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CPS Position Statement on An Affirming Approach to Caring for Transgender and Gender-diverse Youth: Part 2

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Introduction:

Hi! I'm Annaliese Beck-McKenzie and I use the pronouns she/her. I am a fourth-year medical student at the University of British Columbia. This PedsCases episode is the second of a two-part series based on the 2023 CPS Position Statement on an affirming approach to caring for transgender and gender-diverse youth (1). In the first part, we discussed the approach to gender diverse youth and diagnosing gender dysphoria. In today's episode, we will discuss gender affirming treatment options. Thanks to Dr. Ashley Vandermorris, Staff Physician in the Division of Adolescent Medicine at the University of Toronto SickKids hospital and lead author of the CPS statement, for her guidance in creating this podcast.

The main objectives today are to:

1. Discuss the use of hormone blocking therapy in gender diverse youth.
2. Discuss gender affirming hormones.
3. Briefly discuss gender affirming surgery options.
4. Apply your knowledge to a clinical case!

Case:

Let's get back to our case! Recall Avery, a 13-year-old who was assigned male at birth (AMAB) who uses the pronouns she/her and has expressed a consistent and marked gender incongruence; in your last appointment, you did a thorough HEEDSSS assessment and diagnosed her with gender dysphoria. Avery returns to your clinic today with her parents to begin to discuss options for gender affirming medical therapy. They tell you that they've heard a lot about hormone blockers. They ask: are these safe? What is the difference between hormone blockers and gender affirming hormones? What changes will Avery experience if she takes hormone blockers or gender affirming hormones? Are these changes reversible? What are the impacts on fertility? Before we answer these questions, let's discuss the basics.

Puberty Blockers:

That brings us to **objective 1: Discuss the use of hormone blocking therapy in gender diverse youth.** Hormone blockers, otherwise known as puberty blockers, are medications that modify the effect of endogenous sex steroid hormones. In doing so, these medications can suppress gendered experiences such as menses, erections, and pause or slow physical changes involved in puberty. This provides time for gender diverse youth to explore their gender identity without the additional pressures of pubertal changes.

Puberty blockers are not prescribed before the onset of puberty (Tanner 2) because prepubertal sex hormone levels are low, and the onset of puberty serves as an important time for exploration of gender identity.

We'll focus the most on GnRHa, such as leuprolide acetate, or Lupron, since these are the main puberty blockers used in both assigned sexes at birth. To start, let's quickly review the hypothalamic, pituitary, gonadal (HpG) axis. Recall that at the onset of puberty, the hypothalamus begins releasing GnRH in a pulsatile and surge manner, regulating the pattern of release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary (2). LH and FSH act on the gonads (in AMAB, testes, and in AFAB, ovaries), to regulate production of sex hormones such as testosterone and estrogen. GnRH pulsatility is key to the mechanism of GnRHa. Now you might be asking yourself: why do we use an agonist to suppress sex hormone production? The answer lies in GnRH pulsatility: when GnRH is constantly present, this inhibits sex steroid production from the gonads which rely on pulsatile secretion of GnRH. If started before the completion of pubertal development, GnRHa pause the progression of puberty (1). It is important to note that hormonal suppression is reversible and endogenous hormonal production will restart if hormone blockers are stopped.

GnRHa can be useful in gender affirming care as they:

- 1) Allow youth to explore their gender without the pressure of further physical changes in puberty.
- 2) Prevent irreversible development of secondary sex characteristics.
- 3) Allow for lower doses of gender affirming hormones should the patient pursue this in the future.
- 4) Additionally, for transgender youth, access to GnRHa has been associated with improved mental health outcomes and decreased odds of suicidal ideation across the lifespan.

GnRHa are administered as a depot injection every 4-12 weeks. Important side effects relate to the lack of exposure to endogenous sex steroids, which play a role in growth and bone density. If administered during the pubertal growth spurt, GnRHa can slow the rate of linear growth. This side effect is reversible with gender affirming hormones or resumption of endogenous sex steroid production, and final adult height is not affected by use of GnRHa. To promote bone health while puberty blockers are used, prescribers should advise weight bearing exercise, vitamin D, calcium, and consider baseline DEXA scanning. Another rare potential side effect is QT interval prolongation. If there is concern for this (e.g., using another medication that prolongs the QT interval), an ECG is recommended 1-2 months after initiating GnRHa.

You might be wondering how these risks translate into clinical practice. When used as monotherapy for an extended period of time (typically considered >2yrs), GnRHa may increase

the potential risks associated with the lack of sex hormone exposure. However, it is important to note that GnRHa are not meant to be used as monotherapy indefinitely; rather, they are meant to essentially provide time for the exploration of gender identity. At some point, GnRHa are stopped and/or a gender affirming sex hormone is introduced; thus patients are not deficient of protective sex steroids for prolonged periods of time. Also remember that if GnRHa are stopped, endogenous sex hormone production resumes within 6 months.

A common concern from opponents of gender affirming care is that hormone blockers in adolescents may lead to long term changes in cognitive function, but to date this is not supported by the research. There is also a lot of misinformation around the effects on fertility. Puberty blockers have no permanent effect on fertility; if stopped, fertility returns to the individual's baseline. However, since some individuals started on a puberty blocker may eventually wish to start gender-affirming hormones, which can permanently impact fertility, discussions about the option of fertility preservation should therefore happen prior to blocker initiation, as fertility preservation cannot always be initiated while on a blocker and some may not wish to stop their hormone blocker to pursue fertility preservation once a blocker has been started. Furthermore, for assigned males in early puberty, fertility may not have yet been reached. This may influence the timing of initiation of puberty blockers. More on fertility preservation later. Puberty blockers can also have some implications for gender affirming surgery in the future should patients pursue this. In AMAB, puberty blockers may lead to less scrotum tissue for future vaginoplasty, if desired; whereas in AFAB, hormone blockers may increase the surgical options for chest wall masculinization, if desired.

Some downsides to GnRHa include cost as well as the need to be taken on a schedule to avoid the resumption of puberty. Patients with a uterus may experience a surge bleed after the initial dose. In AMAB, on initiation of GnRHa, patients may experience a transient increase in the frequency of erections, but over time, GnRHa will reduce the frequency and duration of erections.

Some other potential side effects include injection site reactions (e.g., pain, redness, sterile abscess) and hormonal effects such as hot flashes and mood fluctuations initially as well as decreased libido.

Now that's a lot on GnRHa. Recall that they can be used to suppress puberty in both AMAB and AFAB. There are also other medications that can suppress gendered experiences specific to AFAB or AMAB youth.

First let's talk about menstrual suppression for AFAB. You might be familiar with these as contraceptives. We will discuss a brief overview of their uses for gender affirming care. Oral contraceptive pills, Depomedroxyprogesterone acetate injection, levonorgestrel-containing intrauterine device (LNG-IUD), and the progestin-only pill can be used as contraceptives as well as in the treatment of dysmenorrhea by reducing or stopping menstrual bleeds. These medications do not stop pubertal development. Additionally, they also contain female hormones, which may be distressing for some TGD youth.

Now let's discuss other medications used for AMAB. These include spironolactone and cyproterone acetate. Unlike GnRHa, which block the production of testosterone, these medications work differently. Spironolactone works by blocking the action, rather than the production, of testosterone. However, there may still be exposure to small amounts of testosterone which can result in some preserved sexual function. Spironolactone may slow the

progression of puberty but will not completely halt it. Spironolactone requires electrolyte monitoring due to the risk of electrolyte imbalances. Other side effects to consider are gynecomastia, which may be a desirable effect for some TGD youth. Spironolactone can also cause fatigue, mood fluctuations, decreased libido, headache, increased urination.

The third puberty blocking medication for AMAB is cyproterone acetate. This medication acts peripherally and centrally, and thus is more effective than spironolactone. Like spironolactone, cyproterone acetate may slow the progression of puberty but will not completely halt it. Cyproterone can contribute to mood fluctuations (more pronounced than for spironolactone), fatigue, decreased libido, bloating, and acne.

Unlike spironolactone, cyproterone acetate requires prolactin monitoring because in rare cases it can lead to hyperprolactinemia, especially when used alongside estrogen. This medication also has been associated with an increased risk of meningioma and hepatotoxicity and should be avoided in those with liver disease.

Gender Affirming Hormones:

Let's move on to objective 2: discuss gender affirming hormones. For some patients with significant, persistent formally diagnosed gender dysphoria, gender affirming hormones can be an important component of treatment by helping to facilitate physical features that align with one's gender identity. Psychological, medical, or psychosocial issues that interfere with treatment should be addressed before gender affirming hormone therapy (GAHT) is initiated in adolescents. When appropriately prescribed, GAHT has been shown to be associated with improved perceived well-being and mental health, decreased suicidality, and decreased body dissatisfaction. GAHT is safe for adolescents, however providers should be aware of potential side effects and long-term health implications, as well as recommended monitoring outlined by the Endocrine Society and WPATH-SOC8. Providers who do not feel equipped to provide GAHT should ensure timely referral to specialized centres.

Now, let's get into the details. For AFAB who wish to appear more masculine, testosterone esters can be prescribed. For AMAB who wish to appear more feminine, 17 β -estradiol can be used. Typically, starting doses are lower than adult doses, and doses are up-titrated over time to simulate pubertal progression.

Gender affirming hormones are considered partially reversible therapy because they cause both reversible and irreversible changes. Testosterone therapy irreversibly causes voice deepening, clitoral enlargement, body and facial hair growth, and, possibly, androgenetic alopecia. Reversible side effects include changes to body composition, increased libido, acne, mood fluctuations, and menstrual suppression. Once serum testosterone levels reach the adult range, menses is typically suppressed. In the meantime, GnRHa or other menstrual suppression agents can also be used.

Over time, estradiol causes irreversible breast tissue development. Reversible effects of estradiol include skin softening, changes in body composition (e.g., fat redistribution, decreased muscle mass), fewer spontaneous erections, and changes in body hair. It should be noted that estradiol monotherapy is insufficient to suppress endogenous testosterone production, thus patients typically use hormone blockers in conjunction with estradiol, unless gonadectomy is eventually pursued.

One important consideration is that both testosterone and estradiol therapy can irreversibly decrease fertility to an extent that is not yet known. This must be discussed with patients and a referral for fertility preservation should be made if the patient is interested in having biologically-related children in the future. Prescribers should also make clear that GAHT is not a method of contraception and contraceptives should be used during penile-vaginal intercourse.

Gender Affirming Surgery:

Let's now discuss objective 3. Describe options for gender affirming surgery. You may have heard the term "top surgery". This refers to chest wall masculinization, which involves bilateral mastectomy with male chest contouring. For AMAB who have not experienced any breast development despite at least 12 months of estrogen therapy, breast augmentation may be pursued (3). "Bottom surgery" can include creation of a phallus (for instance, clitoral release, metoidioplasty, phalloplasty) or hysterectomy with or without bilateral salpingo-oophorectomy for AFAB individuals, Vaginoplasty or orchiectomy are options for AMAB. It should be noted that "bottom surgery" is not offered to those less than 18 (4).

Case Recap and Conclusion:

Now I know that's been a whirlwind, so let's summarize for Avery and her family:

Medical options for gender affirming care include hormone blockers, gender affirming hormone therapies, and gender affirming surgery. The main difference between hormone blockers and gender affirming hormones is that hormone blockers suppress sex steroid production to decrease distressing gendered experiences during puberty, whereas gender affirming hormones replace sex steroids to promote development of physical features that align with one's gender identity. Before pursuing gender affirming hormones, hormone blockers can be started to allow for the exploration of gender identity without the pressure of distressing physical changes. If one experiences persistent gender dysphoria down the road, gender affirming surgery can be considered which can include "top" and/or "bottom" surgery. It is also important to emphasize that not all transgender and gender-diverse individuals pursue medical interventions, and this does not invalidate their transgender identities.

Avery decides that she would like to start a hormone blocker to pause the distressing physical changes she is experiencing with puberty. You explain that GnRHa, spironolactone, and cyproterone acetate are options for AMAB, along with risks and benefits of each. You give her information to read, and suggest she spend some time fully educating herself and discussing her thoughts with her parents. You see her for follow up in 1 month, and she shares that she would like to start Lupron depot, a GnRHa. You review with her again the potential side effects, including effects on bone density and linear growth. To mitigate these risks, you recommend weight bearing exercise, vitamin D, and calcium. Avery may also experience hormonal side effects such as hot flashes and mood fluctuations initially as well as decreased libido. You explain that although GnRHa do not permanently affect fertility, some patients choose to delay initiation for pursuit of fertility preservation. She feels comfortable starting GnRHa at this time but is interested in a fertility clinic referral in case she decides to pursue it down the road prior to starting 17 β -estradiol, a gender affirming hormone. Avery is not sexually active at this time, but you remind her that GnRHa do not provide STI protection nor

contraception. Given the cost of GnRHa, you request that Avery's parents ensure they are registered for their provincial pharmacare plan and look into their private insurance to ensure the Lupron Depot kit will be covered. Avery is able to both understand and appreciate these risks and benefits, and therefore indicates capacity to consent to initiation of this medication. Her parents are supportive of this decision. You write Avery a prescription and arrange a follow up appointment for the first injection.

Fast forward four months when you see Avery back in clinic. She feels happier now that the pressure of further pubertal changes has been removed. She is tolerating the Lupron depot well and denies side effects. For now, she is happy to continue exploring her gender and does not yet wish to start gender affirming hormones but may consider it in the future. Avery and her parents thank you for all that you've done to help improve Avery's wellbeing. You will continue seeing Avery for ongoing follow-up and support in her gender exploration process.

Thanks for taking the time to listen to this PedsCases podcast. We hope it helps you to understand the importance of timely access to gender affirming care and feel more comfortable discussing these options with patients. For more information on this topic, check out the CPS statement linked in the script. Until next time!

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