Endotext

MEDICAL INTERVENTIONS FOR TRANSGENDER YOUTH

Natalie J. Nokoff, MD, MSCS, Division of Endocrinology, Department of Pediatrics, University of Colorado Anschutz Medical Campus. Natalie.Nokoff@childrenscolorado.org

Received January 17, 2022

ABSTRACT

Up to 1.8% of youth and 0.6% of adults in the United States identify as transgender, meaning their gender identity differs from or is opposite their sex designated at birth. This chapter provides an overview including epidemiology and gender development. Then, it aims to summarize medical interventions for transgender youth as outlined in the Endocrine Society Clinical Practice Guidelines and World Professional Association for Transgender Health standards of care. The chapter concludes with research on mental health in this population and future directions.

INTRODUCTION

Throughout history and across cultures there have been people who live with, what we would now term, gender incongruence (definitions in Table 1). Prior to identification of sex steroids in the 1930s (1-5), and the development of exogenous sex steroids and surgical techniques, there were no options to change one's secondary sex characteristics. The first modern orchiectomy for gender reassignment was performed in 1930 (6), and the first feminizing genital surgeries in the 1940s and 50s in Germany and Denmark, respectively (7,8). Harry Benjamin, known for his 1966 book, The Transsexual Phenomenon__(9), treated Christine Jorgensen, the first widely published case of a transgender female in the United States (U.S.), treated with feminizing hormones and surgery. In 1979, the Harry Benjamin International Gender Dysphoria Association was formed, now the World Professional Association for Transgender Health (WPATH). The first standards of care were published in 1979, with the 7th edition released in 2012, and the 8th edition coming soon. The Endocrine Society first published a clinical practice guideline regarding the care of transgender persons, including support for pubertal suppression and gender affirming hormone therapy (GAHT) in 2009, with an updated guideline released in 2017 (10,11). In the over 40 years since the first edition of the WPATH Standards of Care, transgender rights, access to care, bathroom use, and sports participation, among other topics, are often featured and debated in mainstream media, politics, and healthcare (12). Furthermore, as care becomes increasingly politicized, numerous bills to both expand or limit the rights of transgender people and their access to medical care are being introduced in the U.S.(13). Medical care that respects the gender identity of the patient is recommended by numerous medical organizations, including the American Academy of Pediatrics (14), Endocrine Society (11), and the American Psychological Association (15).

Table 1. Definitions	
Agender	A person with very little or no connection to the traditional systems of gender; existing without gender
Cisgender	Gender identity aligns with biologic sex
Gender affirming hormone therapy	Hormones, including testosterone and /or estradiol, that are prescribed to eligible individuals to induce development of secondary sex characteristics that align with gender identity
Gender affirming surgery (sometimes referred to as gender-confirming or gender-reassignment surgery)	Surgery or surgeries to align one's body with one's gender identity
Gender diverse	Individuals with a variety of gender identities across the gender spectrum, including those who identify as transgender
Gender dysphoria	Distress experienced when gender identity and body are not congruent. Defined in the DSM-5, which replaced "gender identity disorder" in the DSM-IV
Gender expression	External manifestations of gender, expressed through name, pronouns, clothing, haircut, behavior, voice, or other characteristics
Gender identity/experienced gender	One's internal, deeply held sense of gender; not visible to others
Gender incongruence	Umbrella term used when gender identity and/or expression differ from what is typically/societally associated with their sex designated at birth
Gender role	Behaviors, attitudes, and personality trait that a society (in a given culture and historical period) designates as masculine or feminine and/or that society associates with the typical social role of men or women
Non-binary	A person whose gender identity is neither male nor female, both male and female or some combination of genders
Sex designated at birth	Sex at birth, typically based on external appearance of genitalia
Sex	Attributes that characterize biologic maleness or femaleness; factors that influence sex include sex chromosomes, gonads, sex steroids, internal reproductive structures, external genitalia, secondary sex characteristics
Sexual orientation	Physical and emotional attraction to others. Gender

	identity and sexual orientation are not the same
Transgender	Gender identity differs from sex designated at birth
Transgender male (also transgender man, female-to-male)	Individuals designed female at birth who identify and live as men
Transgender female (also transgender woman, male-to-female)	Individuals designated male at birth who identify and live as women
Transition	Process during which persons change their physical, social, and/or legal characteristics consistent with their affirmed gender identity

Adapted from Table 1 in the 2017 Endocrine Society Guidelines (11)

Centers around the world are seeing a rise in the number of transgender and gender diverse (TGD, Table 1) people seeking care to align their bodies with their identities (16). Despite the rise in the number of TGD people seeking care, there remains a lack of education and knowledge among providers as to how best serve this group (17). This article will define terminology, briefly review gender development, review current guidelines regarding medical treatment of pediatric TGD individuals, and mental health considerations.

Recent population-based studies in the U.S. report that 1.8% of youth and 0.6% of adults identify as transgender (18,19). Gender diverse describes individuals with a variety of gender identities across the gender spectrum, including those who identify as transgender (Table 1). Gender dysphoria, which describes the distress associated with a conflict between gender identity and anatomy or sex, is a listed diagnosis in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5, Table 2) (20).

EPIDEMIOLOGY

Table 2. DSM-5 Criteria for Gender Dysphoria (20)
A marked incongruence between one's experienced/expressed gender and natal gender of at least 6 months in duration, as manifested by at least two of the following: A) A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics) B) A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics) C) A strong desire for the primary and/or secondary sex characteristics of the other gender D) A strong desire to be of the other gender (or some alternative gender different from one's designated gender) E) A strong desire to be treated as the other gender (or some alternative gender different from one's designated gender) F) A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's designated gender)
The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning. Specify if: A) The condition exists with a disorder of sex development. B) The condition is post-transitional, in that the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one sex-related medical procedure or treatment regimen—namely, regular sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in natal males; mastectomy or phalloplasty in natal females).

One's sex refers to the physical attributes that characterize biologic maleness or femaleness and is typically assigned or designated at birth based on the appearance of the external genitalia (or prior to birth based on sex chromosome complement and/or the appearance of the genitalia on the prenatal anatomy ultrasound).

Note that terminology in this field is constantly evolving, and for clinicians, it is important to ask individuals what terms they use to describe their gender identity, and what that term means to them. Table 3 includes suggestions on how to ask these questions.

Table 3. Suggested Ways of Asking About Name and Gender Identity	
Name	"Is there a name you go by other than your legal name?" "What name do you go by?" "What would you like me to call you?"
Pronouns	"What pronouns do you use?" "I'd like to use the pronouns that feel best to you. What pronouns would you like me to use?" Model pronoun use: "Hello, my name is Dr. ____ I use ___ pronouns."
Gender identity	"How do you identify your gender?" "What does [gender identity term] mean to you?" Suggestion for children: "Some kids tell me think of themselves as girls, some as boys, some as part girl and boy, or something entirely different. How do you think about yourself?" Suggestion for adolescents: "There are lots of ways people think about their gender identity, how do you think of yours?"

GENDER IDENTITY DEVELOPMENT AND NATURAL HISTORY OF GENDER INCONGRUENCE

Gender identity is multidimensional with biological, cultural, and environmental contributions (21,22). Studies of gender identity among individuals with differences/disorders of sex development underscore the influence of the hormonal milieu, and prenatal androgen exposure in particular, in gender development (23-26). There are also genetic influences, as some studies show concordance rates of gender dysphoria up to 39% among identical twins (27). Although studies have sought to identify genes associated with transgender identity, results have largely been inconsistent or inconclusive, with a possible role for genes related to sex steroids and their receptors (28-32).

In childhood, learning about gender starts early, and progress through many stages (33). In their review of gender development in childhood, Perry, Pauletti, and Cooper describe eight dimensions of gender identity: (1) gender self-categorization, (2) felt same-gender typicality, (3) felt other-gender typicality, (4) gender contentedness, (5) felt pressure for gender differentiation, (6) intergroup bias, (7) gender centrality, and (8) gender frustration. By age 18-24 months most children can categorize their own and others' gender (34), and by age 6, have a developed gender identity (35). More individuals with a female sex designated at birth express dissatisfaction with their gender (36,37). This reflects the current sex ratio of individuals being referred to gender clinics, with more individuals with a female sex designated at birth currently referred, but the opposite being true prior to the 2000s (38-40).

Despite adolescence being a period of identity formation (41,42), there is a surprising lack of research on adolescent gender identity development. Development of identity is an individual and social process and shaped by external surroundings (42). However, there are also numerous psychological and biological factors that influence gender identity, as outlined in a review by Steensma and colleagues (43).

Overall, there is still much to learn about gender development among gender variant or nonconforming individuals. Prospective studies of children referred to gender clinics, primarily in Europe, show that less than a quarter of children will remain or meet criteria for gender identity disorder (the DSM-IV diagnosis prior to the DSM-5 gender dysphoria) after adolescence (44-47). In follow-up studies, the period of early adolescence/puberty, age 10-13 is critically important. There are three possible factors that contribute to an increase or decrease in gender discomfort and cross-gender identification: (1) physical puberty, (2) changing environment and being treated as their sex assigned at birth, and (3) the discovery of sexuality (47). More recent studies that reflect the rise in referral rates, and in various places around the world, will be critically important.

MEDICAL MANAGEMENT

The WPATH Standards of Care (48) outline three categories of physical interventions for adolescents, indulging (1) fully reversible interventions, such as the use of gonadotropin releasing hormone (GnRH) agonists, medications to suppress menses (such as progestins), and medications to decrease the effects of androgens (such as spironolactone); (2) partially reversible interventions, including testosterone or estradiol; and (3) irreversible interventions, such as surgical procedures. Many individuals also seek care, including behavioral health consultation, for reversible interventions such as name, pronoun and gender marker change, discussing gender identity with friends, family and school, voice therapy, or wearables (including binders and packers to flatten the chest or give the appearance of male genitalia, respectively) (48).

It is important to note, as outlined in the WPATH Standards of Care (48), individuals who have gender variance or incongruence, but whom do not experience distress may not require clinical attention or intervention. Furthermore, there is an increasing recognition that interventions should align with one's individuals gender goals and gender embodiment (49).

Pubertal Blockade

The onset of puberty (gonadarche) is characterized by breast budding in people designated female at birth and by testicular enlargement to 4mL or greater in people designated male at birth, characterized as Tanner or Sexual Maturity Rating stage 2 (50,51). The average age of pubertal onset is age 10-11 years in someone designated female at birth (range 8-13 years, can be younger in African Americans), and 11-12 years in individuals designated male at birth (range 9-14 years). For individuals designated male at birth, external virilization typically starts around a testicular volume of 10 mL (11), voice drop at $\geq$8-10mL (52), and spermarche at 11-12 mL (53). In individuals designated female at birth, breast developmental progresses from stage 2 to 5 (fully developed) within 4-5 years and menarche typically occurs about 2-2.5 years after breast budding (54). Pubic hair and/or axillary hair and/or body odor reflect the onset of adrenarche or adrenal androgen production, which, by themselves are not indicative of central puberty (50,51). Height velocity increases during puberty and peaks about 2.5 years after the start of pubertal growth acceleration (55). An understanding of typical pubertal development and timing of external secondary sex characteristics is useful in counseling families about the timeliness and risk/benefit of GnRH agonist therapy to halt further pubertal progression. For example, towards the end of puberty or in post-pubertal individuals, GnRH agonist therapy may be used in certain circumstances for sex steroid suppression but would not block any pubertal changes, as these are complete.

GnRH agonists were first used in youth for the treatment of central precocious puberty in the 1980s (56). In 1998, Drs. Cohen-Kettenis and van Goozen in the Netherlands published the first report of a transgender patient treated with triptorelin, a GnRH

agonist (57). The “Dutch model” of using pubertal suppression followed by gender affirming hormones (testosterone or estradiol) subsequently became incorporated into the WPATH and Endocrine Society standards of care (10,48). Their use became more widespread in the U.S. after publication of the 2009 Endocrine Society guidelines (10). The 2017 Endocrine Society guidelines suggest that “adolescents who meet diagnostic criteria for gender dysphoria/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development”(11). The guidelines suggest beginning pubertal hormone suppression after the onset of the physical changes of puberty (Tanner Stage or Sexual Maturity Rating 2) for individuals who meet criteria, including being diagnosed with gender dysphoria, experienced worsening dysphoria with the onset of puberty, existing psychological, medical and/or social problems are addressed and the adolescent has sufficient mental capacity to consent to treatment (11). Treatment with a GnRH agonists suppresses gonadotropins (after an initial increase of gonadotropins) (58). There are also gonadotropin releasing hormone antagonists that immediately suppress gonadotropins, but are not available in children. GnRH agonists are typically administered as either an injection (IM or SQ) or as an implant (preparations listed in Table 4). Insurance coverage for this off-label, and costly therapy, varies (59). GnRH agonist treatment will pause or halt pubertal changes and may cause slight regression of breast tissue or testicular volume (11). On their own, these are reversible interventions, and if the individual decided that they wanted to progress through their endogenous puberty, these medications can be discontinued. During GnRH agonist treatment, the Endocrine Society recommends measurement of height, weight, sitting height, blood pressure, and Tanner stages every 3-6 months, measurement of LH, FSH, estradiol or testosterone, and 25OH vitamin D every 6-12 months, and bone density using dual-energy X-ray absorptiometry (DXA) and bone age x-ray of the left hand every 1-2 years (11).

Table 4. Hormonal Interventions for Transgender Adolescents	
Pubertal blockade/inhibition of sex steroid secretion	
GnRH agonist: inhibition of the hypothalamic-pituitary-gonadal access	Leuprolide acetate IM (1-, 3-, 4- or 6-mo preparations) or SQ (1-, 3-, 4- or 6-mo preparation) Triptorelin IM (4-, 12- or 24-week preparation) Histrelin acetate SQ implant (one-yearly dosing, although reports of longer effectiveness)
Medroxyprogesterone acetate: inhibition of the hypothalamic-pituitary-gonadal access and direct inhibition of gonadal steroidogenesis	Orally (up to 40 mg/day) or IM (150 mg every 3 mo, may be given more frequently for suppression of sex steroids)
Inhibition of testosterone secretion or action	
Spironolactone: inhibition of testosterone synthesis and action	Titrate up to 10-300 mg/day orally (typically in divided doses)
Cyproterone acetate: inhibition of testosterone synthesis and action (not available in US)	25-50 mg/day orally
Finasteride: inhibition of type II 5 α-reductase, blocks conversion of testosterone to 5 α-	2.5-5 mg/day orally

dihydrotestosterone	
Bicalutamide: androgen receptor blockade	50 mg/day orally
Sex steroids	
Estrogen/17β-estradiol	Oral/sublingual: start with lower doses for pubertal induction, titrate up to adult doses 2-6 mg/day Transdermal: start with lower doses for pubertal induction, titrate up to adult doses 0.025-0.2 mg/day (patches are typically once or twice weekly) Parenteral: estradiol valerate (5-30 mg every 2 weeks) or cypionate (2-10 mg IM every week)
Testosterone	Parenteral IM or SQ testosterone cypionate or enanthate (start at 12.5 mg/week or 25 mg q2 week with gradual increases to 50-100 mg/week or 100-200 mg every 2 weeks) Transdermal (typically after full adult dose has been achieved parenterally): patch (2.5-7.5 mg/day or 1% or 1.6% gel

Note that all medications are currently off-label for gender non-conforming/transgender youth. Note that certain GnRH preparations are approved in children for central precocious puberty and other formulations are approved for adults only, with off-label use in children. Different formulations are available in different countries. This table was adapted from the following references (11,178). Note that some centers/providers also use GnRH agonists for testosterone blockade in older adolescents and/or adults. GnRH: gonadotropin releasing hormone, IM: intramuscular, SQ: subcutaneous

Recent reviews of puberty blockade have been published (60-62). Small studies have demonstrated effectiveness of GnRH agonist treatment for suppression of the hypothalamic-pituitary-gonadal axis in transgender youth (63). Studies, primarily in Europe, have demonstrated improvements in psychological functioning, behavioral/emotional problems, and depressive symptoms during GnRH agonist treatment in transgender youth (64,65). A recent systemic review found that GnRH agonist therapy is associated with decreased suicidality in adulthood, improved affect and psychological functioning, and improved social life (61).

Potential risks of GnRH agonist therapy include impacts on growth, bone health, body composition, fertility, and neurodevelopment, as well as difficulties accessing treatment due to cost and insurance coverage (61,62,66). GnRH agonist use in TGD youth is associated with increased body fat and decrease in lean mass after initiation (67,68), and compared to age- and BMI-matched control youth (69), and may also have an adverse effect on insulin sensitivity (69). If GnRH agonists are started prior to skeletal maturity, they will decrease skeletal advancement during monotherapy due to suppression of sex steroids, which are necessary for growth plate closure (70,71). There is a dearth of research on growth trajectories during treatment with a GnRH agonist in this population. One multicenter study in the U.S. showed that transgender youth treated with GnRH therapy have growth velocity similar to prepubertal children, but those who start

GnRH agonist treatment later in puberty have growth velocity below the prepubertal range (72). The growth spurt and skeletal advancement will progress either when exogenous testosterone or estradiol are started, or if the GnRH agonists are discontinued and the individual progresses through their endogenous puberty. There is a growing body of research of bone health in transgender individuals, as well as the impact of GnRH agonists and later gender affirming hormones on bone health. Studies in the Netherlands have demonstrated decreased bone turnover, and a decrease in bone mineral apparent density Z-scores of the lumbar spine in transwomen after initiation of GnRH agonist therapy (73). However, studies in the U.S. (74), United Kingdom (75) and Netherlands (73,76) have also shown decreased bone mineral density Z-scores determined by DXA are low prior to treatment with GnRH agonist, and some studies showing Z-scores did not completely normalize with sex hormone treatment (73,76). In the U.S., the individuals with lower baseline bone mineral density Z-scores also reported less physical activity, an area warrants further research (74).

Overall, there is a paucity of research on neurodevelopment and a recent consensus parameter was published with recommended research methodologies to evaluate the neurodevelopmental effects of puberty suppression in this population (77). There is also very little research on sexual function and future surgical options among individuals who received early puberty blockade. Recently, there has been a call for more information to better inform the impacts on future sexual function(78,79) (as GnRH agonists limit penile and testicular growth/size (80)) and on implications for future surgical intervention for those individuals pursuing vaginoplasty (as the scrotal tissue is used to construct the vagina) (80). Finally, treatment with GnRH agonists will impair spermatogenesis and oocyte maturation temporarily, and the Endocrine Society recommends fertility counseling (11). Treatment may be delayed to preserve fertility, but many individuals do not choose this, as delay will also cause further progression of unwanted secondary sex characteristics (11). There are limited options available for early tissue cryopreservation, an area that is gaining more attention (81).

If GnRH analogues are not available or are cost prohibitive, medroxyprogesterone may be used as an alternative agent for pubertal suppression (Table 4) (11,48). At high doses, medroxyprogesterone inhibits the pituitary-gonadal axis and suppresses testosterone (82-84). Medroxyprogesterone was used for treatment of precocious puberty in the 1960s and 70s (85-87). It is typically safe, although may have some side effects, including due to the estrogenic effects (bloating, nausea/vomiting, breast fullness, breakthrough bleeding for those menstruating, irritability, headache, hypertension), progestational effects (headache, breast pain/tenderness, hypertension), and androgenic effects (acne, oily skin, weight gain, hirsutism, fatigue, depression) (88). At extremely high doses (100 mg four times a day), it may cause Cushing's syndrome, adrenal insufficiency, and diabetes (89). There is one small study of medroxyprogesterone in transgender youth demonstrating effective sex steroid suppression with doses of oral medroxyprogesterone 10-30 mg BID or 150 mg IM every 2-3 months (90).

Gender Affirming Hormone Therapy

Gender affirming hormone therapy (GAHT) refer to hormones that induce secondary sex characteristics to align the body with one's gender identity. The Endocrine Society recommends treatment with sex steroids (testosterone or estradiol) "using a gradually increasing dose schedule after a multidisciplinary team of medical and mental health professionals has confirmed the persistence of gender dysphoria/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years" (full criteria in guidelines) (11). However, they also state that "there

may be compelling reasons to initiate sex hormone treatment prior to age 16 years in some adolescents" (11). The WPATH Standards of Care, 8th version are forthcoming, but in the current 7th version, the criteria for hormone therapy are: "(1) persistent, well-documented gender dysphoria; (2) capacity to make a fully informed decision and to consent for treatment; (3) age of majority in a given country; (4) if significant medical or mental concerns are present, they must be reasonably well-controlled" (48). It is recommended, that for adolescents who have not reached the age of majority in their country, that consent from all parents or medical decision-makers is obtained prior to starting this partially irreversible therapy.

Feminizing Hormone Therapy

ESTRADIOL THERAPY

For eligible adolescents, the Endocrine Society recommends a gradually increasing dose schedule of oral or transdermal 17β-estradiol (11). This will cause feminization of the body, with expected effects including body fat redistribution, decreased muscle mass/strength, softening of the skin/decreased oiliness, decreased libido/erections, breast growth, decreased testicular volume, decreased sperm production, and thinning and slowed growth of body and facial hair occurring one to several months after treatment with maximum effects generally about 2-3 years or more into treatment (11,48). For younger individuals, the Endocrine Society recommends starting oral estradiol at a dose of 5 μg/kg/day and increasing doses every 6 months up to a dose of 2-6 mg/day for an adult (11). In post-pubertal individuals, the starting dose may be higher and titrated more quickly (start at 1 mg/day for 6 months and increase to 2 mg/day orally) (11). For transdermal estradiol, it is recommended to start at a dose of 6.25-12.5 μg/24 hours and increase the dose every 6 months to an adult dose of 50-200 μg/24 hours. During induction of puberty, it is recommended to measure height, weight, sitting height, blood pressure, and Tanner stages every 3-6 months, and measure prolactin, estradiol and 25OH vitamin D every 6-12 months (11). Additionally, DXA and bone age (if clinically indicated or a growing patient) is recommended every 1-2 years (11).

Potential Adverse Effects of Estradiol Therapy

Risks with estradiol therapy as outlined in the Endocrine Society guidelines include thromboembolic disease, macroprolactinoma, breast cancer, coronary artery disease, cerebrovascular disease, cholelithiasis, and hypertriglyceridemia (11).

In adults, studies using three large cohorts have shown an increased risk of myocardial infarction and venous thromboembolism. In Europe, transgender women on estradiol therapy have a higher risk of stroke and venous thromboembolism than both cisgender reference women and men, and a higher risk of myocardial infarction than cisgender women (but not men) (91). In the U.S., two large cohorts have been used to examine outcomes, the Kaiser STRONG cohort and self-report data from the Behavioral Risk Factor Surveillance System (BRFSS). Data on hormone treatment is not collected in BRFSS. Transgender women in BRFSS were more likely (>2-fold increase risk) to have a history of myocardial infarction than cisgender women (but not men) (92,93). In the Kaiser STRONG cohort (94), both prevalent and incident type 2 diabetes was more common in the transfeminine cohort compared to cisgender females (95). In a meta-analysis commissioned by the Endocrine Society to accompany the 2017 updated guidelines, transgender women on estradiol therapy had increased triglycerides, but no changes in other lipid parameters (96). There were few reports of myocardial infarction, stroke, venous thromboembolism or death (96). It is well-known that transgender women on estradiol therapy have increases in body weight and fat and decreases in lean body mass (97). Estradiol therapy is associated

with increases in lumbar spine bone mineral density compared to baseline (98).

In youth, there is a growing body of literature on the effects of GAHT, particularly on cardiometabolic health. TGD youth on estradiol have changes in HDL, aspartate aminotransferase, potassium, prolactin, and hemoglobin after about two years (99). One study found that transgender females on estradiol therapy were more insulin resistant than matched cisgender males (100). The presence of obesity attenuates the beneficial effect of estradiol on HDL (101). There are also studies investigating baseline differences between TGD youth and cisgender controls prior to hormone therapy, with recent studies showing TGD youth have lower HDL and low bone mineral density (72,102).

Testosterone Blockade/Suppression

There are many options for blockade and/or suppression of testosterone (all off-label use, Table 4). When available and affordable, some centers utilize GnRH agonists for suppression of testosterone. For example, in the United Kingdom, GnRH analogues are heavily subsidized (103). There are also many antiandrogens available, and a systemic review of options has recently been published (104). Spironolactone is widely available, inexpensive, and commonly used in the U.S. and Australia. Spironolactone is a weak androgen receptor antagonist (105,106), weak progesterone receptor agonist, and weak estrogen receptor agonist (104). It also partially inhibits 17α-hydroxylase/17,20 lyase, which are involved in testosterone synthesis (107). Even at high doses, spironolactone does not cause a significant reduction in serum total testosterone concentration (108). Although the combination of spironolactone with estradiol does appear to suppress testosterone in transgender women (109). Side effects include irregular menses (only for people who are menstruating, not a consideration for transgender women), hypotension, polyuria, and hyperkalemia (110,111).

Cyproterone acetate is available in Europe and Australia, but not in the U.S. and is a moderate androgen receptor antagonist, strong progesterone receptor agonist, and does not have any estrogen receptor activity but does suppress the hypothalamic pituitary gonadal axis (104). Cyproterone acetate has been associated with increased risk of meningiomas (112) and prolactinomas (113). Other side effects include weight gain, headache, gastrointestinal disorders, mood effects, and edema (114).

Nonsteroidal antiandrogens, such as bicalutamide have also been used at some centers. Bicalutamide has strong androgen receptor antagonist activity and does not have any estrogen or progesterone agonist activity (104). It does not cause a reduction in testosterone concentrations. There is some feminization, thought to be due to increased aromatization of testosterone to estradiol (115). There is currently one published study of the use of bicalutamide in transgender adolescents as an alternative to GnRH agonists (115). In that study, hepatic enzymes remained normal and there were no adverse effects, however, effectiveness and the potential risk of liver toxicity needs to be examined in larger studies.

Finally, 5-alpha reductase inhibitors, such as finasteride, block conversion of testosterone to dihydrotestosterone. These are not recommended by the Endocrine Society due to adverse effects (11), but the WPATH guidelines state, “these medications have beneficial effects on scalp hair loss, body hair growth, sebaceous glands, and skin consistency” (48). Side effects include sexual dysfunction and decreased muscle (which may be perceived as a risk or benefit in this population), anhedonia, and trouble concentrating (116).

Overall, the selection of which agent alone or in combination with estradiol depends on many factors including patient age, country, insurance coverage, cost, goals of care, and tolerability of side effects

(e.g. severe and fatal hepatotoxicity has been reported with cyproterone acetate and bicalutamide (117)). Further studies are needed to determine superiority for relevant patient outcomes including body composition, breast development, facial and body hair (104).

Masculinizing Hormone Therapy

TESTOSTERONE

For eligible adolescents, the Endocrine Society recommends a gradually increasing dose schedule of testosterone (typically injectable IM or SQ) (11). This will cause masculinization of the body, with expected effects including skin oiliness/acne, facial/body hair growth, scalp hair loss, increased muscle mass/strength, body fat redistribution, cessation of menses, clitoral enlargement, vaginal atrophy, and deepened voice with onset occurring one to several months after treatment with maximum effects generally about 2-5 years or more into treatment (11,48). For younger individuals, the Endocrine Society recommends starting injectable testosterone esters at a dose of 25 mg/m^2 IM or SQ every 2 weeks and increasing every 6 months up to an adult dose of 100-200 mg every 2 weeks (11). In post-pubertal individuals, the starting dose may be higher and titrated more quickly (start at 75 mg every 2 weeks for 6 months and increase to 125 mg every 2 weeks) (11). Subcutaneous testosterone is gaining in popularity, and has shown to be effective and preferred by patients (118-120). Pharmacokinetic studies of weekly subcutaneous testosterone injections show that steady state is approached after the third dose, and that serum concentrations stay relatively constant throughout the week between doses (121). Finally, SQ testosterone doses may be lower than those delivered IM, with two studies reporting doses of 50-80 mg/week to achieve target testosterone concentrations in adults or older adolescents (118,119). During induction of puberty, it is recommended to measure height, weight, sitting height, blood pressure, and Tanner stages every 3-6 months, and measure hemoglobin/hematocrit, lipids, testosterone, and 25OH vitamin D every 6-12 months (11). Additionally, DXA and bone age (if clinically indicated or a growing patient) is recommended every 1-2 years (11).

The most common adverse effect of testosterone is erythrocytosis/polycythemia (hematocrit >50%) (11). Other risks as outlined in the Endocrine Society guidelines include liver dysfunction, coronary artery disease, cerebrovascular disease, hypertension, and breast or uterine cancer (11).

In adults, studies using three large cohorts have shown conflicting results. In Europe, transgender men on testosterone therapy have a higher risk of myocardial infarction than cisgender women (but not men) and no increased risk of stroke or venous thromboembolism compared to reference populations (91). Transgender men in the 2015 U.S. BRFSS survey had no increased risk of hypertension, myocardial infarction, stroke, angina/coronary heart disease compared to cisgender men or women (92). However, another analysis of BRFSS data (years 2014-2017) reported a >2-fold increase risk of myocardial infarction compared to cisgender men and 4-fold increase compared to cisgender women (93). In the Kaiser STRONG cohort, there was no increased risk of type 2 diabetes among transgender men compared to cisgender men (95). In a meta-analysis, testosterone therapy in transgender men was associated with increases in serum triglycerides and low-density lipoprotein cholesterol (LDL-C) concentrations and decreases in high-density lipoprotein cholesterol (HDL) (96). Testosterone therapy in transgender men is known to result in increased body weight and lean mass and decreased body fat (97). In meta-analyses, testosterone therapy is not associated with significant changes in bone mineral density (98,122). There is a recent position statement from the International Society for Clinical Densitometry on bone densitometry in TGD individuals (123).

Among TGD youth starting testosterone therapy, there is an increase in BMI and decrease in HDL (124). The decrease in HDL is exacerbated by obesity (101). Other studies have found that testosterone treatment in TGD youth is associated with statistical, but not clinically significant increases in triglycerides, alanine aminotransferase, potassium, and hemoglobin (99).

Non-Binary Care

Non-binary or gender non-conforming individuals represent a growing proportion of patients presenting to gender clinics and may have additional challenges accessing healthcare (125). Limited studies have reported worse mental and physical health among individuals who identify as gender non-conforming compared to matched controls (92). An individualized approach to understand the individual's gender identity, sources of dysphoria (if any), and gender goals are important. Some individuals may desire reversible interventions such as menstrual suppression, others may request certain hormones and/or surgical interventions as a part of their gender goals. The 8th version of the WPATH standards of care will include a chapter on non-binary care.

Menstrual Management

Many transmasculine and non-binary individuals who are designated female at birth seek medical attention or desire interventions for menstrual management (126). Some also utilize these methods for contraception. It is important to ask individuals about their individual goals, as well as their sexual orientation, partners (including sex assigned at birth and what body parts they currently have), and types of sex they are engaging in. These factors can guide choice of intervention for menstrual management and/or contraception. An overview of options is in Table 5. Progestin-only methods, including norethindrone or depo medroxyprogesterone are particularly popular choices among this population (126). Review of options for menstrual management and contraceptive options for transgender individuals was recently published (127). For those patients wishing to and eligible for testosterone therapy, menses suppression typically is achieved within 6-12 months of the start of testosterone therapy (128).

Table 5. Options for Menstrual Suppression/Management
Combined hormonal contraceptives (pills, patch, ring)
Progestins
Norethindrone acetate (5-15 mg/day orally)
Medroxyprogesterone acetate (150 mg IM every 3 months)
Etonogestrel implant
Levonorgestrel IUD

IUD: intrauterine device

SURGICAL MANAGEMENT

Surgeries that impact fertility are generally not available until the individual has reached the age of majority in their country. There are a wide variety of surgical options for transgender adults (and some options, primarily chest surgery, for adolescents), and this has recently been reviewed (129). Physicians (including surgeons and non-surgeons) and behavioral health providers should be aware of the criteria needed for each surgical procedure, including whether social transition is recommended, whether hormonal therapy is needed (and length), and how many referral letters are needed and by whom (48,130). In general, a documentation of persistent gender dysphoria by a qualified mental health provider is a requirement for surgery (48).

Additionally, guidelines may change over time (the 8th version of the WPATH standards of care are coming soon) and may vary by location (country/state) and insurance coverage. Table 6 summarizes the various gender affirming surgical options. Genital surgery or removal of the gonads is generally not performed until the individual is the age of majority in a given country (age 18 years or older in the U.S.). Individuals younger than 18 may be eligible for chest/breast surgery, with consent from medical decision-makers. The WPATH Standards of Care state for mastectomy/chest masculinizing surgery or for breast augmentation surgery, the individual must have "(1) persistent, well-documented gender dysphoria, (2) capacity to make s fully informed decision and to consent for treatment, (3) age of majority in a given country, (4) if significant medical or mental health concerns are present, they must be reasonably well controlled." Although masculinizing hormone therapy (testosterone) is not a prerequisite for chest masculinizing surgery in the WPATH guidelines, it is recommended (although not an explicit criterion) that individuals on feminizing hormone therapy be on for a minimum of 12 months prior to breast augmentation surgery for better aesthetic results (48). However, the Endocrine Society Guidelines recommend 2 years of testosterone therapy prior to mastectomy/chest masculinizing surgery. Neither the WPATH or Endocrine Society guidelines recommend a specific age cutoff, but "suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual" (11).

Table 6. Gender Affirming Surgical Options	
Feminizing surgeries	
Breast augmentation	Increasing the size of the breasts
Facial feminization surgery	May include: forehead feminization, rhinoplasty, periorbital rejuvenation, rhytidectomy (face lift), cheek augmentation, rhinoplasty, lip feminization, gonial angle shave, genioplasty
Genital surgery/vaginoplasty	May include penectomy, orchiectomy, surgical creation of a vagina (penile inversion, intestinal conduit), clitoroplasty, labiaplasty
Orchiectomy	Removal of testes
Tracheal shave	Thyroid cartilage shave
Masculinizing surgeries	
Chest masculinizing surgery (mastectomy)	Removal of breast tissue
Facial masculinization surgery	Rhinoplasty, gonial implants, genioplasty
Hysterectomy, salpingectomy, oophorectomy	Removal of uterus and/or fallopian tubes, and/or ovaries
Metoidioplasty	Creation of a phallus using existing genital tissue
Phalloplasty	Construction of phallus, glansplasty, urethroplasty, erectile prosthesis, scrotoplasty, testicular implants

MENTAL HEALTH

Recently studies have demonstrated a strikingly high prevalence of behavioral health diagnoses among youth diagnosed with gender dysphoria (up to 60%) (131,132). Studies evaluating behavioral health outcomes among TGD youth have most frequently demonstrated disproportionate anxiety (132-134), depression (133-136), suicidality (19,132-134,137), self-harm (132-135), and substance use problems (19). Large surveys of TGD individuals in the U.S. have shown that 40% of adults (138) and 35% of youth (19) have attempted suicide. Poor behavioral health outcomes may be conceptualized as the result of complex and layered socio-cultural and political factors that impact TGD youth (15,139). Risk factors that are likely to impact overall mental health for TGD individuals include minority stress (e.g., victimization, discrimination) (19,140), gender dysphoria and appearance congruence (141), feelings of isolation, inadequate family support (142), emotional/social isolation (143), lack of autonomy over decision making (143), barriers to accessing gender affirming care (143-145), employment discrimination (143), and limited financial resources (143). In the Youth Risk Behavior Survey, TGD youth were two to six times more likely to be victimized, including experiencing sexual dating violence, experiencing physical dating violence, being bullied at school, being electronically bullied, feeling unsafe during travel to or from school, and being forced to have sexual intercourse (19).

The co-occurrence of autism spectrum disorders (ASD) and gender dysphoria is a growing area of interest (132,146-150). A recent meta-analysis found that the prevalence of ASD among those with GD has ranged from 6% to 68% depending on the methodology of the study (151). In a large 2020 study, TGD individuals were 3.0 to 6.4 times more likely to be diagnosed with ASD than their cisgender counterparts (136). Other samples have shown that youth with gender dysphoria are about 2-3x as likely to have a diagnosis of ASD than their matched cisgender counterparts (131,132). The exact link between GD and ASD is not known, but factors contributing may include: symptom overlap between the two diagnoses, misclassification due to symptom overlap, children with ASD may be more likely to express their gender identity and dysphoria, or they may be more likely to be referred to care to be diagnosed with either GD or ASD (152).

Protective factors including social support (153,154), parental support/affirmation of gender identity (155,156), higher self-esteem (153), resiliency (153,157), and access to affirming care (144,158,159) have improved well-being and decreased mental health distress. Access to gender-affirming interventions, including hormone therapy and surgery, has been shown to improve gender dysphoria, psychological symptoms and quality of life in small samples and meta-analyses (28). Recent studies have shown that those who were older at presentation have worse mental health than those who presented to care at a younger age (160) and those who had access to GnRH agonists had lower lifetime odds of suicidal ideation than those who did not have access (144).

Finally, there are many other important topics that impact the care of transgender individuals that are beyond the scope of this chapter including dermatologic considerations and hair loss (161-163), chest binding (164), sexual health (79), HIV prevention and treatment (165-167), fertility (81), sleep (168), athletic performance and sports participation (169), eating disorders (170,171), homelessness, the impact of family support, and the underpinnings of links between gender diversity and neurodiversity (172).

CONCLUSION

An improved understanding of the variety of individual gender trajectories is needed, as well as how best to individualize care, how to improve mental health, and minimize risks of medical intervention. Large, multi-center, prospective cohorts, as are currently established in the U.S. (94,173) and Europe (174), will help answer some of these important questions. And community-based participatory research and hearing the voices of individuals from the community about their own research priorities and dissemination of results is of utmost importance. There is also much to be learned about the impact of early GnRH agonist therapy on growth, bone health, physical development, long-term health, mental health, cognitive development, and overall wellbeing. Finally, an improved understanding on the impact of other stressors including minority stress and depression on overall health (175,176) for TGD persons is needed. The American Heart Association published a scientific statement with recommendations to assess and address cardiovascular health among TGD people (177).

REFERENCES

1. David K, Dingemanse E, Freud J, Laqueur E. On crystalline male hormone from testicles (testosterone). Hoppe Seylers Z Physiol Chem 1935; 233:281
2. Veler CD, Thayer S, Doisy EA. The preparation of the crystalline follicular ovarian hormone: theelin. Journal of Biological Chemistry 1930; 87:357-371
3. Butenandt A. Über „Progynon “ein krystallisiertes weibliches Sexualhormon. Naturwissenschaften 1929; 17:879-879
4. Slotta K, Ruschig H, Fels E. Reindarstellung der Hormone aus dem Corpus luteum (II. Mitteil.). Berichte der deutschen chemischen Gesellschaft (A and B Series) 1934; 67:1624-1626
5. Wintersteiner O, Allen WM. Crystalline progestin. Journal of Biological Chemistry 1934; 107:321-336
6. Elbe L, Jacobsen ELH. Man into Woman: An Authentic Record of a Change of Sex. The True Story of the Miraculous Transformation of the Danish Painter, Einar Wegener (Andreas Sparre). Jarrolds.
7. Huelke H. Ein Transvestit. Z Kriminalistische Wissen 1949; 3:91-92
8. Hamburger C, Stürup GK, Dahl-Iversen E. Transvestism: Hormonal, psychiatric, and surgical treatment. Journal of the American Medical Association 1953; 152:391-396
9. Benjamin H. The transsexual phenomenon. Ace Publishing Company.
10. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ, III, Spack NP, Tangpricha V, Montori VM. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2009; 94:3132-3154
11. Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, Rosenthal SM, Safer JD, Tangpricha V, T'Sjoen GG. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2017; 102:3869-3903
12. Gillig TK, Rosenthal EL, Murphy ST, Folb KL. More than a media moment: The influence of televised storylines on viewers' attitudes toward transgender people and policies. Sex Roles 2018; 78:515-527
13. Equality Federation. https://www.equalityfederation.org/state-legislation. Accessed 1/14/22.
14. Rafferty J. Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents. Pediatrics 2018; 142:e20182162
15. Association AP. Guidelines for psychological practice with transgender and gender nonconforming people. American Psychologist 2015; 70:832-864
16. Skordis N, Butler G, de Vries MC, Main K, Hannema SE. ESPE and PES International Survey of Centers and Clinicians Delivering Specialist Care for Children and Adolescents with Gender Dysphoria. Horm Res Paediatr 2018; 90:326-331
17. Korpaisarn S, Safer JD. Gaps in transgender medical education among healthcare providers: A major barrier to care for transgender persons. Reviews in Endocrine and Metabolic Disorders 2018; 19:271-275
18. Herman JL, Flores, A.R., Brown, T.N.T., Wilson, B.D.M., & Conron, K.J. . Age of individuals who identify as transgender in the United States. . Los Angeles, CA: The Williams Institute 2017;

19. Johns MM, Lowry R, Andrzejewski J, Barrios LC, Demissie Z, McManus T, Rasberry CN, Robin L, Underwood JM. Transgender Identity and Experiences of Violence Victimization, Substance Use, Suicide Risk, and Sexual Risk Behaviors Among High School Students - 19 States and Large Urban School Districts, 2017. MMWR Morbidity and mortality weekly report 2019; 68:67-71
20. Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub.
21. Perry DG, Pauletti RE, Cooper PJ. Gender identity in childhood: A review of the literature. International Journal of Behavioral Development 2019; 43:289-304
22. Fausto-Sterling A. Sex/gender: Biology in a social world. Routledge.
23. Berenbaum SA, Meyer-Bahlburg HF. Gender development and sexuality in disorders of sex development. Horm Metab Res 2015; 47:361-366
24. Dessens AB, Slijper FM, Drop SL. Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. Arch Sex Behav 2005; 34:389-397
25. Meyer-Bahlburg HF, Dolezal C, Baker SW, Ehrhardt AA, New MI. Gender development in women with congenital adrenal hyperplasia as a function of disorder severity. Arch Sex Behav 2006; 35:667-684
26. Meyer-Bahlburg HF, Dolezal C, Baker SW, Carlson AD, Obeid JS, New MI. Prenatal androgenization affects gender-related behavior but not gender identity in 5-12-year-old girls with congenital adrenal hyperplasia. Arch Sex Behav 2004; 33:97-104
27. Heylens G, De Cuypere G, Zucker KJ, Schelfaut C, Elaut E, Vanden Bossche H, De Baere E, T'Sjoen G. Gender identity disorder in twins: a review of the case report literature. The journal of sexual medicine 2012; 9:751-757
28. Fernández R, Esteva I, Gómez-Gil E, Rumbo T, Almaraz MC, Roda E, Haro-Mora JJ, Guillamón A, Pásaro E. Association study of ERβ, AR, and CYP19A1 genes and MtF transsexualism. The journal of sexual medicine 2014; 11:2986-2994
29. Henningsson S, Westberg L, Nilsson S, Lundström B, Ekselius L, Bodlund O, Lindström E, Hellstrand M, Rosmond R, Eriksson E, Landén M. Sex steroid-related genes and male-to-female transsexualism. Psychoneuroendocrinology 2005; 30:657-664
30. Hare L, Bernard P, Sánchez FJ, Baird PN, Vilain E, Kennedy T, Harley VR. Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. Biol Psychiatry 2009; 65:93-96
31. Lombardo F, Toselli L, Grassetti D, Paoli D, Masciandaro P, Valentini F, Lenzi A, Gandini L. Hormone and genetic study in male to female transsexual patients. J Endocrinol Invest 2013; 36:550-557
32. Ujike H, Otani K, Nakatsuka M, Ishii K, Sasaki A, Oishi T, Sato T, Okahisa Y, Matsumoto Y, Namba Y, Kimata Y, Kuroda S. Association study of gender identity disorder and sex hormone-related genes. Prog Neuropsychopharmacol Biol Psychiatry 2009; 33:1241-1244
33. Kohlberg LA. A cognitive-developmental analysis of children's sex role concepts and attitudes. The development of sex differences 1966:82-173
34. Eichstedt JA, Serbin LA, Poulin-Dubois D, Sen MG. Of bears and men: Infants' knowledge of conventional and metaphorical gender stereotypes. Infant Behav Dev 2002; 25:296-310
35. Diamond LM, Butterworth M. Questioning gender and sexual identity: Dynamic links over time. Sex roles 2008; 59:365-376
36. Carver PR, Yunger JL, Perry DG. Gender identity and adjustment in middle childhood. Sex roles 2003; 49:95-109
37. Egan SK, Perry DG. Gender identity: a multidimensional analysis with implications for psychosocial adjustment. Developmental psychology 2001; 37:451
38. Zucker K, Aitken M. Sex ratio of transgender adolescents: A meta-analysis. Paper presented at: 3rd biennal EPATH Conference Inside Matters. On Law, Ethics and Religion2019
39. Arnoldussen M, Steensma TD, Popma A, van der Miesen AI, Twisk JW, de Vries AL. Re-evaluation of the Dutch approach: are recently referred transgender youth different compared to earlier referrals? European child & adolescent psychiatry 2020; 29:803-811
40. Aitken M, Steensma TD, Blanchard R, VanderLaan DP, Wood H, Fuentes A, Spegg C, Wasserman L, Ames M, Fitzsimmons CL. Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. The journal of sexual medicine 2015; 12:756-763
41. Erikson EH. Identity: Youth and crisis. WW Norton & company.
42. Marcia JE. Development and validation of ego-identity status. Journal of personality and social psychology 1966; 3:551
43. Steensma TD, Kreukels BP, de Vries AL, Cohen-Kettenis PT. Gender identity development in adolescence. Horm Behav 2013; 64:288-297
44. Drummond KD, Bradley SJ, Peterson-Badali M, Zucker KJ. A follow-up study of girls with gender identity disorder. Dev Psychol 2008; 44:34
45. Zucker KJ. On the "natural history" of gender identity disorder in children. J Am Acad Child Adolesc Psychiatry 2008; 47:1361-1363
46. Wallien MSC, Cohen-Kettenis PT. Psychosexual outcome of gender-dysphoric children. J Am Acad Child Adolesc Psychiatry 2008; 47:1413-1423
47. Steensma TD, Biemond R, de Boer F, Cohen-Kettenis PT. Desisting and persisting gender dysphoria after childhood: A qualitative follow-up study. Clin Child Psychol Psychiatry 2011:1359104510378303

48. Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People. World Professional Association for Transgender Health (WPATH).
49. Keo-Meier CE, Ehrensaft DE. The gender affirmative model: An interdisciplinary approach to supporting transgender and gender expansive children. American Psychological Association.
50. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child 1970; 45:13-23
51. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969; 44:291-303
52. Harries ML, Walker JM, Williams DM, Hawkins S, Hughes I. Changes in the male voice at puberty. Archives of disease in childhood 1997; 77:445-447
53. Nielsen CT, SKAKKEBÆK NE, Richardson DW, Darling JA, Hunter WM, Jørgensen M, Nielsen A, Ingerslev O, Keiding N, Müller J. Onset of the release of spermatozia (supermarche) in boys in relation to age, testicular growth, pubic hair, and height. The Journal of Clinical Endocrinology & Metabolism 1986; 62:532-535
54. Kleigman RM, Behrman RE, Jenson HB, Stanton B. Nelson textbook of pediatrics. Stanton, chapter 2007;
55. Abbassi V. Growth and normal puberty. Pediatrics 1998; 102:507-511
56. Mansfield MJ, Beardsworth DE, Loughlin JS, Crawford JD, Bode HH, Rivier J, Vale W, Kushner DC, Crigler JF, Jr., Crowley WF, Jr. Long-term treatment of central precocious puberty with a long-acting analogue of luteinizing hormone-releasing hormone. Effects on somatic growth and skeletal maturation. N Engl J Med 1983; 309:1286-1290
57. Cohen-Kettenis PT, Van Goozen S. Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent. Eur Child Adolesc Psychiatry 1998; 7:246-248
58. Roth CL, Brendel L, Rückert C, Hartmann K. Antagonistic and agonistic GnRH analogue treatment of precocious puberty: tracking gonadotropin concentrations in urine. Horm Res 2005; 63:257-262
59. Stevens J, Gomez-Lobo V, Pine-Twaddell E. Insurance coverage of puberty blocker therapies for transgender youth. Pediatrics 2015; 136:1029-1031
60. Panagiotakopoulos L, Chulani V, Koyama A, Childress K, Forcier M, Grimsby G, Greenberg K. The effect of early puberty suppression on treatment options and outcomes in transgender patients. Nat Rev Urol 2020; 17:626-636
61. Rew L, Young CC, Monge M, Bogucka R. Review: Puberty blockers for transgender and gender diverse youth-a critical review of the literature. Child Adolesc Ment Health 2021; 26:3-14
62. Mahfouda S, Moore JK, Siafarikas A, Zepf FD, Lin A. Puberty suppression in transgender children and adolescents. Lancet Diabetes Endocrinol 2017; 5:816-826
63. Mejia-Otero JD, White P, Lopez X. Effectiveness of Puberty Suppression with Gonadotropin-Releasing Hormone Agonists in Transgender Youth. Transgender Health 2021; 6:31-35
64. de Vries ALC, Steensma TD, Doreleijers TAH, Cohen-Kettenis PT. Puberty Suppression in Adolescents With Gender Identity Disorder: A Prospective Follow-Up Study. J Sex Med 2011; 8:2276-2283
65. de Vries ALC, McGuire JK, Steensma TD, Wagenaar ECF, Doreleijers TAH, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 2014; 134:696-704
66. Harris RM, Tishelman AC, Quinn GP, Nahata L. Decision making and the long-term impact of puberty blockade in transgender children. The American Journal of Bioethics 2019; 19:67-69
67. Schagen SE, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE. Efficacy and Safety of Gonadotropin-Releasing Hormone Agonist Treatment to Suppress Puberty in Gender Dysphoric Adolescents. The journal of sexual medicine 2016; 13:1125-1132
68. Klaver M, de Mutsert R, Wiepjes CM, Twisk JWR, den Heijer M, Rotteveel J, Klink DT. Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents. The journal of sexual medicine 2018; 15:251-260
69. Nokoff NJ, Scarbro SL, Moreau KL, Zeitler P, Nadeau KJ, Reirden D, Juarez-Colunga E, Kelsey MM. Body Composition and Markers of Cardiometabolic Health in Transgender Youth on Gonadotropin-Releasing Hormone Agonists. Transgend Health 2021; 6:111-119
70. Cutler GB, Jr. The role of estrogen in bone growth and maturation during childhood and adolescence. J Steroid Biochem Mol Biol 1997; 61:141-144
71. Sasano H, Uzuki M, Sawai T, Nagura H, Matsunaga G, Kashimoto O, Harada N. Aromatase in human bone tissue. Journal of Bone and Mineral Research 1997; 12:1416-1423
72. Schulmeister C, Millington K, Kaufman M, Finlayson C, Olson-Kennedy J, Garofalo R, Chan Y-M, Rosenthal SM. Growth in Transgender/Gender-Diverse Youth in the First Year of Treatment With Gonadotropin-Releasing Hormone Agonists. Journal of Adolescent Health 2021;
73. Vlot MC, Klink DT, den Heijer M, Blankenstein MA, Rotteveel J, Heijboer AC. Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers

and bone mineral apparent density (BMAD) in transgender adolescents. Bone 2017; 95:11-19
74. Lee JY, Finlayson C, Olson-Kennedy J, Garofalo R, Chan Y-M, Glidden DV, Rosenthal SM. Low bone mineral density in early pubertal transgender/gender diverse youth: Findings from the Trans Youth Care Study. Journal of the Endocrine Society 2020; 4:bvaa065
75. Joseph T, Ting J, Butler G. The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort. J Pediatr Endocrinol Metab 2019; 32:1077-1081
76. Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. J Clin Endocrinol Metab 2015; 100:E270-275
77. Chen D, Strang JF, Kolbuck VD, Rosenthal SM, Wallen K, Waber DP, Steinberg L, Sisk CL, Ross J, Paus T, Mueller SC, McCarthy MM, Micevych PE, Martin CL, Kreukels BPC, Kenworthy L, Herting MM, Herlitz A, Haraldsen I, Dahl R, Crone EA, Chelune GJ, Burke SM, Berenbaum SA, Beltz AM, Bakker J, Eliot L, Vilain E, Wallace GL, Nelson EE, Garofalo R. Consensus Parameter: Research Methodologies to Evaluate Neurodevelopmental Effects of Pubertal Suppression in Transgender Youth. Transgend Health 2020; 5:246-257
78. Holmberg M, Arver S, Dhejne C. Supporting sexuality and improving sexual function in transgender persons. Nat Rev Urol 2019; 16:121-139
79. Stephenson R, Riley E, Rogers E, Suarez N, Metheny N, Senda J, Saylor KM, Bauermeister JA. The sexual health of transgender men: a scoping review. The Journal of Sex Research 2017; 54:424-445
80. van de Grift TC, van Gelder ZJ, Mullender MG, Steensma TD, de Vries ALC, Bouman MB. Timing of Puberty Suppression and Surgical Options for Transgender Youth. Pediatrics 2020; 146
81. Nahata L, Chen D, Moravek MB, Quinn GP, Sutter ME, Taylor J, Tishelman AC, Gomez-Lobo V. Understudied and under-reported: fertility issues in transgender youth—a narrative review. The Journal of pediatrics 2019; 205:265-271
82. Rivarola MA, Camacho AM, Migeon CJ. Effect of treatment with medroxyprogesterone acetate (Provera) on testicular function. The Journal of Clinical Endocrinology & Metabolism 1968; 28:679-684
83. KUPPERMAN HS, Epstein JA. Medroxyprogesterone acetate in the treatment of constitutional sexual precocity. The Journal of Clinical Endocrinology & Metabolism 1962; 22:456-458
84. Lee PA. Medroxyprogesterone therapy for sexual precocity in girls. American Journal of Diseases of Children 1981; 135:443-445
85. Collipp PJ, Kaplan SA, Boyle DC, Plachte F, Kogut MD. CONSTITUTIONAL ISOSEXUAL PRECOCIOUS PUBERTY. EFFECTS OF MEDROXYPROGESTERONE ACETATE THERAPY. Am J Dis Child 1964; 108:399-405
86. Hahn HB, Jr., Hayles AB, Albert A. MEDROXYPROGESTERONE AND CONSTITUTIONAL PRECOCIOUS PUBERTY. Mayo Clin Proc 1964; 39:182-190
87. Schoen EJ. Treatment of idiopathic precocious puberty in boys. J Clin Endocrinol Metab 1966; 26:363-370
88. Grundy V, Columbus G. Selecting and monitoring hormonal contraceptives: an overview of available products. US Pharm 2006; 6:62-70
89. Merrin PK, Alexander WD. Cushing's syndrome induced by medroxyprogesterone. BMJ: British Medical Journal 1990; 301:345
90. Lynch MM, Khandheria MM, Meyer III WJ. Retrospective study of the management of childhood and adolescent gender identity disorder using medroxyprogesterone acetate. International Journal of Transgenderism 2015; 16:201-208
91. Nota NM, Wiepjes CM, de Blok CJM, Gooren LJG, Kreukels BPC, den Heijer M. Occurrence of Acute Cardiovascular Events in Transgender Individuals Receiving Hormone Therapy. Circulation 2019; 139:1461-1462
92. Nokoff NJ, Scarbro S, Juarez-Colunga E, Moreau KL, Kempe A. Health and Cardiometabolic Disease in Transgender Adults in the United States: Behavioral Risk Factor Surveillance System 2015. J Endocr Soc 2018; 2:349-360
93. Alzahrani T, Nguyen T, Ryan A, Dwairy A, McCaffrey J, Yunus R, Forgione J, Krepp J, Nagy C, Mazhari R, Reiner J. Cardiovascular Disease Risk Factors and Myocardial Infarction in the Transgender Population. Circ Cardiovasc Qual Outcomes 2019; 12:e005597
94. Quinn VP, Nash R, Hunkeler E, Contreras R, Cromwell L, Becerra-Culqui TA, Getahun D, Giammattei S, Lash TL, Millman A. Cohort profile: Study of Transition, Outcomes and Gender (STRONG) to assess health status of transgender people. BMJ open 2017; 7:e018121
95. Islam N, Nash R, Zhang Q, Panagiotakopoulos L, Daley T, Bhasin S, Getahun D, Haw JS, McCracken C, Silverberg MJ, Tangpricha V, Vupputuri S, Goodman M. Is There a Link Between Hormone Use and Diabetes Incidence in Transgender People? Data from the STRONG Cohort. J Clin Endocrinol Metab 2021;
96. Maraka S, Singh Ospina N, Rodriguez-Gutierrez R, Davidge-Pitts CJ, Nippoldt TB, Prokop LJ, Murad MH. Sex Steroids and Cardiovascular Outcomes in Transgender Individuals: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab 2017; 102:3914-3923
97. Klaver M, Dekker M, de Mutsert R, Twisk JWR, den Heijer M. Cross-sex hormone therapy in transgender persons

affects total body weight, body fat and lean body mass: a meta-analysis. Andrologia 2017; 49
98. Singh-Ospina N, Maraka S, Rodriguez-Gutierrez R, Davidge-Pitts C, Nippoldt TB, Prokop LJ, Murad MH. Effect of Sex Steroids on the Bone Health of Transgender Individuals: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab 2017; 102:3904-3913
99. Olson-Kennedy J, Okonta V, Clark LF, Belzer M. Physiologic Response to Gender-Affirming Hormones Among Transgender Youth. J Adolesc Health 2018; 62:397-401
100. Nokoff NJ, Scarbro SL, Moreau KL, Zeitler P, Nadeau KJ, Juarez-Colunga E, Kelsey MM. Body composition and markers of cardiometabolic health in transgender youth compared to cisgender youth. J Clin Endocrinol Metab 2019;
101. Millington K, Finlayson C, Olson-Kennedy J, Garofalo R, Rosenthal SM, Chan YM. Association of High-Density Lipoprotein Cholesterol With Sex Steroid Treatment in Transgender and Gender-Diverse Youth. JAMA Pediatr 2021; 175:520-521
102. Lee JY, Finlayson C, Olson-Kennedy J, Garofalo R, Chan YM, Glidden DV, Rosenthal SM. Low Bone Mineral Density in Early Pubertal Transgender/Gender Diverse Youth: Findings From the Trans Youth Care Study. Journal of the Endocrine Society 2020; 4:bvaa065
103. Mamoojee Y, Seal LJ, Quinton R. Transgender hormone therapy: understanding international variation in practice. The Lancet Diabetes & Endocrinology 2017; 5:243-246
104. Angus LM, Nolan BJ, Zajac JD, Cheung AS. A systematic review of antiandrogens and feminization in transgender women. Clinical endocrinology 2021; 94:743-752
105. Bonne C, Raynaud JP. Mode of spironolactone anti-androgenic action: inhibition of androstanolone binding to rat prostate androgen receptor. Mol Cell Endocrinol 1974; 2:59-67
106. Fagart J, Hillisch A, Huyet J, Bärfacker L, Fay M, Pleiss U, Pook E, Schäfer S, Rafestin-Oblin ME, Kolkhof P. A new mode of mineralocorticoid receptor antagonism by a potent and selective nonsteroidal molecule. J Biol Chem 2010; 285:29932-29940
107. Kossor DC, Kominami S, Takemori S, Colby HD. Role of the steroid 17 alpha-hydroxylase in spironolactone-mediated destruction of adrenal cytochrome P-450. Mol Pharmacol 1991; 40:321-325
108. Stripp B, Taylor AA, Bartter FC, Gillette JR, Loriaux DL, Easley R, Menard RH. Effect of spironolactone on sex hormones in man. J Clin Endocrinol Metab 1975; 41:777-781
109. Prior JC, Vigna YM, Watson D. Spironolactone with physiological female steroids for presurgical therapy of male-to-female transsexualism. Arch Sex Behav 1989; 18:49-57
110. Yemisci A, Gorgulu A, Piskin S. Effects and side-effects of spironolactone therapy in women with acne. Journal of the European Academy of Dermatology and Venereology 2005; 19:163-166
111. Helfer EL, Miller JL, Rose LI. Side-effects of spironolactone therapy in the hirsute woman. The Journal of Clinical Endocrinology & Metabolism 1988; 66:208-211
112. Weill A, Cadier B, Nguyen P, Coste J. Exposition prolongée à de fortes doses d'acétate de cyprotérone et risque de méningiome chez la femme. Etude pharmaco-épidémiologique de cohorte à partir des données du SNDS 2019;
113. Nota NM, Wiepjes CM, De Blok CJ, Gooren LJ, Peerdeman SM, Kreukels BP, Den Heijer M. The occurrence of benign brain tumours in transgender individuals during cross-sex hormone treatment. Brain 2018; 141:2047-2054
114. Regidor P, Speer K, Regidor M, Schindler E. Long-term side-effects following cyproterone acetate containing therapy in gynecology. Zentralblatt fur Gynakologie 2000; 122:268-273
115. Neyman A, Fuqua JS, Eugster EA. Bicalutamide as an androgen blocker with secondary effect of promoting feminization in male-to-female transgender adolescents. Journal of Adolescent Health 2019; 64:544-546
116. Chiriacò G, Cauci S, Mazzon G, Trombetta C. An observational retrospective evaluation of 79 young men with long-term adverse effects after use of finasteride against androgenetic alopecia. Andrology 2016; 4:245-250
117. Thole Z, Manso G, Salgueiro E, Revuelta P, Hidalgo A. Hepatotoxicity induced by antiandrogens: A review of the literature. Urol Int 2004; 73:289-295
118. Spratt DI, Stewart II, Savage C, Craig W, Spack NP, Chandler DW, Spratt LV, Eimicke T, Olshan JS. Subcutaneous injection of testosterone is an effective and preferred alternative to intramuscular injection: demonstration in female-to-male transgender patients. The Journal of Clinical Endocrinology & Metabolism 2017; 102:2349-2355
119. Olson J, Schrager SM, Clark LF, Dunlap SL, Belzer M. Subcutaneous testosterone: an effective delivery mechanism for masculinizing young transgender men. LGBT health 2014; 1:165-167
120. Wilson DM, Kiang TK, Ensom MH. Pharmacokinetics, safety, and patient acceptability of subcutaneous versus intramuscular testosterone injection for gender-affirming therapy: a pilot study. The Bulletin of the American Society of Hospital Pharmacists 2018; 75:351-358
121. Kaminetsky J, Jaffe JS, Swerdloff RS. Pharmacokinetic profile of subcutaneous testosterone enanthate delivered via a novel, prefilled single-use autoinjector: a phase ii study. Sexual medicine 2015; 3:269-279

122. Rothman MS, Iwamoto SJ. Bone Health in the Transgender Population. Clin Rev Bone Miner Metab 2019; 17:77-85
123. Rosen HN, Hamnvik O-PR, Jaisamrarn U, Malabanan AO, Safer JD, Tangpricha V, Wattanachanya L, Yeap SS. Bone densitometry in transgender and gender non-conforming (TGNC) individuals: 2019 ISCD official position. Journal of Clinical Densitometry 2019; 22:544-553
124. Valentine A, Nokoff N, Bonny A, Chelvakumar G, Indyk J, Leibowitz S, Nahata L. Cardiometabolic Parameters Among Transgender Adolescent Males on Testosterone Therapy and Body Mass Index-Matched Cisgender Females. Transgender health 2021; 6:369-373
125. Clark BA, Veale JF, Townsend M, Frohard-Dourlent H, Saewyc E. Non-binary youth: Access to gender-affirming primary health care. International Journal of Transgenderism 2018; 19:158-169
126. Kanj RV, Conard LAE, Corathers SD, Trotman GE. Hormonal contraceptive choices in a clinic-based series of transgender adolescents and young adults. Int J Transgend 2019; 20:413-420
127. Krempasky C, Harris M, Abern L, Grimstad F. Contraception across the transmasculine spectrum. American journal of obstetrics and gynecology 2020; 222:134-143
128. Ahmad S, Leinung M. The response of the menstrual cycle to initiation of hormonal therapy in transgender men. Transgender health 2017; 2:176-179
129. Colebunders B, Brondeel S, D'Arpa S, Hoebeke P, Monstrey S. An Update on the Surgical Treatment for Transgender Patients. Sex Med Rev 2017; 5:103-109
130. Berli JU, Knudson G, Fraser L, Tangpricha V, Ettner R, Ettner FM, Safer JD, Graham J, Monstrey S, Schechter L. What Surgeons Need to Know About Gender Confirmation Surgery When Providing Care for Transgender Individuals: A Review. JAMA Surg 2017; 152:394-400
131. Nunes-Moreno M, Buchanan C, Cole FS, Davis S, Dempsey A, Dowshen N, Furniss A, Kazak AE, Kerlek AJ, Margolis P, Pyle L, Razzaghi H, Reirden DH, Schwartz B, Sequeira GM, Nokoff NJ. Behavioral Health Diagnoses in Youth with Gender Dysphoria Compared with Controls: A PEDSnet Study. J Pediatr 2021;
132. Becerra-Culqui TA, Liu Y, Nash R, Cromwell L, Flanders WD, Getahun D, Giammattei SV, Hunkeler EM, Lash TL, Millman A, Quinn VP, Robinson B, Roblin D, Sandberg DE, Silverberg MJ, Tangpricha V, Goodman M. Mental Health of Transgender and Gender Nonconforming Youth Compared With Their Peers. Pediatrics 2018; 141
133. Connolly MD, Zervos MJ, Barone CJ, 2nd, Johnson CC, Joseph CL. The Mental Health of Transgender Youth: Advances in Understanding. J Adolesc Health 2016; 59:489-495
134. Reisner SL, Vetters R, Leclerc M, Zaslow S, Wolfrum S, Shumer D, Mimiaga MJ. Mental health of transgender youth in care at an adolescent urban community health center: a matched retrospective cohort study. J Adolesc Health 2015; 56:274-279
135. Almeida J, Johnson RM, Corliss HL, Molnar BE, Azrael D. Emotional distress among LGBT youth: the influence of perceived discrimination based on sexual orientation. J Youth Adolesc 2009; 38:1001-1014
136. Warrier V, Greenberg DM, Weir E, Buckingham C, Smith P, Lai MC, Allison C, Baron-Cohen S. Elevated rates of autism, other neurodevelopmental and psychiatric diagnoses, and autistic traits in transgender and gender-diverse individuals. Nat Commun 2020; 11:3959
137. Grossman AH, D'Augelli AR. Transgender youth and life-threatening behaviors. Suicide Life Threat Behav 2007; 37:527-537
138. James SE, Herman, J. L., Rankin, S., Keisling, M., Mottet, L., & Anafi, M. The Report of the 2015 U.S. Transgender Survey. Washington, DC: National Center for Transgender Equality 2016;
139. Hendricks ML, Testa RJ. A conceptual framework for clinical work with transgender and gender nonconforming clients: An adaptation of the Minority Stress Model. Professional Psychology: Research and Practice 2012; 43:460-467
140. Chodzen G, Hidalgo MA, Chen D, Garofalo R. Minority stress factors associated with depression and anxiety among transgender and gender-nonconforming youth. Journal of Adolescent Health 2019; 64:467-471
141. Kozee HB, Tylka TL, Bauerband LA. Measuring transgender individuals' comfort with gender identity and appearance: Development and validation of the Transgender Congruence Scale. Psychology of Women Quarterly 2012; 36:179-196
142. Durwood L, McLaughlin KA, Olson KR. Mental Health and Self-Worth in Socially Transitioned Transgender Youth. J Am Acad Child Adolesc Psychiatry 2017; 56:116-123 e112
143. Singh AA, Meng SE, Hansen AW. "I am my own gender": Resilience strategies of trans youth. Journal of Counseling & Development 2014; 92:208-218
144. Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. Pediatrics 2020; 145
145. Rider GN, McMorris BJ, Gower AL, Coleman E, Eisenberg ME. Health and Care Utilization of Transgender and Gender Nonconforming Youth: A Population-Based Study. Pediatrics 2018; 141
146. Skagerberg E, Di Ceglie D, Carmichael P. Brief Report: Autistic Features in Children and Adolescents with Gender Dysphoria. J Autism Dev Disord 2015; 45:2628-2632

147. Hisle-Gorman E, Landis CA, Susi A, Schvey NA, Gorman GH, Nylund CM, Klein DA. Gender Dysphoria in Children with Autism Spectrum Disorder. LGBT Health 2019; 6:95-100
148. Strang JF, Kenworthy L, Dominska A, Sokoloff J, Kenealy LE, Berl M, Walsh K, Menvielle E, Slesaransky-Poe G, Kim KE, Luong-Tran C, Meagher H, Wallace GL. Increased gender variance in autism spectrum disorders and attention deficit hyperactivity disorder. Arch Sex Behav 2014; 43:1525-1533
149. van der Miesen AIR, de Vries ALC, Steensma TD, Hartman CA. Autistic Symptoms in Children and Adolescents with Gender Dysphoria. J Autism Dev Disord 2018; 48:1537-1548
150. de Vries AL, Noens IL, Cohen-Kettenis PT, van Berckelaer-Onnes IA, Doreleijers TA. Autism spectrum disorders in gender dysphoric children and adolescents. J Autism Dev Disord 2010; 40:930-936
151. Thrower E, Bretherton I, Pang KC, Zajac JD, Cheung AS. Prevalence of autism spectrum disorder and attention-deficit hyperactivity disorder amongst individuals with gender dysphoria: a systematic review. Journal of autism and developmental disorders 2020; 50:695-706
152. Shumer DE, Reisner SL, Edwards-Leeper L, Tishelman A. Evaluation of Asperger Syndrome in Youth Presenting to a Gender Dysphoria Clinic. LGBT Health 2016; 3:387-390
153. Grossman AH, D'augelli AR, Frank JA. Aspects of psychological resilience among transgender youth. Journal of LGBT youth 2011; 8:103-115
154. Watson RJ, Veale JF, Saewyc EM. Disordered eating behaviors among transgender youth: Probability profiles from risk and protective factors. Int J Eat Disord 2017; 50:515-522
155. Simons L, Schrager SM, Clark LF, Belzer M, Olson J. Parental support and mental health among transgender adolescents. J Adolesc Health 2013; 53:791-793
156. Olson KR, Durwood L, DeMeules M, McLaughlin KA. Mental Health of Transgender Children Who Are Supported in Their Identities. Pediatrics 2016; 137:e20153223
157. Delozier AM, Kamody RC, Rodgers S, Chen D. Health Disparities in Transgender and Gender Expansive Adolescents: A Topical Review From a Minority Stress Framework. Journal of Pediatric Psychology 2020; 45:842-847
158. Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. Pediatrics 2020; 145:e20191725
159. van der Miesen AIR, Steensma TD, de Vries ALC, Bos H, Popma A. Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared With Cisgender General Population Peers. J Adolesc Health 2020; 66:699-704
160. Sorbara JC, Chiniara LN, Thompson S, Palmert MR. Mental Health and Timing of Gender-Affirming Care. Pediatrics 2020:e20193600
161. Gao Y, Maurer T, Mirmirani P. Understanding and Addressing Hair Disorders in Transgender Individuals. Am J Clin Dermatol 2018; 19:517-527
162. Yeung H, Kahn B, Ly BC, Tangpricha V. Dermatologic conditions in transgender populations. Endocrinology and Metabolism Clinics 2019; 48:429-440
163. Ginsberg B. Dermatologic care of the transgender patient. Vol 3: Elsevier; 2017:65-67.
164. Julian JM, Salvetti B, Held JI, Murray PM, Lara-Rojas L, Olson-Kennedy J. The Impact of Chest Binding in Transgender and Gender Diverse Youth and Young Adults. J Adolesc Health 2021; 68:1129-1134
165. Baral SD, Poteat T, Strömdahl S, Wirtz AL, Guadamuz TE, Beyrer C. Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. Lancet Infect Dis 2013; 13:214-222
166. Herbst JH, Jacobs ED, Finlayson TJ, McKleroy VS, Neumann MS, Crepaz N. Estimating HIV prevalence and risk behaviors of transgender persons in the United States: a systematic review. AIDS Behav 2008; 12:1-17
167. Becasen JS, Denard CL, Mullins MM, Higa DH, Sipe TA. Estimating the Prevalence of HIV and Sexual Behaviors Among the US Transgender Population: A Systematic Review and Meta-Analysis, 2006-2017. Am J Public Health 2019; 109:e1-e8
168. Bowen AE, Staggs S, Kaar J, Nokoff N, Simon SL. Short sleep, insomnia symptoms, and evening chronotype are correlated with poorer mood and quality of life in adolescent transgender males. Sleep Health 2021; 7:445-450
169. Jones BA, Arcelus J, Bouman WP, Haycraft E. Sport and Transgender People: A Systematic Review of the Literature Relating to Sport Participation and Competitive Sport Policies. Sports Med 2017; 47:701-716
170. Hartman-Munick SM, Silverstein S, Guss CE, Lopez E, Calzo JP, Gordon AR. Eating disorder screening and treatment experiences in transgender and gender diverse young adults. Eat Behav 2021; 41:101517
171. Coelho JS, Suen J, Clark BA, Marshall SK, Geller J, Lam PY. Eating Disorder Diagnoses and Symptom Presentation in Transgender Youth: a Scoping Review. Curr Psychiatry Rep 2019; 21:107
172. Glidden D, Bouman WP, Jones BA, Arcelus J. Gender Dysphoria and Autism Spectrum Disorder: A Systematic Review of the Literature. Sex Med Rev 2016; 4:3-14
173. Olson-Kennedy J, Chan YM, Rosenthal S, Hidalgo MA, Chen D, Clark L, Ehrensaft D, Tishelman A, Garofalo R. Creating the Trans Youth Research Network: A Collaborative Research Endeavor. Transgender health 2019; 4:304-312

174. Reardon S. The largest study involving transgender people is providing long-sought insights about their health. Nature 2019; 568:446-450
175. Flentje A, Heck NC, Brennan JM, Meyer IH. The relationship between minority stress and biological outcomes: A systematic review. Journal of Behavioral Medicine 2019:1-22
176. Ditmars HL, Logue MW, Toomey R, McKenzie RE, Franz CE, Panizzon MS, Reynolds CA, Cuthbert KN, Vandiver R, Gustavson DE. Associations between depression and cardiometabolic health: A 27-year longitudinal study. Psychological Medicine 2021:1-11
177. Streed Jr CG, Beach LB, Caceres BA, Dowshen NL, Moreau KL, Mukherjee M, Poteat T, Radix A, Reisner SL, Singh V. Assessing and addressing cardiovascular health in people who are transgender and gender diverse: A scientific statement from the American heart association. Circulation 2021; 144:e136-e148
178. Rosenthal SM. Approach to the Patient: Transgender Youth: Endocrine Considerations. J Clin Endocrinol Metab. 2014 2014;99:4379-4389.