloplasty, metoidoplasty, and scrotoplasty with the goal being standing micturition, coital ability, aesthetic recognition of a phallus, and sexual sensation. Use of a forearm flap is currently the preferred technique for phallus construction.

For male-to-female transition, a similar progression of procedures is typically performed. Many patients will undergo breast reconstruction with subsequent facial feminization surgery. Genital surgery often involves orchiectomy, penectomy, vaginoplasty, labioplasty, and

clitoroplasty. The most commonly performed procedure is the penile inversion technique. Many modifications of this surgery exist. The gold standard method for creating a sensate clitoris is the dorsal neurovascular pedicle glans penis flap method (18). In most techniques, the scrotal skin is used for the vaginoplasty, but for failed cases and in cases of underdeveloped penile anatomy, an intestinal vaginoplasty may be performed. Postoperatively, patients must dilate the neovagina regularly in order to avoid vaginal stenosis. Patients who do not desire a functional vagina have the option of having a no-depth or partial-depth vaginoplasty, which involves creation of a short vaginal canal only, and lowers the overall risk associated with surgery.

Numerous studies have confirmed excellent outcomes following gender-affirming surgeries. These studies have shown not only aesthetic satisfaction following these procedures, but also improved quality of life with virtually a zero rate of mortality. Post-operative complications include urinary tract, bowel, and pelvic floor dysfunction (19, 20).

e. Mental Health:

As mentioned above, mental health professionals are an essential resource to help support a patient's gender transition. These providers must screen patients for signs of stigmatization /oppression/ostracization. This is in addition to being vigilant for high-risk sexual behavior, depression, anxiety, substance abuse which are more prevalent in the transgender population (1). In addition, these providers should be consulted throughout the time a patient is undergoing gender-affirming treatment. Such treatment not only improves quality of life, but also can lead to a decrease in suicidal behavior (1, 21).

Overall, immense strides have been made in transgender care over the past 60 years. Consistent and effective protocols for hormonal therapy are in use and numerous robust techniques are available for gender-affirming surgery. While barriers still exist, the movement to solidify a multidisciplinary approach to transgender care continues to advance and to be increasingly accepted.

References:


1. Wylie K, Knudson G, Khan SI, Bonierbale M, Watanyusakul S, Baral S. Serving transgender people: clinical care considerations and service delivery models in transgender health. Lancet. 2016;388(10042):401-11.
2. Khan SI, Hussain MI, Parveen S, Bhuiyan MI, Gourab G, Sarker GF, et al. Living on the extreme margin: social exclusion of the transgender population (hijra) in Bangladesh. J Health Popul Nutr. 2009;27(4):441-51.
3. Chokrungvaranont P, Selvaggi G, Jindarak S, Angspatt A, Pungrasmi P, Suwajo P, et al. The development of sex reassignment surgery in Thailand: a social perspective. ScientificWorldJournal. 2014;2014:182981.
4. Nieder TO, Strauss B. Transgender health care in Germany: Participatory approaches and the development of a guideline. Int Rev Psychiatry. 2015;27(5):416-26.
5. Ming LC, Hadi MA, Khan TM. Transgender health in India and Pakistan. Lancet. 2016;388(10060):2601-2.
6. Zucker KJ. Epidemiology of gender dysphoria and transgender identity. Sex Health. 2017;14(5):404-11.
7. Ettner FM. Primary Care for the Transgender and Gender Nonconforming Patient. Clin Plast Surg. 2018;45(3):301-6.
8. Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017;102(11):3869-903.

9. Weinand JD, Safer JD. Hormone therapy in transgender adults is safe with provider supervision; A review of hormone therapy sequelae for transgender individuals. J Clin Transl Endocrinol. 2015 (2): 55-60.
10. Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol. 2011;164(4):635-42.
11. Cheng PJ, Pastuszak AW, Myers JB, Goodwin IA, Hotaling JM. Fertility concerns of the transgender patient. Transl Androl Urol. 2019 8 (3): 209-18.
12. Wierckx K, Van Caenegem E, Pennings G, Elaut E, Dedecker D, Van de Peer F, et al. Reproductive wish in transsexual men. Hum Reprod. 2012;27(2):483-7.
13. Armuand G, Dhejne C, Olofsson JI, Rodriguez-Wallberg KA. Transgender men's experiences of fertility preservation: a qualitative study. Hum Reprod. 2017;32(2):383-90.
14. Donnez J, Dolmans MM. Ovarian cortex transplantation: 60 reported live births brings the success and worldwide expansion of the technique towards routine clinical practice. J Assist Reprod Genet. 2015;32(8):1167-70.
15. Flyckt R, Davis A, Farrell R, Zimberg S, Tzakis A, Falcone T. Uterine Transplantation: Surgical Innovation in the Treatment of Uterine Factor Infertility. J Obstet Gynaecol Can. 2018;40(1):86-93.
16. Jones BP, Williams NJ, Saso S, Thum MY, Quiroga I, Yazbek J, et al. Uterine transplantation in transgender women. BJOG. 2019;126(2):152-6.
17. Chen D, Simons L, Johnson EK, Lockart BA, Finlayson C. Fertility Preservation for Transgender Adolescents. J Adolesc Health. 2017;61(1):120-3.
18. Fang RH, Chen CF, Ma S. A new method for clitoroplasty in male-to-female sex reassignment surgery. Plast Reconstr Surg. 1992;89(4):679-82; discussion 83.
19. Rossi Neto R, Hintz F, Krege S, Rubben H, Vom Dorp F. Gender reassignment surgery--a 13 year review of surgical outcomes. Int Braz J Urol. 2012;38(1):97-107.
20. Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, et al. Long-term assessment of the physical, mental, and sexual health among transsexual women. J Sex Med. 2009;6(3):752-60.
21. Lawrence AA. Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. Arch Sex Behav. 2003;32(4):299-315.