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INVITED REVIEW

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Feminizing gender-affirming hormone therapy for the transgender and gender diverse population: An overview of treatment modality, monitoring, and risks

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Abstract

Aims: Feminizing gender-affirming hormone therapy (GAHT) can be utilized to help transfeminine transgender and gender diverse (TGD) individuals achieve the transformation of outward sex characteristics, thereby leading to improvements in psychological and social well-being. In this narrative review, we aim to summarize current guidelines for feminizing GAHT management as well as the available literature describing the associated health risks pertaining to cardiovascular disease, thromboembolic disease, bone health, and cancer risks.

Methods: Relevant literature from January 2019 through July 2022 pertaining to feminizing GAHT was identified using PubMed, Cochrane Library, EMBASE, and MEDLINE. A narrative summary was performed with the inclusion of more recently published guidance from the World Professional Association for Transgender Health, Standards of Care Version 8.

Results: Guidance regarding the prescribing of feminizing GAHT with estrogen, antiandrogen, and progesterone medications is summarized along with considerations of the cardiovascular, thromboembolic, bone health, and cancer risks associated with these therapies.

Conclusions: Feminizing GAHT is a highly effective method for transfeminine TGD patients to achieve medically necessary changes in secondary sex characteristics. Knowledge of the health risks of feminizing GAHT is largely drawn from research in the cisgender population, with a growing body of literature in TGD-specific patient populations. Feminizing GAHT appears to carry a low risk profile for most patients; however, further research describing the risks of hormone management around the time of gender-affirming surgery and in the aging TGD population is needed to optimize GAHT in the context of the evolving health risks over a TGD patient's lifespan.

KEYWORDS
androgen-blocker, estrogen, gender-affirming hormone therapy, hormone therapy, transgender

1 | INTRODUCTION

Recent estimates find that approximately 0.5%–1.6% of adults, over 1.3 million, living in the United States and up to 4.5% worldwide identify as transgender or nonbinary, otherwise known as Transgender and Gender Diverse (TGD) individuals.[1-4] Age-related trends show a higher incidence in the young adult age group 18–29 years old (5.1%) versus those age 50 and older (0.3%).[1,2] Much of this trend may be attributable to growing awareness of the diagnosis and accessibility to health professionals offering treatment. Understandings of the definitions of transgender (a person who identifies as a different gender than that assigned at birth) and gender nonbinary (a person who identifies as neither male nor female) in the field of medicine are becoming more commonplace across specialties. Accordingly, care for gender dysphoria, defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as gender incongruence that leads to significant psychological, physical, and emotional distress,[5] is no longer being provided exclusively by psychiatrists, endocrinologists, and plastic surgeons, but by primary care physicians, gynecologists, and many others familiar with standards of care for the treatment of transgender and nonbinary individuals.[6,7] Moreover, recent practice has evolved to recognize that gender incongruence, a marked and persistent incompatibility between an individual's gender identity and the gender expected of them based on their assigned sex at birth, is not pathological or a mental disorder; as such, gender-affirming treatment may be offered to TGD individuals to prevent significant distress or dysphoria.[4] Several organizations, including the World Professional Association for Transgender Health (WPATH), the Endocrine Society, and the University of California San Francisco Center of Excellence for Transgender Health have published summary guidance and evidence-based recommendations based on historical and emerging evidence. Newly published recommendations from WPATH, Standards of Care, Version 8 (SOC-8), reflect this more appropriate diagnostic starting point. In addition, gender incongruence is recognized in the International Classification of Disease and Related Health Problems, 11th Version, of the World Health Organization (ICD-11).

Gender-affirming care should be patient-centered, with an emphasis placed on informed-decision making and harm reduction.[4] The spectrum of gender-affirming care includes four key components: (1) patient-driven changes in gender expression and role (also known as real-life experiencing), (2) psychotherapy (including psychological, social, and peer support), (3) gender-affirming hormone therapy (GAHT), and (4) gender-affirming surgery to change primary and/or secondary sex characteristics.[4,6] SOC-8 frequently includes gender-affirming medical and/or surgical treatments (GAMSTs) together as an umbrella term when discussing universally applicable indications and recommendations. Comprehensive care for the TGD person typically requires the deployment of a coordinated team approach,[7–9] and such institutional teams are becoming more commonplace in the United States, Europe, and Canada. A team approach helps to ensure quality comprehensive gender-affirming care while reducing the burdens placed on a single-provider-care which encompasses the initiation of gender-affirming treatment, maintenance and monitoring, and surgical planning, as well as gender inclusive routine healthcare including cancer and other health screening.

GAHT for transgender women and feminine nonbinary persons includes the simultaneous development and maintenance of feminine secondary sex characteristics with the suppression of masculine secondary sex characteristics.[6,9,10] Feminizing GAHT always includes the use of some formulation of natural estrogen (estradiol, E2), typically in combination with a testosterone-blocking, or antiandrogen, therapy, and occasionally in combination with progesterone, although the data on the indications, safety, and benefits of progesterone use is limited and thus less frequently employed.[11,12] Estradiol may be administered orally, transdermal, or via intramuscular injection.[7–9] Antiandrogen treatment most commonly includes spironolactone, a gonadotropin-releasing hormone agonist (GnRH-a) (particularly if pubertal suppression is desired), or in Europe, cyproterone acetate (CPA) (not currently approved for use by the U.S. Food and Drug Administration). While antiandrogen treatment is often discontinued if, and when, orchiectomy is performed or if individualized treatment success is obtained with estrogen-alone, E2 therapy is often lifelong.

In this review article we include more recent data examining the secondary health risks of estrogen therapy into a summary of known standards of care for feminizing GAHT.[4,6,7,9,10] Specifically, this article will illustrate what is known about the primary risks of venous thromboembolism, cardiovascular disease, hyperlipidemia, bone health, and cancer risk in the TGD

population, drawing at times from what is known in the cisgender population. Additionally, we aim to summarize how this data might impact a provider's choice of treatment and formulation. Lastly, the authors include relevant summary recommendations from the recently published WPATH SOC-8 where applicable.

2 | METHODS

This paper was designed as a narrative review with a focus on including the most recent literature from January 2019 through July 2022, as well as recommendations from WPATH SOC-8. Articles were collected from PubMed, Cochrane Library, EMBASE, and MEDLINE by searching article title and abstract for one of the primary terms "transgender," "transsexual," "gender incongruence," "transfeminine," "transgender female," "gender non-conforming," or "nonbinary," in combination with one of the terms "hormone therapy," "puberty blocker," "androgen blocker," "antiandrogens," "estrogen," "estradiol," and/or "spironolactone." Further studies that dated outside of this period were identified from previous literature reviews on GAHT in transgender women via cross-search of listed references. As a result, some studies regarding the effects of sex-hormones in the cisgender population were included. Exclusion criteria included: (1) non-English articles; (2) textbooks or editorial commentary; (3) articles in which full text was not available. Articles that focused on a population outside of transfeminine patients as well as in the pediatric/adolescent/teenage (<18-year-old) population were manually excluded, except where relevant data from the cisgender population helps to fill and inform gaps in TGD care knowledge. Some of the literature included in this review pertains to gender nonbinary or gender nonconforming people undergoing feminization therapy, however, due to limited literature discussing hormonal management in this population, treatment in this population is not specifically highlighted in this review. Additionally, topics pertaining to gender-affirming surgery and fertility preservation procedures were considered outside the scope of this article.

3 | GENDER-AFFIRMING Hormone THERAPY—OVERVIEW

Feminizing GAHT aids in the development of secondary feminine sex characteristics and suppresses secondary male sex characteristics. SOC-8 recommends that GAHT should be offered when gender incongruence is marked and sustained, and may be prescribed by primary care physicians, other nonspecialists, and even specialists who have received GAHT training so as to overcome concerns over access to GAHT and other barriers to care (Table 1).[4] This recommendation differs from previous WPATH Standards of Care versions which began with a diagnosis of gender dysphoria.[6] While there is limited evidence to determine the requisite length of persistence, assessment by a healthcare professional experienced in making this diagnosis while ruling out or stabilizing other mental health and psychosocial concerns that may impact treatment success and confirming that the TGD person has the capacity to consent for treatment should precede the initiation of GAHT.[4] A patient-centered informed decision-making model which values harm-reduction is advised. Pretreatment counseling should include a discussion of the impact of GAHT on fertility before GAHT initiation with referral to a specialist who provides fertility preservation treatments, if desired.

Most patients on feminizing GAHT will experience desired physical changes within the first 3–6 months, including chest/breast growth (to Tanner stage 2 or 3, or up to a "B-cup"), redistribution of body fat to the hips/waist, reduced muscle mass, and softening of the skin with less oiliness (Table 2).[6-8,13] Patients may notice a decrease in libido or erections sooner than this, within 1–3 months, owing to decreasing testosterone production, however it is important to note that lower sperm production and testicular volume size may trail this effect by an additional 3 months, and all of these effects could take up to 3 years to peak.[7,14] A complete restitution of semen production may not be achievable with cessation of GAHT.[15] Changes are seen most slowly in terminal

TABLE 1 Criteria for initiation of GAHT in adults

Criteria for Initiation of Gender-Affirming Hormone Therapy (GAHT) in TGD adults
Updated per WPATH Standards of Care, Version 8
1. Gender incongruence is marked and sustained
2. Meets diagnostic criteria for gender incongruence before gender-affirming hormone treatment in regions where a diagnosis is necessary to access healthcare
3. Demonstrates capacity to consent for the specific gender-affirming hormone treatment
4. Other possible causes of apparent gender incongruence have been identified and excluded
5. Mental health and physical conditions that could negatively impact the outcome of treatment have been assessed, with risks and benefits discussed
6. Understands the effect of gender-affirming hormone treatment on reproduction and they have explored reproductive options

TABLE 2 Anticipated onset of physical changes in response to feminizing GAHT (estrogen + testosterone-lowering agents)

Onset Effect (maximum time course)
1–3 months
Decreased spontaneous erections (3–6 months)
Decreased sexual desire (unknown)
3–6 months
Decrease in muscle mass and strength (1–2 years)
Redistribution of body fat (2–5 years)
Breast growth (2–5 years)
Decreased testicular volume (variable)
Softening of skin/decreased oiliness (unknown)
6–12 months
Decreased terminal hair growth (>3 years)
Variable
Increased scalp hair (variable)
Unknown
Decreased sperm production (2 years)
None
Voice changes

Abbreviation: GAHT, gender-affirming hormone therapy.

Source: Adapted from Hembree et al.[7]

TABLE 3 Hormone formulations for feminizing GAHT[a]

Estrogen	
Oral or sublingual	
Estradiol	2.0–6.0 mg/day
Transdermal	
Estradiol transdermal patch	0.025–0.2 mg/day
Estradiol gel various	daily to skin[b]
Parenteral	
Estradiol valerate or cypionate	5–30 mg IM every 2 weeks
	2–10 mg IM every week
Antiandrogen	
Spironolactone	100–300 mg/day
Cyproterone acetate	10 mg/day[c]
GnRH agonist	3.75–7.50 mg SQ/IM monthly
GnRH agonist depot formulation	11.25/22.5 mg SQ/IM every 3/6 months

Abbreviations: GAHT, gender-affirming hormone therapy; GnRH, gonadotropin-releasing hormone.

[a]Doses increased or decreased until sex steroid hormone levels are in therapeutic range (E2 = 100–200 pg/ml, T < 50 ng/dL).

[b]Amount applied varies to formulation and strength.

[c]Kuijpers et al.[18]

Source: Adapted from WPATH Standards of Care, Version 8 (Coleman et al.[4]).

hair growth, and treatment of hirsute or androgenic hair distribution typically requires frequent shaving, waxing, or more long-lasting treatments such as electrolysis or laser hair removal. When initiated after puberty, feminizing GAHT will not restore previously lost scalp hair, that is, "male-pattern baldness," or impede facial hair development where terminal hair growth will continue in the absence of androgen stimulation.[8,16] In addition, feminizing GAHT will not induce voice changes for which feminizing voice surgery and/or voice therapy from specially trained speech language pathologists must be pursued if desired. Physiologic pubertal changes can be distressing for gender incongruent peripubertal adolescents, and so while estrogen therapy is restricted from use until the age of 16 and after the completion of puberty, antiandrogen or puberty-blocking agents can be considered in this population once Tanner stage 2 is achieved.[4]

Feminizing GAHT for the postpubertal adolescent or adult patient typically begins with estrogen therapy coupled with antiandrogen therapy (Table 3). Medications that suppress the pituitary-gonadal axis in peripubertal pediatric and adolescent patients, or "puberty blockers," such as GnRH agonists, will be discussed, but protocols for their administration are outside the scope of this review. These treatments generally result in increased serum estrogen concentration, decreased serum testosterone concentration, increased breast growth, and changes in body composition. Estrogen therapy provides direct estrogen action coupled with suppression of the pituitary-gonadal reproductive axis with a resultant decrease in testosterone production in patients who retain the testes.[17] For patient who desire quicker-onset reduction of testosterone production, or who do not achieve satisfactory testosterone suppression from estrogen therapy alone, androgen-lowering agents such as spironolactone (a potassium-sparing diuretic which inhibits the androgen receptor), leuprolide (a GnRH-agonist which induces central suppression of the pituitary-gonadal axis), or CPA (not approved for use in the United States) can be prescribed before or in combination with estrogen therapy.

Following initiation of GAHT, hormone levels are monitored with the conventional therapeutic goal of achieving physiologic estrogen and testosterone levels in

TABLE 4 Risks associated with Estrogen-based GAHT regimens

Risk level Adverse event
Likely increased risk
Venous thromboembolism
Infertility
Hyperkalemia[a]
Hypertriglyceridemia
Weight gain
Likely increased risk with presence of additional risk factors
Cardiovascular disease
Cerebrovascular disease
Meningioma[b]
Polyuria/dehydration[a]
Cholelithiasis
Possible increased risk
Hypertension
Erectile dysfunction
Possible increased risk with presence of additional risk factors
Type 2 diabetes
Low bone mass/osteoporosis
Hyperprolactinemia
No increased risk or inconclusive
Breast cancer
Prostate cancer

[a]Spironolactone-based regimens.

[b]Cyproterone-based regimens.

Source: Adapted from WPATH Standards of Care, Version 8 (Coleman et al.[4]).

the cisfemale range,[13] although optimal target ranges have not been established.[7] The desired range of estradiol concentration is generally 100–200 pg/ml (cisfemale physiologic levels), and the desired range of testosterone concentration is less than 50 ng/dL.[7] Ongoing monitoring for potential long-term risks and adverse medical events is essential (Table 4).[7,19] Physicians treating transfeminine patients should bear in mind patient-specific goals for physiologic changes, as increases in estrogen dosage will not always correlate to specific sex-characteristic changes (e.g., higher physiologic estrogen levels do not correlate to larger breasts) and may only introduce unnecessary cardiovascular and thromboembolic risks. Patient-centered informed decision-making and counseling is paramount from the outset, which includes discussion of reasonable expectations, timeline of anticipated sex characteristic changes, and a clear discussion of the risks of feminizing GAHT with an emphasis on risk mitigation pursuant to the ethical principle of nonmaleficence.

3.1 | Estrogen therapy

Estrogen can be formulated for administration in the form of a "bio-identical" hormone *17β-estradiol* (or more commonly referred to as simply estradiol), conjugated equine estrogens (such as the brand Premarin), and the synthetic estrogen ethinyl estradiol. Ethinyl estradiol carries a notable pro-coagulant and thrombotic risk.[20–22] When used in the context of contraception, these risks are offset by the well-studied and desired improvement on menstrual cycle control[23]; however, in the context of gender-affirming treatment for transfeminine patients assigned male at birth, this benefit is not applicable, assumption of the thromboembolic risks is not warranted, and ethinyl estradiol is avoided. Similarly, conjugated equine estrogens can be difficult to monitor with conventional serologic laboratory testing, and given their association with increased thrombogenicity and cardiovascular risks and inherent challenges with therapeutic titration, are typically avoided in the context of feminizing GAHT.[24,25] As a result, "bio-identical" 17β-, or what will simply be termed estradiol in the remainder of this discussion, remains the formulation of choice.

Estradiol can be administered via oral or sublingual tablet, transdermal patch, transdermal gel/spray (although infrequently used and will not be reviewed here), or intramuscular injection (estradiol valerate or cypionate) (Table 3). In cisgender males, most E2 is produced in low levels through the aromatization of testosterone, and is involved in endothelial repair and regeneration, preservation of bone health, and increases in growth hormone secretion.[26,27] Oral estradiol (17β-estradiol, or E2) is subject to "first-pass metabolism" in the liver and intestines, becoming metabolized to estrone (E1) and estrogen conjugates.[28] Transdermal estradiol bypasses hepatic metabolism and is directly absorbed into the circulatory system. As a result, transdermal E2 produces lower ratios of circulating E1:E2 (1:1) than oral E2 (5:1), and offers more consistent levels of E2 with less estrogen metabolites[29] and favorable cardio-metabolic side effects, particularly in patients over the age of 40.[30] Dosages for oral E2 are initiated at 1–2 mg/day and can be adjusted up to 2–6 mg/day. Transdermal estradiol begins at 0.025–0.05 mg/day with a new patch placed every 3–5 days and can be adjusted to 0.1–0.2 mg/day.[7,16] Transdermal 17β-estradiol gel dosing begins at 1.5 mg/day.[4]

The comparative effectiveness of parenteral (intramuscular injection) estradiol valerate versus estradiol cypionate have not been thoroughly examined in the TGD population, however data from contraceptive literature suggests that cypionate may yield a lower peak estradiol level with a longer duration to peak level (4 vs. 2 days) and longer total estrogen elevation (11 vs. 7–8 days).[31] Any intramuscular administration of E2 raises serum E2 levels to some degree for about 2 weeks. At its peak, E2 serum levels are six-fold greater when administered intramuscularly than the E2 serum concentration of cisgender women.[32] Thus, while estradiol valerate may have more predictable and desired pharmacokinetics for the purposes of contraception, the relative desirability of either, or the efficacy of weekly versus bi-weekly dosing, for the purposes of GAHT remains undetermined. Conventional dosages of parenteral estradiol valerate begin at 5 mg every 2 weeks and are adjusted up to 10–30 mg every 2 weeks; estradiol cypionate begins at 2 mg weekly with titration up to 10 mg weekly. Prescriber's comfort level with, availability of, or patient preference for either formulation are reasonable considerations in the initial choice of parenteral formulation, and either formulation can be administered bi-weekly (e.g., for cost-reduction) or weekly (for reduction of cyclic symptoms). If significant cyclic symptoms persist despite an adjustment of the dosing interval, peak-trough estradiol levels may be assessed and if wide fluctuations exist, consideration should be given to changing to an oral or transdermal preparation.[33] Prescribers should consider the potential impact of peak-trough levels in weekly versus bi-weekly injections, balancing bi-weekly dosing's risks of higher peak levels and lower trough levels and their associated impact on the patient's mental health with the drawbacks of lower-dose weekly injections, which some patients may perceive to be less therapeutic. Injectable estradiol remains a popular choice in the United States but is not available in most European countries.

All estrogen formulations will suppress androgen production through central pituitary-gonadal suppression while inducing feminizing effects and preserving bone health.[16] In general, however, the time course of these feminizing effects is largely based on clinical observation[7,34–36] with sparse literature comparing specific formulations or a more exact time course for effect. Breast development in transgender women is the most well-described, with a peak effect at around 2 years after initiation of therapy.[37] Individual physical responses to a variety of formulations and dosages makes investigation of specific effects challenging. The comparative effectiveness of oral and transdermal estrogen-based therapies in secondary female development have been debated. A 2021 prospective study found that transdermal estrogen therapy resulted in faster increase in breast development after 6 months; however, breast growth after 1 year was similar between oral and transdermal estrogen-based therapies.[38] Transgender women undergoing estrogen therapy have been shown to progress to Tanner stage 3 after 1 year and Tanner stage 4 after 3–4 years.[39] While standard practice commonly allows for chest augmentation in adult patients after completion of at least 12 months of GAHT, and some pursue it in as little as 6 months,[6,40] many experts advocate for delaying chest augmentation surgery until 2 years of completed estrogen therapy as some patients will continue to see growth in breast tissue after the first 12 months of GAHT.[7,8,37,41] Ultimately, 60% of patients will pursue chest augmentation surgery, with high rates in self-medicated individuals and individuals taking spironolactone.[40,42] In addition to estrogen formulation, factors including age, serum E2 levels, BMI, and tobacco use do not appear to correlate to development of breast tissue.[42]

A 2020 systematic review found that feminizing GAHT consistently produces an increase in total body fat mass and more peripheral fat distribution while decreasing lean body mass and muscle strength (although still higher than cisgender women), and suggests these effects may correlate to worsened insulin resistance although data on insulin resistance is limited and inconsistent.[43] These effects are more difficult to control through diet and exercise, but the effects of obesity and insulin resistance on overall health should be monitored carefully.

3.2 | Antiandrogens

Antiandrogen therapies aim to reduce overall testosterone levels or their effects and to suppress secondary male characteristics. This class of treatment includes spironolactone (most used in the United States), GnRH-agonists (GnRH-a) (most used in the United Kingdom), and CPA (most used in Europe).[18,44] GnRH-a are most frequently used for the halting of pubertal changes in peri-pubertal patients. Many of the masculinizing and anabolic effects of testosterone are difficult or impossible to reverse even with complete androgen suppression, including terminal hair growth, development of muscle mass, and the growth of the male reproductive tract; however, antiandrogen therapy can augment the effect of estrogen therapy in the reduction of body hair growth, prostate size, and testicular volume[13] more quickly than estrogen therapy alone. GnRH-a and CPA appear to be more effective than spironolactone at suppressing total serum testosterone levels,[45] likely due to their more

central effect on hypothalamic-pituitary-gonadal suppression. Individuals who desire only suppressed androgen levels, such as peri-pubertal adolescents or any individual who wants to experience reduced testosterone levels before deciding to initiate estrogen therapy, or those with strong contra-indications to estrogen therapy, may choose to receive treatment with antiandrogen therapy alone. Hot flashes and low mood and energy are common side effects in this treatment group in the absence of estrogen therapy.[33] However, there are no studies yet published examining the efficacy and safety of antiandrogens or E2 alone or in combination.[10,44,46] A systematic review did not find that any one of these testosterone-lowering medications has a preferred overall safety profile.[47]

While antiandrogens are effective at suppressing secondary male characteristics, they do not revert them. Therefore, the patient may continue to have a deepened voice or course hair growth, and many patients will pursue vocal training, voice feminization surgery, or cosmetic hair removal.[3] Antiandrogen treatments will inhibit spermatogenesis.[48–50] Within a few months of antiandrogen therapy, patients are expected to observe testicular atrophy and azoospermia.[51] Several studies have found that discontinuation of antiandrogen or GnRH-a therapy will result in resumption of spermatogenesis in about 3 months,[52–55] but data are limited and sperm quality may also be impacted by life-style specific factors such as infrequent masturbation and packing genitals tight against the body.[56–59] After 2–3 years of treatment, fertility is considered almost irreversible.[60,61] If orchiectomy is pursued, antiandrogen therapy is typically discontinued.

3.2.1 | Spironolactone

Spironolactone is an orally administered nonselective mineralocorticoid receptor and androgen receptor antagonist used primarily in the United States. Its blockade of aldosterone-mediated action in the distal renal tubules and collecting ducts results in decreased sodium reabsorption and water retention and decreased potassium excretion. As an antihypertensive and potassium-sparing diuretic, it may lead to hyperkalemia, increased urinary frequency, and a reduction in blood pressure. Additionally, it blocks the binding of dihydrotestosterone to androgen receptors and decreases testosterone production through the inhibition of 17α-hydroxylase and 17–20 lyase.[45] The end effect is a reduction in sebum production and hirsutism which aids in the treatment of acne vulgaris and unwanted hair growth in both transgender and cisgender women.[45,62,63] It is worth noting that spironolactone also weakly interacts with progesterone and estrogen receptors[41,64,65] and may lead to premature breast bud fusion. Thus, while these androgenic masculine characteristics are highly distressing to patients, and many choose immediate initiation of spironolactone antiandrogen therapy, some authors advocate for an alternative approach in those prioritizing breast growth with a delayed initiation of spironolactone until estrogen is titrated to near-therapeutic levels. Overall, though, data on the optimal timing of initiation of spironolactone in the context of feminizing GAHT remains limited.[11]

The dosage of spironolactone ranges from 100–300 mg/day,[4,7] typically with an initial divided dose of 50 mg twice daily, or as low as 25 mg once daily for those who develop orthostasis or polyuria, or who desire a slower titration. Doses should not exceed 400 mg/day total (200 mg twice daily). For patients who cannot tolerate or who have contraindications to the use of spironolactone, desire only partial feminization, are concerned about already-present "male-pattern baldness" or have yet to reverse virilization even after androgen blockade or orchiectomy, a trial of a 5-α reductase inhibitor such as finasteride 1 mg daily or dutasteride 0.5 mg daily can be attempted. However, due to their mechanism of action in inhibiting the conversion of testosterone to dihydrotestosterone via inhibition of the 5-α reductase type 2 and 3 enzymes, they have a more modest antiandrogenic effect.[33,66,67] Moreover, data on the use of 5-α reductase inhibitors in the transfeminine population is very limited,[68] and their routine use in this population is not recommended.[4]

3.2.2 | CPA

In general, spironolactone is considered a weaker androgen receptor antagonist than CPA, a synthetic progestogen with strong androgen-receptor antagonist and gonadotropin suppression activity.[44] CPA is preferred in Europe and is administered orally. CPA dosage historically had begun at a recommended 25 mg/day.[69] Recent studies show that CPA dose of 10 mg might be as effective as 25 mg/day, with less adverse side effects of depression and hyperprolactinemia.[18,70] For these reasons, SOC-8 recommends the lower starting dose of 10 mg/day.[4] A randomized control trial from 2017 compared the effectiveness of CPA and spironolactone over the course of 12 weeks. The CPA group had a more significant decrease in testosterone serum level. Additionally, at the completion of the 12 weeks, 90% of the patients in the CPA group achieved cisgender female range testosterone (<50 ng/dL) whereas only 19% of

patients in the spironolactone group achieved female range testosterone.[71] However, due to its associated risks of rare but significant cases of meningiomas, hyperprolactinemia, and fulminant hepatitis,[16,72] it is not FDA-approved for use for GAHT in the United States, particularly where spironolactone, which bears less risk of hyperprolactinemia[47,73] and severe side effects, is readily available. CPA may have quicker impact in reducing serum testosterone levels; however, the risks associated with CPA as compared to spironolactone still must be further studied.

3.2.3 | GnRH-a

GnRH-agonists induce central suppression of the pituitary-gonadal axis via stimulation and downregulation of the gonadotropin-releasing hormone receptor, thereby inhibiting the release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary without impacting adrenal androgen function.[74] GnRH-agonists are first-line treatment for puberty-blockade in gender-transitioning peri-pubertal adolescent patients who desire puberty delay following the onset of the first physical changes of puberty (Tanner stage 2).[4] They may also be used as a second-line agent for testosterone suppression in adults with inadequate androgen suppression from estrogen and/or spironolactone alone who retain testes after ruling out other causes of excess testosterone (e.g., testicular neoplasms, androgen-secreting tumors, and exogenous undisclosed testosterone use).[75–77] The two main types of GnRH-agonists used in the United States are leuprolide acetate and goserelin acetate. Both GnRH-agonists are administered parenterally (typically intramuscularly, although subcutaneous use has been described but is less well-studied). The use of implantable (e.g., goserelin) and nasal spray (e.g., naferelin) GnRH-agonists have not been sufficiently characterized in these populations for routine use.

The recommended dosage for leuprolide acetate is 3.75 mg/month or 11.25 mg/3 months.[7] The recommended dosage for goserelin acetate is 3.6 mg/month.[7] No significant difference was found between CPA and GnRH-agonist therapies in changes in body composition.[78] It is important to note that GnRH-a treatment is generally costly when insurance coverage cannot be obtained, limiting its long-term efficacy. In addition, administration of GnRH-a in early puberty may lead to underdevelopment of the penis (compromising future vaginoplasty), underdeveloped testes, and decreased semen production, particularly with long-term use. Due to these risks and frequent uncertainty about patient-desired future fertility or gender-affirming surgery, initiation of puberty-blockade should await Tanner stage 2–3, with introduction of GAHT and discussion of GnRH-a discontinuation at about age 16.[8] However, some transfeminine patients will choose to continue GnRH-a therapy into early adulthood to reduce the amount of estrogen required to receive therapeutic feminizing effects and decrease the risks associated with estrogen therapy, or until gonadectomy is performed if desired. This must be balanced against the risks of osteopenia/osteoporosis caused by slower bone mineralization at a prepubertal rate and resultant decreased peak bone mineral density.

3.2.4 | Progesterone

The use of progestins in feminizing GAHT may offer some anecdotal improvement in breast and/or areolar development, mood, or libido,[11,12] although the effects may be variable due to the combined mechanism of central gonadotropin blockade with direct androgenizing effects. Adverse effects of progestins can include weight gain, depression, and lipid changes. In cisgender females, progesterone stimulation of breast development and alveologenesis and ductal side branching has been described[79]; however GAHT protocols which include progesterone medications have not been shown to decrease requests for chest augmentation surgery compared to protocols without.[11] Micronized bioidentical preparations (e.g., Prometrium) and synthetic formulations (e.g., Provera) are used most commonly. Protocols for the use of progestins in the context of feminizing GAHT have not been extensively studied, however there has also been no demonstrated significant increase in risks, particularly as pertains to cardiovascular disease or breast cancer. Risks demonstrated in the Women's Health Initiative are not directly generalizable to the younger transgender population.[80] In addition, conjugated equine estrogens used in the Women's Health Initiative study are not used in feminizing GAHT protocols. Overall, no strong recommendations exist surrounding the use of progestins for feminizing GAHT, but in general there is insufficient evidence to support a beneficial use of progesterone that outweighs potential risks.[81]

4 | RISK CONSIDERATIONS—CARDIOVASCULAR DISEASE (CVD), VENOUS THROMBOEMBOLISM (VTE), BONE HEALTH, CANCER

4.1 | Overview

Ongoing monitoring for long-term risks and adverse events associated with feminizing GAHT is an essential component of comprehensive gender-affirming care. The

major categories of risk which have been studied include cardiovascular health, venous thrombus embolism, bone health, and cancer (Table 4).

4.1.1 | Cardiovascular disease

The use of estrogen therapy for gender affirming hormone treatment has been closely examined for potential negative impacts on cardiovascular health and VTE risk. While some epidemiologic data suggest that GAHT, particularly estrogen therapy, may lead to increased risk of myocardial infarctions (MI) and thromboembolic events, the research is limited by the absence of large cohort studies, lack of appropriate control populations, and inadequate data acquisition from gender identity services.[82] National health survey data collected by the Center for Disease Control and Prevention showed that transgender women were more than two times more likely to have MIs compared to cisgender women (odds ratio, 2.56; 95% CI, 1.78–3.68) but not compared to cisgender men (odds ratio 1.32; 95% CI, 0.92–1.90) after adjusting for age, diabetes mellitus, chronic kidney disease, smoking status, hypertension, hypercholesterolemia, and exercise.[83]

A large cohort retrospective self-reported observational study from 2014 to 2017 compared the incidence of prior stroke and MI between transgender women and cisgender groups. Transgender women were more likely to have had a stroke (adjusted odds ratio, 1.88, 95% CI 1.16–3.03), MI (2.98, 2.14–4.17), or "any cardiovascular disease (CVD)" (2.24, 1.65–3.06) compared to cisgender women. When compared to cisgender men, only "any CVD" was significantly higher in transgender women (adjusted OR 1.38, 95% CI 1.01–1.88) after adjusting for health behaviors (tobacco use, alcohol consumption, exercise), metabolic risk factors (obesity, diabetes, and others), and sociodemographic factors (race, ethnicity, income, education, self-rated health, state of residence, and others).[84] Transgender women reported less exercise compared to cisgender men and were more likely to be overweight and have diabetes compared to cisgender women.

A 2017 systematic review and meta-analysis found that serum triglyceride levels were significantly higher at ≥24 months (31.9 mg/dL; 95% CI, 3.9–59.9) with no significant differences in serum LDL-C, HDL-C, and total cholesterol[85] in transgender females on estrogen therapy. Few incidents of myocardial infarction, stroke, VTE, and deaths were reported, which may be attributable to a lack of reported outcomes from many eligible studies, and lack of long-term study follow-up as cardiovascular events typically occur years later in cisgender women as compared to men.[86] The age of initiation and duration feminizing GAHT may be important albeit minimally modifiable risk factors for cardiovascular disease. Hypertension, obesity, diabetes mellitus, cholesterol and lipid abnormalities, and smoking status are important and modifiable risk factors with treatments and interventions available. Being transgender is also associated with increased social stressors, poorer socioeconomic status, substance use, and other health disparities.[21,87,88] Prior studies have been limited by small sample sizes, and long-term controlled studies are lacking. Taken together, this data suggests that GAHT may worsen the risks of MI, stroke, or any CVD compared to cisgender women or men, but the statistical significance, magnitude of impact, and direct correlation to estrogen therapy versus being transgender with other risk factors remains unclear. Cardiovascular risk calculators recommended by the American College of Cardiology/American Heart Association use sex-specific risks to guide interventions, but for transgender individuals it is not clear whether the sex assigned at birth, affirmed gender, or age of initiation or duration of GAHT should guide the determination of risk scoring.[89] Regardless, an emphasis should be placed on the modification of cardiovascular risk factors and consideration of transdermal estrogen which may mitigate lipid abnormalities and hypercoagulability in high-risk individuals.

4.1.2 | Venous thromboembolic events

The risk of thromboembolic events seems to be higher following treatment with estrogen based GAHT. Type of estrogen therapy and route of administration play a role in thromboembolic events. There are limited randomized control trials studying the role of estrogen based GAHT in VTE risk in transgender women alone; however, most studies indicate that estrogen therapies increase VTE risk in transgender and cisgender women. In cisgender women, combined oral contraceptives increased VTE risk by two to four-fold.[90] A 2021 meta-analysis compared VTE risk of transgender women taking GAHT and cisgender women on hormone replacement therapies. The incidence of VTE was higher in patients assigned male at birth on GAHT compared to those assigned female at birth not on GAHT (i.e., cisgender women) (42.8 vs. 10.8 VTE per 10 000 patient-years; $p = 0.02$).[91] The rate of VTE incidences in patients on feminizing GAHT appeared similar or higher than the rate demonstrated in cisgender women on hormone replacement therapy, which VTE incidences in cisgender women comparable to published rates in cisgender males on hormone replacement therapy. A 2018 prospective cohort study followed 2842 transfeminine individuals and found that transfeminine individuals had a higher incidence of VTE, with a 2- and 8-year risk difference of 4.1 (95%, CI 1.6–6.7) and 16.7 (95% CI, 6.4–27.5), respectively, relative to

cisgender women; however, the study was somewhat limited by an inability to determine whether any patients received hormone therapy outside the health system.[92] Overall, though, since VTE risk in cisgender women taking hormone replacement therapy is high, and VTE risk may be higher in transgender women on GAHT as compared to cisgender women, estrogen GAHT is likely associated with an increased VTE risk in transgender women. Postmenopausal cisgender women on hormone replacement therapy or cisgender women on oral contraceptives remain difficult comparators, as the risk factors between these groups and transgender women differ and the thrombogenic risks of ethinyl-estradiol and 17β-estradiol are different.

The route of estrogen treatment (oral vs. transdermal) has shown to have altering risks for VTE and serum triglyceride levels. Studies in postmenopausal cisgender women support that transdermal estrogen therapies are not associated with significant VTE risk.[93,94] Additionally, transdermal estrogen-based therapy was shown to decrease serum triglyceride levels while oral estrogen-based treatment significantly increased triglyceride levels.[85] This difference is attributed to avoidance of first-pass hepatic metabolism by transdermal hormone therapy. Another meta-analysis review also supports the conclusion that transdermal formulations are the least thrombogenic.[95]

Overall, the route of estrogen therapy administration has been shown to impact the CVD and VTE risks associated with estrogen therapy in transgender women. Oral estrogen treatment has been shown to increase cardiovascular risk compared to transdermal estrogen-based therapy. While oral estrogen-based therapy has been shown to increase serum triglyceride levels in transgender women, transdermal estrogen-based therapy has been shown to decrease serum triglyceride levels.[85] For patients at high risk for VTE or CVD, consideration should be given to opting for transdermal rather than oral estrogen GAHT, however insufficient evidence exists to provide definitive guidance, and routine VTE prophylaxis with aspirin or routine screening for prothrombotic mutations in the absence of other risk factors is not recommended.[33] SOC-8 levels a recommendation for using transdermal preparations for older transgender women (age >45 years) or those with a previous history of VTE[4] based on studies demonstrating a decreasing incidence of VTE in transgender women transitioned to transdermal estrogen after the age of 40 or 45.[96–98] Madeline Deutsch, MD, at the University of California San Francisco Gender Affirming Health Program has described a useful approach to the management of estrogen GAHT in patients with a personal or family history of VTE.[33]

4.1.3 | Bone health

Overall, the impact of GAHT on bone health for transgender women appears to be minimal or inconclusive, which may be partly due to short observation periods within studies on this topic.[99] One area which demonstrates a change in bone mineral density across studies is the lumbar spine, which shows a slight increase in bone density after 12 and 24 months of GAHT compared with baseline values.[85,100] Regarding estrogen therapy in particular, transgender women can lose lean body mass in association with testosterone deprivation, which may also lead to a lower bone size[101] and lower bone mass[100]—however this may also be related to lower levels of physical activity.[100,101] Additionally, GAHT appears to be a protective factor for bone density following gonadectomy, as transgender women who do not start or continue GAHT following gonadectomy are most at risk of bone loss.[102] One clinical concern related to bone health and GAHT has been the possibility of increased fracture incidence; however, transgender women have comparable rates of fracture to age-matched reference cisgender men and women.[103]

Although absolute bone mineral density does not appear to change over time in young transgender females on GnRH-a monotherapy, bone mineral density is reduced compared to peers.[104] Similarly, antiandrogenic CPA limits normal bone expansion and reduces pubertal bone mass accrual in young transgender females.[105] However, it is unclear if these effects have a longitudinal clinical impact.[102,104] The influence of obesity on bone density among transgender women is also an area which requires further study, as research thus far has been limited.[100]

4.1.4 | Body composition

Overall, feminizing GAHT is associated with an increase in fat mass and a decrease in lean body mass for transgender women.[99] The pattern of fat distribution also becomes increasingly gynoid, leading to a lower waist-to-hip ratio.[106] Although further research is warranted on the clinical impact of this change, it is possible that it might have health benefits, as a lower waist-to-hip ratio is correlated with a lower risk of myocardial infarction in cisgender women and men.[107] However, the increase in fat mass is still a concern in that an elevated BMI can exclude transgender women from gender-affirming surgeries.[108] Additionally, there is a possibility that the increasing fat mass associated with GAHT is linked to increased insulin resistance, although long-term research on this topic is insufficient.[43] Multiple studies have also demonstrated a decrease in muscle strength and muscle

cross-sectional area in transgender women after 12–36 months of GAHT, as well as a decrease in hemoglobin levels after 3–4 months of GAHT.[109]

4.1.5 | Cancer risks

The potential relationship between GAHT and breast cancer risk in transgender women is unclear, in part due to small sample sizes and low overall rates of breast cancer incidence in existing studies.[110] The theoretical concern that GAHT may increase breast cancer risk stems from a study of cisgender women which found a link between short-term estrogen plus progesterone use and increased breast cancer incidence.[111]

One study found that breast cancer incidence in transgender women who have received GAHT appears comparable to incidence among cisgender men, although the number of patients and duration of GAHT in that study were limited.[29] A study from the Netherlands found that transgender women receiving GAHT had a higher incidence of invasive breast cancer than cisgender men, but a lower incidence than cisgender women.[112] This study also found that most of the tumors were of ductal origin and were estrogen- and progesterone-receptor positive.[112] Another study analyzing 10 case reports found that when breast cancer does occur in transgender women, it generally occurs at a younger age and is more frequently estrogen-receptor negative than in cisgender men with breast cancer.[113] Overall, although the incidence of breast cancer in transgender women is less than in cisgender women, it is still recommended to follow the standard breast cancer screening guidelines for cisgender women for transgender women undergoing GAHT.[114]

Documented cases of prostate cancer have been reported in transgender females with various hormonal and surgical histories.[115–117] Antiandrogen treatment in transgender women is associated with a lower incidence of prostate cancer than in cisgender men.[118] Prostate cancer rarely occurs before the age of 40, and removal of the gonads in addition to estrogen and/or antiandrogen therapy likely further reduces this risk.[119–122]

4.2 | Peri-operative hormone management

For patients planning to undergo feminizing gender-affirming surgery, including augmentation mammoplasty, orchiectomy, and vaginoplasty, cessation of hormone therapy is commonly recommended from 1 to 4 or 2 to 6 weeks preoperatively and until patients are fully ambulatory (e.g., 2 to 3 weeks) postoperatively to mitigate the risk of VTE associated with exogenous estrogen therapy. However, there is limited evidence to support this practice.[8,123] In contrast, several studies have found no increase in the rate of VTE among transgender individuals continued on sex steroid treatment compared to those for whom it was discontinued perioperatively.[8,124-126] Guidance regarding the use of the ASCVD ACC/AHA Risk Estimator and the Caprini Risk-Assessment Module for the stratification of cardiovascular and thromboembolic disease is unclear regarding how to incorporate affirmed gender and type and duration of GAHT. Various authors have suggested different approaches, including calculating the greatest risk based on all possible available factors, or using an average. Accordingly, professional guidance is lacking regarding the risks and benefits of discontinuation of gender-affirming or menopausal hormone therapy in the perioperative period. The American College of Obstetrics and Gynecology (ACOG) notes a lack of trials demonstrating a reduction in postsurgical VTE with preoperative discontinuation of hormone therapy in their recommendation against routine discontinuation of HRT preoperatively for cisgender women.[127] The American Association of Plastic Surgeons (AAPS) recommendations rely on the Caprini Risk-Assessment Module.[128,129] Rates of venous thromboembolism in transgender women undergoing vaginoplasty may be less than 1%.[124,130-133] Yet, while chemoprophylaxis such as heparin use postoperatively carries a significant venous thromboembolic risk reduction, increased rates of hematoma formation requiring reoperation have been noted following plastic surgery.[128] The absence of clear increased VTE or CVD risks for patients remaining on estrogen GAHT must be balanced against the emotional and psychological consequences of GAHT cessation and abrupt changes in hormone levels including postoperative depression. One study found that 35% of transgender women who discontinue GAHT before gender-affirming procedures reported a "difficult" experience with symptoms of hot flashes (20%), mood swings, irritability (20%), and increases in facial and body hair (6%).[134] Some authors suggest that perioperative deep vein thrombosis prophylaxis, including early ambulation and mechanical and/or chemoprophylaxis are likely sufficient without the discontinuation of estrogen GAHT. Nicotine and tobacco cessation should be advised before and after surgery. Using a lower dose of estrogen and/or changing to a transdermal estrogen route if not already in use have also been suggested.[135] Continuation of sex steroid treatment after gonadectomy can mitigate the sequelae of hypogonadism, the risk of developing osteoporosis, and the maintenance of mental health and quality of life.[136,137] Antiandrogen therapy

can be safely discontinued after orchiectomy. One review suggests that an emphasis ought to be placed on informed consent discussion, shared decision-making, and an acknowledgment of the patient experience while addressing modifiable risks factors such as obesity, hypertension, and diabetes mellitus as an alternative approach to routine preoperative discontinuation of feminizing GAHT.[123]

5 | MONITORING

Throughout the duration of GAHT, which may include a person's entire lifetime after initiation, the focus of treatment should be aimed at minimizing the risk of adverse health events while striving to achieve a person's individual goals for sex-characteristic changes and maintaining physiological estradiol levels in the cisfemale range.[6–8] Clinicians should first confirm the diagnosis of gender dysphoria/gender incongruence before beginning treatment. Additional criteria for the initiation of GAHT in adults include the person's capacity to make fully informed decisions and consent for treatment, the person has reached the age of consent in a given country or state, and mental health diagnoses should be addressed and reasonably well controlled insofar as they may impact treatment success.[6–8] A care plan including pretreatment assessment and education, including evaluation of other comorbidities, should be established. In addition, a referral to an appropriate specialist for fertility preservation consultation should be discussed, recommended, and facilitated before the initiation of GAHT, although patients reserve the right to decline. Once GAHT is initiated, monitoring should include individualized dosing, routine laboratory screening, and standard breast and prostate screening.[7–9]

No standardized clinical criteria exist for the monitoring of changes in body fat distribution, increased chest/breast growth, decreased muscle mass, decreased oiliness and softening of the skin, decreased erections/libido or variable changes in sexual function, or hair thinning in this population. Such changes are individually assessed, and patient satisfaction is self-reported. These changes typically occur in the first 3 to 12 months of estrogen and antiandrogen therapy, although breast growth may take up to 2 to 5 years to maximize.[34,35,37,96,101,138] Practice guidelines recommend that clinicians measure serum testosterone and E2 levels every 3 months for the first year or until these levels are at goal, followed by repeat measurements one to two times per year.[7,8,13,139] Laboratories assessing E2 levels should participate in external quality control.[140] E2 levels should be kept within the normal cisfemale physiologic range of 100–200 pg/ml, and testosterone levels should be suppressed to <50 ng/dL. Supraphysiologic E2 levels should be avoided, as these levels may increase the risk for thromboembolic disease, liver dysfunction, and hypertension.[7] Given spironolactone's mechanism of action as a potassium-sparing diuretic, serum electrolytes, particularly potassium, should be monitored at the same interval, but may be spaced to annually once the dosing is stable. E2 levels are typically assessed half-way between E2 dosing intervals (e.g., mid-week for weekly doses or on the noninjection day for bi-weekly doses) for those on injectable E2, although it should be noted there are no universal recommendations on the optimal timing of E2 assessment.[141] If transdermal estrogen is used, contamination of the blood sample should be avoided.[10] Prolactin levels may be monitored less frequently, but at least annually while E2 dosing is being adjusted and at least every 2 years thereafter. E2 therapy can increase the growth of pituitary lactotroph cells, and both prolactinomas and elevated prolactin levels have been reported in up to 20% of individuals on long-term, high-dose estrogen therapy,[142-146] although a more recent retrospective study did not found an estrogen-related dose response.[73] Nonetheless, hyperprolactinemia will typically reverse with a reduction or discontinuation of estrogen therapy[147-149] or after gonadectomy.[148] Microdosing hormones, or low-dose GAHT, is becoming increasingly more popular among nonbinary-identifying individuals who desire more subtle changes in sex-characteristics, or in transgender individuals who wish to minimize E2-related health risks at the accepted expense of more subtle changes; however, no validated dosing guidelines have yet been established for this purpose.

As in cisgendered individuals, routine cancer surveillance should be employed for all tissues still present, particularly breast and prostate cancer screening. While data on breast cancer incidence in the transgender female population is limited, very few cases of breast cancer have been reported[21,114,151–153]; as such, screening for those with no increased risk of breast cancer should follow breast-screening guidelines recommended for cis-females. However, it should be noted that transgender females have been shown to have a higher incidence of dense breasts, which increases the risks of both breast cancer and false negative mammograms.[29]

It is recommended that prostate cancer screening begin at age 50, in line with U.S. Preventative Services Task Force recommendations.[154] If a prostate exam is indicated, both rectal and digital neovaginal approaches, if applicable, should be considered for those who have undergone vaginoplasty, as the prostate lies anterior to the neovaginal wall. If prostate-specific antigen (PSA) testing is performed, reducing the upper limit of normal

to 1.0 ng/mL should be considered as antiandrogen therapy and gonadectomy will lower testosterone levels and decrease PSA results.[120–122]

Bone mineral density (BMD) screening should be considered at treatment initiation and is recommended again by age 65 or sooner if other risk factors exist, including nonadherence to treatment or absence of GAHT utilization for at least 5 years following gonadectomy.[7] Long-term studies of agonadal individuals not using hormone replacement are lacking, and it is unclear if sex assigned at birth or affirmed gender should be considered when utilizing the FRAX® risk assessment tool.

Evidence regarding testicular cancer incidence and screening is lacking. It is theorized that androgen suppression decreases the risk of testicular cancer, and in fact only one case of testicular cancer in a transgender female has been reported.[75] Accordingly, routine testicular cancer screening is not recommended in transgender women.

6 | CONCLUSIONS

Feminizing GAHT is an effective medical intervention with a profound clinical impact, providing reliable improvements in mental, physical, and sexual well-being for transgender women who chose to undergo hormonal affirmation. WPATH, the Endocrine Society, and the University of California San Francisco Center of Excellence for Transgender Health provide sound guidelines for the safe prescribing and monitoring of feminizing GAHT. When initiating GAHT, clinicians must ensure that the patient is emotionally and physically prepared to undergo hormonal transition, including a social support system and reasonable control of psychological and medical comorbidities, although SOC-8 suggests consideration of improvements in mental health comorbidities that may be dependent on GAHT. An important component of the informed-consent process includes helping patients understand their individual risks pertaining to cardiovascular disease, thromboembolic disease, bone health, and cancer risks, all of which may evolve over the lifespan of a patient's treatment. Knowledge of these risks is largely drawn from research in the cisgender population, with a growing body of literature in TGD-specific patient populations. In addition, a patient's individual risk profile may impact recommendations regarding continuation or discontinuation of GAHT around the time of surgery, and professional guidelines in this regard may change as evidence emergences regarding these risks in trans-specific patient populations as well as in the aging transgender population. What remains certain is that more research is needed to better understand the incidence of medical risks in transgender-specific study populations and the evolution thereof in an aging transfeminine patient population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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