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COMMENT

A comment from SIGIS, SIE and SIAMS: "Puberty blockers in transgender adolescents—a matter of growing evidence and not of ideology"

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The Italian Society of Gender, Identity and Health (SIGIS), together with the Italian Society of Endocrinology (SIE) and the Italian Society of Andrology and Sexual Medicine (SIAMS), supports the use of gonadotropin-releasing hormone agonist (GnRHa) to temporary suspend puberty in accurately evaluated transgender and gender diverse (TGD) adolescents by a multidisciplinary team.

TGD adolescents have a gender identity that differs from the assigned gender at birth. Being TGD is an expected aspect of human development, and all gender identities are possible variations of a person's sexual identity as strongly emphasized by the World Health Organization and the American Psychiatric Association [1, 2].

Some TGD adolescents may have distress because of their gender incongruence, both psychological and physical [2]. Psychological distress seems to derive largely from living in contact with social prejudice and stigma of those who do not recognize the existence of gender variance as a normal expression of the wide spectrum, in which gender identities can develop [3]. Stigma is present also within healthcare as TGD people still face too many barriers in accessing care and have to confront with professionals who are not properly trained on gender care issues and therefore do not respond properly to TGD people needs [3]. Also, some evidence suggests that exposure to conversion therapy substantially increases the likelihood a transgender adolescent will attempt suicide and run away [4].

Physical intense distress may arise from puberty's physical changes that develop in an undesired/unwanted direction: For example, growth of facial and body hair, voice deepening and growth of genitalia, in those identified as male at birth, and breast development or onset of menses, in those identified as female at birth, can cause intense dysphoria in many TGD adolescents [2].

For both these reasons (minority stress and body related physical distress), TGD adolescents are a psychologically more vulnerable population with reported higher risk for anxiety and depression, self-harm, and suicidality [5]. Furthermore, psychological vulnerabilities and psychopathologies seem to have onset or worsen during puberty, a particularly challenging phase of life, where the distress of having to confront with unwanted (and out of control) bodily pubertal modifications plays an important role in psychological impairment.

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To reduce the abovementioned psychological and physical distress, in addition to buying time and creating rest to further explore one's gender affirming path, the use of GnRHa represents a valuable solution. Historically, the use of GnRHa in TGD adolescents was firstly introduced in the Netherlands in the late 1980 s by psychologist Peggy Cohen-Kettenis and endocrinologist Henriette Delemarre and is therefore also known as the "Dutch Protocol." In general, GnRHa medication is given as injections, either monthly or every three months. The goal of GnRHa administration in TGD adolescents is to reversibly suspend development of secondary sex characteristics that are not consistent with the adolescent's experienced gender. Their use within TGD adolescent care allows to extend the assessment phase in carefully selected TGD adolescents that satisfy specific clinical criteria. To this regard and according to international recommendations [5–7], it is important to underline that GnRHa are aimed at TGD adolescents (and never children) that have reached at least Tanner Stage 2 in light of the stability of gender identity starting from the pubertal age. Moreover, criteria for treatment require gender incongruence to be marked and sustained over time and the TGD adolescent to show emotional and cognitive maturity to provide informed consent for treatment. Furthermore, TGD adolescents must be informed about the potential loss of fertility and about the available options to preserve fertility [5, 8]. Suspending puberty could allow TGD adolescents to "buy time" and reflect in a more conscious way regarding gender identity and, more importantly, about further medical gender affirming steps with irreversible effects (gender affirming hormonal treatments or surgery). Moreover, the use of GnRHa is demonstrated to reduce the adolescents' distress for pubertal physical changes. Importantly, follow-up studies to date show that treatment with GnRHa can significantly reduce behavioral and emotional problems and suicidal ideation, as well as improve general psychological functioning in treated adolescents [9]. Some possible short-term physical symptoms, such as headaches, hot flashes, and fatigue, may be observed as a result of sex steroids withdrawal [10]. Regarding long-term effects, the main concerns may be related to the potential decrease in bone mineral density (BMD), interfering with the normal pubertal bone mass increment. The available literature [11, 12] demonstrates the BMD z-scores decreased during GnRHa treatment, but increased during gender-affirming hormone treatment, even though the catch up of bone mineral accrual may be incomplete. Lean body mass decreased during the first year of treatment in TGD youth, whereas fat tissue significantly increased. No sustained abnormalities of liver function or creatinine were encountered [13, 14]. Concerning cardiovascular issue, increase in blood pressure (BP), possibly due to estrogen depletion, was reported, but reversible upon cessation of triptorelin. Furthermore, BP levels did not meet criteria for hypertension, and the induction of puberty with gender-affirming testosterone treatment may restore pressure [15, 16]. Moreover, data about cardiovascular safety of gender affirming hormonal treatments suggest an increased risk of subclinical atherosclerosis in adults transgender AFAB but not in transgender AMAB, but additional studies are warranted [17, 18]. According to a recent multicenter study, there is no statistically significant difference in the odds of any cardiometabolic-related diagnosis in unadjusted or adjusted for GnRHa alone (without estradiol or testosterone) [19].

During this treatment, information on the gonadal axis suppression can be obtained through gonadotropin and sex steroids measurement, even if there is insufficient evidence for a specific monitoring scheme [6]. Thus, for all the above reasons, a close clinical, laboratory and instrumental (especially bone densitometry) monitoring of TGD adolescents during GnRHa treatment is highly recommended, following the Endocrine Society suggested clinical protocol [6].

At present, the use of GnRHa for TGD adolescents has been endorsed in the Standards of Care of the World Professional Association for Transgender Heath (WPATH) since their fifth edition in 1998 and by multiple medical societies, in particular by the Endocrine Society since 2009 [20, 21]. Currently, it is supported by international guidelines and recommendations that have been subscribed at a national level by several dedicated scientific societies, such as SIGIS, SIAMS, SIE, Italian Society of Pediatric Endocrinology and Diabetology (SIEDP) and Italian Observatory of Gender Identity (ONIG).

Despite this treatment option has currently become common practice in most gender identity clinics around the Western world, the use of GnRHa for TGD adolescents is still controversial and has not been endorsed worldwide [22]. In some cases, this treatment has been criticized as being experimental; however, possible negative consequences of not offering any medical option should also be considered. In this respect, the use of GnRHa was approved by the Italian Medicines Agency (AIFA), responsible for the regulatory activity of pharmaceuticals in Italy (determination No. 21,756/2019). Moreover, the use of GnRHa received a favorable opinion from the Italian National Committee of Bioethics (CNB) on July 13, 2018. We must stress-out that this medical intervention should be limited to those TGD adolescents that fulfill criteria for GnRHa and following a multidisciplinary and individualized evaluation performed by experienced gender teams as described in the determination by AIFA.

In conclusion, the use of GnRHa has so far proven to be a valuable medical option to be offered to TGD adolescents. At the same time, in view of the complex medical and

psychological intertwining of these interventions, their use within gender affirming paths needs to be supported on evidence based and clinical and scientific knowledge. Conversely, the dissemination of incorrect information, for example using an ideological and journalistic language (e.g., sex-changing treatments in young TGD people, acting against the law of nature), risks to damage the possibility of access gender affirming paths for young TGD people. This may have severe negative consequences on their psychological functioning and physical health both in the short and long terms. In fact, it has widely been described how accessing health care is associated with improvement of psychological functioning and decrease in suicidality in a vulnerable population. The task of professionals is, therefore, to spread a culture linked to transgender health issues based on scientific evidence and not on prejudice.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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