Gender-Affirming Hormone Therapy

What the Head and Neck Surgeon Should Know

C. Michael Haben, MD, MSc*

KEYWORDS

• Transgender • Nonbinary • Hormone • Feminization • Masculinization • Estrogen • Testosterone

KEY POINTS

- Gender-affirming hormone therapy is present nearly universally in the transgender population.
- Understanding of the effects, expectations, limitations, and risks of hormone therapy is vital to optimal care of this population.
- Perioperative management of hormone therapy is an important aspect of surgical planning.

INTRODUCTION

Up to 3% of the US population identifies as transgendered/gender incongruent, nonbinary, or "other."[1] Transgender is defined as having a binary gender identity or expression that is the opposite from the one assigned at birth. In contrast, cis-gender is defined as having the same binary gender or expression that is assigned at birth.

There is a growing number of individuals who do not ascribe to a binary gender classification and consider themselves as nonbinary, a gender, gender neutral, gender bender, third gender, or androgynous. In 2016, New York City identified 31 different, officially recognized gender classifications.[2] Although feminizing or masculinizing gender-affirming hormone therapy (F-GAHT and M-GAHT) has historically been considered for those individuals who are transgender in a binary sense, it is increasingly being used for nonbinary individuals whose identity or expression is more feminine or masculine than the sex assigned at birth without being specifically "male" or "female."

The demographics of this population seem to be changing. In additional to a significant increase in the overall number of individuals self-reporting to this group, the

Center for the Care of the Professional Voice, 980 Westfall road, Suite 1-127, Rochester, NY 14618, USA
* Corresponding Author.
E-mail address: Michael.Haben.MD@professionalvoice.org

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mean age seeking initiation of hormone therapy has decreased steadily with the average age in both male and female dropping to less than 30 years at one institution[3] and a steady increase in the percentage of female-to-male (FTM) such that it is now equivalent to male-to-female (MTF). Regardless of specific prevalence rates, most studies demonstrate two clear trends: (1) growth in the proportion of gender nonconforming self-identifying individuals over time and (2) a higher proportion of nonconforming identities among the younger generations.[4] These findings may be due in part to increasing visibility, acceptance, and understanding of gender nonconforming individuals. Another important factor could be the move away from classifying gender incongruence as a mental disorder. In the latest Diagnostic and Scientific Manual and International Classification of Diseases "gender identity disorder" has been replaced with gender dysphoria (GD) and gender incongruence. GD is defined as a marked incongruence between one's experienced and/or expressed gender and assigned gender at birth.[5]

The American Psychiatry Association in a policy statement makes it important to note that gender nonconformity is not in itself a mental disorder.[6] This population, however, possesses a high prevalence of coexisting anxiety, depression, substance abuse, suicide, lower rates of health utilization, higher rates of tobacco use, obesity, sexually transmitted diseases , and HIV-infections compared with their cisgendered counterparts.[7,8]

There is some evidence that GD manifests commonly in early childhood, with a median age of 6 years for both female and male transgendered individuals and could persist untreated for decades before individuals commence gender transition therapy.[9] There seems to be a movement to identify and treat GD in adolescents and youth earlier in pubertal development.[10] In this population subset, current hormonal regimens aim to achieve full pubertal suppression with the modulation of endogenous sex hormone effects in addition to the development of secondary sex characteristics congruent with the affirmed gender.[11] This trend may ultimately have a significant impact on the timing, feasibility, and practical and ethical considerations of gender-affirming surgery (GAS) of the head and neck for future generations for gender nonconforming youths.[12]

This article will look at some of the most common hormonal therapies used for gender transitioning and the state of research on how or how long a particular therapy might impact the timing of various components of gender confirming surgery in the head and neck.

GENDER-AFFIRMING HORMONAL THERAPY

For most transgendered individuals, accessing GAHT is a necessary and generally first step in their transition. The basic concept of GAHT is to replicate as closely as possible the hormone environment that is concordant with the person's gender identity.[13] The primary endpoints of GAHT are to address the GD[14] (and secondarily improve the coexisting anxiety, substance abuse, suicidal ideation and depression, when present) and promote the secondary sex characteristics of the affirmed gender.

GAHT in accordance with current clinic practice guidelines is generally safe and effective.[15] Hormone therapy was traditionally used in patients with binary gender incongruence, that is, men transitioning to women or vice-versa. Recently, its use has broadened beyond transgendered individuals to include gender neutral, bigender, androgynous, nongender, and other individuals experiencing GD wishing to have secondary sex characteristics more feminine or masculine than those they possess. Although some people may wish to achieve the greatest possible masculinization or

feminization from hormonal interventions, others may only seek sufficient hormones to achieve an androgynous appearance.

Chemically synthesized estrogens and testosterone became commercially available in the 1930s and 1940s. It was not until 1979 that the first standards of care regarding hormonal therapy for transgendered individuals were developed. These standards eventually became an international organization of multidisciplinary trans-health professionals named The World Professional Association of Transgender Health (WPATH)[16] intending to be a global education initiative providing surgeons and other health care professionals the necessary background knowledge to understand and care for this unique population. The most recent updated Standards of Care version 8 is expected by the end of December 2021 at the time of this writing.[17] Additional clinical guidelines have been published by the Endocrinology Society[18] in the United States among others in Europe[19] and elsewhere.[20] Gender-transitioning patients would ideally be served by a multidisciplinary approach which includes providers in primary care, behavioral health, members of various surgical specialties and subspecialties, in addition to endocrinology. In most settings this idealized multidisciplinary approach is simply not practical or even available because of a myriad of barriers to access. More and more, primary care physicians are assuming the lead in the diagnosis of GD, initiation and routine testing of individuals on GAHT as well as screening and management of comorbidities.[21] An often overlooked aspect of care is how the timing of one therapy may impact the timing of subsequent therapies including gender affirmation surgery.

Coordination may be especially problematic when patients are treated by providers that are literally hundreds or thousands of miles away from other members of the team, in an unaffiliated center, or even located in a different country. The proportion of individuals in this population having to travel very long distances to access care, especially surgical specialists, is tremendous.[22]

GAHT may be broadly classified as either feminizing (F-GAHT) or masculinizing (M-GAHT). F-GAHT is based on the use of exogenous estrogen, alone or in various combinations[23] with the goal of increasing serum estradiol concentrations and decreasing serum testosterone concentrations into a range similar to cisgender premenopausal female *[Hembree 18],*[24] When used in combination with estrogen, additional agents fall into four general categories: (1) progestins,[25] (2) androgen blockers including cyproterone and the antiandrogen spironolactone, (3) gonadotropin-releasing hormone agonists such as leuprolide, and (4) 5-alpha reductase inhibitors, typically finasteride.[26] If orchiectomy is completed (alone or as part of full gender affirmation "bottom" surgery), androgen-blockers and GnRH agonists are terminated.

Although a wide variety of hormone regimens have been developed, there are no published reports of randomized clinical trials comparing efficacy in producing physical transition.

Beyond ameliorating GD, the expectations for F-GAHT on secondary sex characteristics in adults are myriad and include enhancement of breast development, skin softening, slowing of androgenic hair loss, fat redistribution (from abdomen to hips), and reduction in testicular and prostate size. Feminizing GAHT has also been shown to decrease strength, lean body mass, and muscle area, effects considered to be desirable.[27] The most commonly cited secondary sex characteristic end point for F-GAHT is breast development.[28] In one study for transgender women, breast development was the most anticipated change in over 35% of respondents, followed by gynoid fat deposition.[29]

Testosterone is the mainstay of M-GAHT and can be administered via a nasal route, weekly subcutaneous/intramuscular injection or transdermal gel/patch. An oral route recently approved by the FDA for cisgendered men with medically low testosterone[30]

may soon be available to transgendered men. The effects of M-GAHT on secondary sex characteristics include cessation of menses, facial hair development, deepening of the voice, clitoromegaly, fat redistribution from the hips to abdomen, oily skin, acne, and increased muscle mass and strength. The most commonly cited secondary sex characteristic end point for M-GAHT is cessation of menses.[31] Amenorrhea and a deeper voice were the secondary sex characteristic most anticipated in adults starting M-GAHT at 52.7% and 32.4%, respectively. Masculinizing GAHT improves GD, quality of life , and social functioning within 6 months of therapy. In contrast, transgendered females do not seem to gain the same early benefit from GAHT and seem to be more likely to require surgical procedures of the head and neck because of the relatively modest impacts of feminizing hormone regimens on highly noticeable secondary sex characteristics of the face and voice.[14]

Most physical changes, whether feminizing or masculinizing, occur over the course of 2 years. The amount of physical change and the exact timeline of effects can be highly variable. This can and should be taken into consideration when contemplating the age, timing, and candidacy of irreversible surgical procedures. A commonly cited approximate time course for physical changes[18] from initiation of F-GAHT are

- Breast growth expected by 3 to 6 months. Maximum benefit usually realized in 2 to 3 years.
- Gynoid body fat redistribution expected by 3 to 6 months. Maximum benefit usually realized in 2 to 5 years.
- Decreased lean body mass, strength, and muscle area expected by 3 to 6 months. Maximum benefit usually realized in 1 to 2 years.
- Skin softening expected by 3 to 6 months. Maximum benefit usually realized in 2 to 3 years.
- Slowed growth of body and facial hair expected by 3 to 6 months. Unknown time to maximum benefit because of the number of dermatologic procedures frequently undertaken.
- Slowed androgenic hair loss (male pattern baldness) expected at 1 to 3 months. Maximum benefit usually realized in 1 to 2 years; however, no regrowth of prior hair loss is expected.
- Voice: no changes are expected or observed.

And from initiation of M-GAHT are:

- Amenorrhea expected by 2 to 6 months. Maximum benefit usually realized in 1 to 2 years.
- Voice deepening expected by 3 to 12 months. Maximum benefit usually realized in 1 to 2 years.
- Facial and body hair virilization expected by 3 to 6 months. Maximized benefit usually realized in 3 to 5 years.
- Oily skin and acne expected at 1 to 6 months. Maximum benefit usually realized in 1 to 2 years.
- Androgenic hair loss expected at 1 to 6 months. Maximum benefit highly dependent on age and genetics.
- Increased muscle mass and strength expected at 6 to 12 months. Maximum benefit usually realized at 2 to 5 years
- Masculine body fat redistribution expected at 3 to 6 months. Maximum benefit usually realized in 2 to 5 years.

The degree to which these changes occur can vary greatly from person to person and may be dependent on the age at which GAHT is initiated, exact regimen

prescribed, as well as the presence and impact of medical comorbidities. It should be noted that the hormone therapy, whether with estrogen or testosterone, is usually continued lifelong, even after oophorectomy or orchiectomy. Overall, adult transgendered men have a higher rate of achieving the head and neck secondary sex characteristics of their affirmed gender using M-GAHT than women using F-GAHT as testosterone therapy typically generates highly visible changes in the face (growth of facial hair, thickening of the skin, increase in frontal bossing, and so forth)[31] and voice.[32] Universally, F-GAHT makes less of a definitive difference in the face[33] with no real effect on facial beard and bony structure or the voice. Without realizing many of the secondary sex characteristics of cisgendered females on hormone therapy alone, transgender females frequently seek out facial feminization surgery, feminization laryngoplasty, and procedures for facial hair removal to address this disparity in GAHT.

Hembree[18] describes three categories or stages of physical interventions for GD:

Fully reversible interventions. These involve the use of GnRH analogues to suppress estrogen or testosterone production before gonad surgery and consequently limit the physical changes and development of secondary sex characteristics of their nonaffirmed gender due to puberty. This category is generally limited to adolescents and young adults who have not completed puberty or had gonad surgery.

Partially reversible interventions. These include GAHT to masculinize or feminize the body. Some hormone-induced changes may need reconstructive surgery to reverse the effect (eg, gynecomastia caused by estrogens or deepening of the voice caused by testosterone) should de-transition back to birth gender become necessary.

Irreversible interventions. These are surgical procedures, including most GAS procedures of the head and neck.

In adolescents, Hembree contends, a stepwise process is recommended to keep options open through the first two stages. Moving from one stage to another should not occur until there has been adequate time for adolescents and their parents to assimilate fully the effects of earlier interventions.

SURGICAL CANDIDACY

WPATH, in its most recent Standards of Care publication (SOC 7, published in 2012),[16] strongly recommended that patients considering genital ("bottom") surgery have not only a persistent, well-documented history of GD but also completed 12 continuous months of hormonal therapy. The SOC 7 rationale for a preoperative, 12-month experience of living in an identity-congruent gender role is based on expert clinical consensus that a year provides sufficient opportunity for most patients to experience and adjust to their affirmed gender role before considering a surgical procedure. Twelve months allow for a range of different life experiences and events that typically take place including family events, holidays, vacations, and etcetera. During this time, patients are encouraged to present themselves in their affirmed gender role consistently on a daily basis and across all settings of life. It has been recommended that this process includes disclosure to partners, family, friends, coworkers, and members of the individual's community.

Although there are no explicit recommendations in the SOC 7 for behavioral health documentation or duration of hormonal therapy before head and neck surgical procedures, some providers extrapolate WPATHs genital surgery recommendations including: living as the affirmed gender and on appropriate GAHT for a minimum of 1 year before considering an individual a reasonable candidate for irreversible surgery. Other providers report a small but not insignificant percentage of patients, notably

male-to-female transgendered individuals, who present either not having initiated GAHT or electing not to pursue hormonal therapy because of a variety of reasons including maintenance of reproductive capabilities or reticence to endure the adverse effects of treatment. A 1-year waiting period and/or GAHT requirement could exacerbate already severe dysphoria, particularly male-to-female transgendered individuals where F-GAHT is not expected to significantly improve most of the visible secondary sex characteristics, namely the face and voice. As such, clinical judgment and an individualized approach would be prudent when extrapolating guidelines across surgical specialities and assessing surgical candidacy.

Although laryngeal and facial plastic procedures do not require referral by mental health providers, such professionals can play an important role assisting patients in making a fully informed decision about the timing and implications of such procedures in the context of the overall transition. Evaluation for psychological suitability for surgery could decrease the risk of postoperative depression or suicide as recovery from major surgery can be very stressful. Questions to be considered are (1) whether the patient has been on GAHT for a sufficient amount of time and with adequate support services to control the GD as much as medically possible allowing for true informed consent for an irreversible surgical procedure; (2) whether the duration of GAHT has been sufficient to permit the expected impact(s) to be fully realized; and (3) has the patient fully embraced their affirmed gender, including disclosure to their immediate circle, sufficient to provide adequate support during the postoperative recovery? This final consideration may be principally vital for patients who traveled hundreds (or thousands) of miles for a procedure and may return home postoperatively to less than ideal support systems.

PERIOPERATIVE GENDER-AFFIRMING HORMONE THERAPY

Gender-affirming surgical procedures of the head and neck invariably occur after starting hormone therapy. Hormone management in the perioperative period requires an understanding of the risks and benefits of GAHT as well as an understanding of risk-mitigation strategies. There are various deleterious effects associated with GAHT that could potentially play a role in perioperative surgical complications[34] including hypertrigliceridemia, hyperprolactinemia, and coronary artery disease on feminizing hormones; erythrocytosis, destabilization of certain psychiatric disorders and hypertension on masculinizing hormones; and weight gain, elevated liver enzymes and blood pressure changes associated with either hormone therapy. The most commonly cited concern with the use of F-GAHT both during and outside of the perioperative period is that of the risk of venous thromboembolism (VTE) due to estrogen. VTE is a known risk for certain formulations of estradiol therapy and is the most common side effect of F-GAHT reported.[18] It is important for surgeons to understand the perioperative risk of VTE and strategies to mitigate the chances of deep venous thrombosis, pulmonary embolism, myocardial infarction, and stroke. The VTE risks associated with exogenous hormones have well-studied in cisgender females on hormone replacement therapy, however, transgender females are unique in that they are typically on much higher doses of hormone therapy; start therapy much younger; and remain on it lifelong in most cases.[35] Extrapolating existing data on cisgender females taking hormonal replacement therapy may not appropriate.

Initial studies reported a 20- to 45-fold risk of thromboembolic events compared with cisgender controls, however these studies failed to control for tobacco use[36] and involved the use of high doses of oral ethinyl estradiol.[37] Ethinyl estradiol is a synthetic estrogen used in combination contraception preparations with a significant VTE risk.

The 17-β estradiol is currently the most commonly used estrogen in feminizing hormone regimens today and is chemically as well as biologically indistinguishable from endogenous ovarian estrogen. It may be administered as an oral/sublingual tablet, transdermal patch, or intramuscular/subcutaneous injection. Conjugated and synthetic estrogens use cannot be monitored serologically and confer no benefits over 17-β estradiol. Combined with their VTE risks, they are rarely used today when obtained through a physician.[18] The route of estradiol administration plays a described role on VTE risk.[38] The impact of estradiol on clotting factor synthesis is enhanced during first-pass metabolism.[39] Transdermal delivery of 17-β estradiol has been associated with a reduction in this risk.[40] Ideally, F-GAHT regimens include transdermal or IM estradiol formulations to address this concern.[41] Unfortunately, oral formulations of 17-β estradiol appear to be the most frequently prescribed in the United States due to cost and insurance limitations.[42]

Much of the rationale for perioperative estradiol discontinuation comes from a landmark study[39] noted that the following cessation of oral ethinyl estradiol a rebound in fibrinogen and antithrombin III concentrations were seen at 2 to 6 weeks. The authors postulated that surgery should be undertaken at least 4 weeks following cessation of oral ethinyl estradiol, at which stage fibrinogen is low, antithrombin III is high, and factor X has returned to baseline. This and subsequent studies evaluating the perioperative risk of estrogen were largely based on high doses of oral ethinyl estradiol. Furthermore, many of these studies were performed before the introduction of routine VTE prophylaxis and may not be applicable today. A recent meta-analysis review[43] of modern and historical feminizing GAHT regimens concluded that to date, there are no data to demonstrate the benefit of discontinuing estrogen-containing hormone regimes before major gender-affirming surgeries. The authors contend that for most young, healthy transgender women, there is little risk of VTE with continuation of perioperative hormone therapy, whereas older patients or those with additional risk factors should be considered on a individual basis.

Given the lack of randomized, controlled studies, many surgeons and societies, based largely on expert opinion recommend holding F-GAHT, in particular estrogens, for 2 to 6 weeks before and 3 to 4 weeks after “major” surgical procedures under general anesthesia.[44–49] Numerous professional societies have looked at perioperative VTE management in patients on F-GATH including the American Society of Plastic Surgeons, who in their VTE Task Force[50] published in 2012, recommended discontinuation of F-GAHT for all inpatient (“major”) procedures under general anesthesia and for elective procedures in patients with Caprini scores $\geq$7. Other societies, including the American Association of Plastic Surgeons in 2016[51] and the European Society of Anaesthesiology in 2007,[52] recommend using the Caprini risk stratification to guide decision-making with less of a universal blanket policy regarding hormone therapy. The American College of Obstetricians and Gynecologists in 2018[53] recommended against routine preoperative discontinuation of hormone therapy and instead taking into consideration the risk of holding treatment as part of the overall calculus in those who may be at increased VTE risk. Perioperative discontinuation of estradiol may result in side effects that can have a significant mental and physical impact on quality of life, body image, and sexual function.[54] Two or six weeks after estradiol is stopped, virilization with testosterone occurs and serum estradiol concentrations may plummet to near the male reference range.[55] This risks preoperative rebound dysphoria with potential exacerbation of anxiety, depression, substance abuse, and suicidal ideation as well as physical effects.[56] This impact may result in perioperative harm and nonsurgical postoperative complications. According to Nolan and colleagues,[57] there is insufficient evidence to support routine discontinuation of estradiol therapy in the

perioperative period. In all cases, it is recommended that patients complete a 2005 Caprini risk factor assessment (or equivalent) to stratify patients' VTE risk based on their individual risk factors and then apply the recommended mitigation strategies including early ambulation, mechanical prophylaxis, and chemoprophylaxis where appropriate. A risk factor common in the transgender population is the frequency in which they travel long distances to assess surgical care. The role of this specific risk factor on the overall calculus of perioperative F-GAHT cessation versus continuation is an area which needs to be investigated.

Although many of the negative effects of feminizing and masculinizing hormone therapies have been described, few studies have looked into how these effects specifically impact perioperative management. On such example is the changes in blood pressure found after initiating hormone therapy. A recent European Network for the Investigation of Gender Incongruence was the largest study (n = 430) that assessed blood pressure before and after initiating GAHT. In contrast to earlier smaller studies, it found that GAHT did not significantly change blood pressure in a clinically significant way.[58,59] Other potential issues which could impact the perioperative period include testosterone induced erythrocytosis, which has been reported in one in 4-to-6 transgender male depending on the formulation of testosterone.[60,61] The largest increase in hematocrit is typically observed within the first year. A reasonable first step in the care for transgender men with erythrocytosis while on testosterone is to advise smokers to quit, switch to a transdermal administration route if not already used, and address suboptimal BMI when present. There are data showing that as a whole the transgender population has a greater risk for cardiovascular disease with relatively high rates of undiagnosed and untreated comorbidities, such as hypertension and dyslipidemia, even before initiation of GAHT. The authors did not note how risk factors changed after GAHT.[62] A thorough preoperative cardiovascular risk assessment in transgender men is advisable.

Acne is a common adverse event with all testosterone formulations available today. Isotretinoin is being prescribed more frequently for refractory cases. Historically, recommendations were to wait 6 to 12 months after completion of isotretinoin therapy before considering elective surgical procedures on the head and neck. Although early reports suggested that isotretinoin use would impair wound healing, recent prospective clinical studies have not found an increased incidence of facial scarring in patients using isotretinoin in the perioperative period.[63]

Finally, individuals on GAHT, especially M-GAHT, have been noted to have modest increases in liver transaminases (ALT and AST concentrations) following testosterone initiation without clear clinical significance of the observed association.[64] Although seen, feminizing GAHT is less likely to induce appreciable changes in liver enzyme levels. Routine preoperative liver function testing is probably not necessary in patients on GAHT unless clinically indicated for other reasons.

SUMMARY

Hormone therapy is present in nearly every individual undergoing gender-affirming surgical procedures of the head and neck. Head and neck surgeons need to be aware of the role, expectations, limitations, and negative effects of GAHT could have in the perioperative period. The limited availability of randomized controlled data sets guiding evidence-based perioperative hormone therapy management in transgender individuals has resulted in guidelines based primarily on expert opinion or limited observational studies. Many of these guidelines fail to take into consideration the risks of perioperative GAHT discontinuation.

CLINICS CARE POINTS

- Patients should be fully living the life of the affirmed gender for at least 12 continuous months on appropriate gender-affirming hormone therapy (GAHT) before considering irreversible gender-affirming surgical procedures of the face, neck, and voice.
- Patients should be given ample time on GAHT to realize reasonably expected changes in secondary sex characteristics.
- Careful postoperative planning is essential as many patients receive surgical care hundreds or thousands of miles from home with suboptimal support systems.
- The perioperative risks of continuing GAHT should also be weighed against the risks of hormone discontinuation.

DISCLOSURE

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