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Pubertal Blockade and Subsequent Gender Affirming Therapy: True, True and Unrelated?

Carly Guss, MD, MPH,

Divisions of Adolescent/Young Adult Medicine and Endocrinology, Boston Children's Hospital and Department of Pediatrics, Harvard Medical School, Boston, MA

Catherine M. Gordon, MD, MS

Department of Pediatrics, Baylor College of Medicine, Houston, TX

For youth who identify as transgender or are unsure and wish to explore possibilities before the development of permanent secondary sex characteristics, use of a gonadotropin releasing analogue (GnRHa) is a key medical option. Sometimes colloquially called "puberty blockers," they have been used safely for decades in children with precocious puberty,[1] endometriosis,[2] among other medical indications. Multiple professional societies now endorse pubertal blockade for youth with gender dysphoria.[3–4] Of recent, use of GnRHa has received attention due to legislated concerns regarding the medical and surgical management of transgender youth, including criminalizing the provision of this care in some states.[5] Without evidence, there has been the assumption circulating that GnRHa treatment leads to increased ultimate use of gender-affirming therapy (GAT) in transgender youth, and that prescription of a GnRHa inappropriately advances the decision to start GAT. A study in this issue of *JAMA Network Open* provides data to the contrary – that this therapy can be offered both for mental health and cosmetic benefits without the concern of increasing the subsequent use of GAT.[6]

An understanding of the medical management of a transgender child or adolescent is needed to appreciate the issues at hand. [3–4,7] A GnRHa is more potent than native GnRH and produces initial stimulation of pituitary gonadotrophs, with increased secretion of follicle-stimulating hormone and luteinizing hormone, and gonadal hormones, followed by down-regulation of the pituitary-gonadal axis. As sex steroid secretion is inhibited, the development of pubertal changes ceases. Pubertal blockade with a GnRHa "buys time" for a child or adolescent, pausing puberty and allowing for the exploration of gender identify. Initiated early in puberty, the GnRHa delays the development of irreversible pubertal changes and in some cases, avoids the need for subsequent surgery. GnRHa therapy is reversable; discontinuation leads to prompt resumption of the pituitary-gonadal axis. While pubertal blockade and GAT are often prescribed as complementary approaches, they are separate phases in transgender treatment.[3]

Corresponding Author: Catherine M. Gordon, MD, MS, Baylor College of Medicine, 1100 Bates Ave, Houston, TX 77030, catherine.gordon@bcm.edu, Phone: (713) 798-8334.

Through a retrospective cohort study of billing and pharmacy records, Nos and colleagues explored the timely question of whether GnRHa use was associated with subsequent use of GAT among transgender and gender-diverse adolescents.[6] They reviewed data between 2010-2018 from the US Military Healthcare System (MHS). Participants had at least two transgender-related encounters, with the first occurring between age 10-17, and at least one encounter after the participant's 14th birthday (the earliest a clinician would start GAT based using current guidelines). [3–4,7] The sample included 458 adolescents, with 71% assigned female at birth and 68% having an enlisted insurance sponsor. Younger patients (age 10-13) were more likely to start GnRHa therapy than older (age 14-17): 58% vs 14%. Younger patients were more likely to discontinue GnRHa therapy; 21.5% stopped all therapy within a year. Assigned males at birth were more likely to receive GnRHa than assigned females (29% vs. 16%) and there was no significant association between GnRHa use and subsequent GAT initiation. In fact, patients who were prescribed GnRHa were less likely to start GAT within 5 years of the first encounter than those who were not (84.3% vs. 92.8%). For clinicians, the take home point is that the prescription of a GnRHa did not imply the assured subsequent use of GAT. The findings suggest that clinicians can offer GnRHa therapy without the concern of influencing the future use of GAT. The decision to initiate GnRHa therapy represents an independent therapeutic decision for a clinician, ideally work in concert with a multidisciplinary team of both medical and mental health clinicians.[5]

Limitations of the study of Nos and colleagues merit discussion. They included younger children compared to earlier studies, a strength of the study, but as younger age was associated with higher GnRHa discontinuation rates, this could explain the finding. However, overall, few patients discontinued treatment. Data were also extracted from an administrative database that did not afford information on the reasons why a clinician initiated therapy or not, and why patients chose to continue or discontinue the treatment. Patients could have obtained prescriptions outside of the MHS that were not captured. However, the high costs out-of-pocket or through private insurance make this possibility unlikely. Lack of official approval for GAT coverage prior to 2016 may have influenced the decisions of patients or clinicians. Lastly, there are potential inherent biases among military medical personnel regarding gender identity, and potential reluctance to provide treatment. The reasons could be personal ones or due to lack of expertise. Replication of these results in a different study setting will be important to expand the generalizability of the current findings.

A question that arises in the course of transgender care is whether GnRHa therapy has long-term adverse medical consequences, including effects on bone health. Over half of an individual's bone density is acquired during adolescence, and transgender youth assigned male at birth are known to be at higher risk for low bone density even before GnRHa therapy.[7] Understanding whether GnRHa use impacts fracture risk will be the critical long-term question that must be answered in future studies. In pediatrics, we are often left needing to weigh risks versus benefits, with limited available evidence, and needing to prescribe medications off-label. For the adolescent who goes on to receive GAT, theoretically and anecdotally, reintroduction of sex steroids appears to mediate skeletal gains, especially for transgender males. In considering bone health and other health outcomes, optimizing bone density must be balanced with the known benefits

of GnRHa for gender dysphoria, including decreased suicidal ideation.[6] Concerns about skeletal losses become less significant in an adolescent with active suicidal ideations. While the significance of the risks may be unclear, there is strong evidence regarding the benefits of GnRHa in transgender youth: it can be a life-changing and lifesaving treatment for a vulnerable population who is at high risk for anxiety, depression, and suicide.[4–5,7]

The treatment decisions for transgender youth can be complex, with many factors that need to be considered. The novel findings provided by the study of Nos and colleagues add to the growing body of work demonstrating that GnRHa therapy is a safe and necessary component of transgender care, especially for the child or adolescent with gender dysphoria.[6] Their results emphasize that use of GnRHa and subsequent GAT are different phases of treatment, and their use should be driven by independent decisions that a clinician makes separately. From a cosmetic standpoint, it is much easier to manage a patient if pubertal changes have only just begun to develop, and gender dysphoria subsides as the worry of continued development of secondary sex characteristics comes to a halt. We hope that an enhanced understanding of transgender medical management, including the separate phases of therapy, and how a GnRHa works therapeutically, will help to dispel myths. The study by Nos and colleagues is hopefully one step forward in that direction. One phase of transgender treatment does not and should not dictate the next phase, thereby enabling clinicians to individualize care. Perhaps, even moving away from the term “puberty blocker” and instead describing mechanistically and clinically how these agents work will help return the focus of gender care to what matters most: the health and wellness of the child or adolescent.

Conflict of Interest Disclosures:

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