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Chapter

Effects of Hypothalamic Blockers in the Treatment of Gender Dysphoria in Preadolescence: Medical and Psychological Implications of Taking Care

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Abstract

Gender identity does not always develop in line with biological sex. Gender dysphoria at young age implies a strong incongruence between gender identity and the assigned sex; the rejection of one's sexual attributes and the desire to belong to the opposite sex; and a significant clinical suffering or impaired individual functioning in life spheres. The purpose of this chapter is a narrative review of the literature available on puberty suppression therapy through GnRH analogues. Biological puberty provides intense suffering to the adolescent with gender dysphoria who does not recognize himself in his own body. These drugs suppress the production of endogenous gametes and sex hormones. Although the effects of therapy are reversible, and biological development resumes spontaneously once the medication is stopped, the administration of GnRH analogues at a young age has fueled a scientific debate on the matter of the ethics of pharmacological intervention with minors. In conclusion, the studies considered show that GnRH analogues do not have long-term harmful effects on the body; prevent the negative psychosocial consequences associated with gender dysphoria in adolescence (suicidal ideation and attempts, self-medication, prostitution, self-harm); improve the psychological functioning of young transsexuals; and are diagnostic tools that allow adolescents to buy time to explore their gender identities.

Keywords: gender dysphoria, puberty suppression, GnRH analogues, preadolescence, AMAB, AFAB

1. Introduction

Gender identity was first defined by Stoller as “a complex system of beliefs that everyone has about himself, that is, his own sense of masculinity or femininity” [1]. According to the current binary system, which rigidly distinguishes male and female, the common expectation is that gender identity in children and adolescents

develops in line with biological sex [2]. However, the developmental trajectories of gender identity are manifold. Only recently has a theorization of gender identity begun as a fluid dimension of the self, in which the boundaries between masculine and feminine are blurred, and of which diversified manifestations are possible [2]. In the case of young gender variants, interests and attitudes do not conform to the social stereotypes of masculinity and femininity [3]. If the gender variance is associated with clinically significant suffering, for which the young person shows a rejection of their sexual attributes and the desire to belong to the other gender, then it is gender dysphoria [4]. Gender dysphoria is a clinical condition and requires specialist intervention, which includes psychological care of the young person and the family, associated with targeted medical and pharmacological treatment [5]. Biological puberty generates severe suffering for adolescents with gender dysphoria who do not recognize themselves in their bodies and can interfere with psychological functioning and individual well-being. Drug therapies are currently available to alleviate the psychological distress associated with gender dysphoria. Suppression of biological puberty involves the administration of gonadotropin-releasing hormone (GnRH) analogues that disrupt the endogenous production of gametes and sex hormones, arresting the development of secondary sexual attributes [5–7]. However, the question of early pharmacological intervention with adolescents with gender dysphoria is still the subject of debate among professionals in the field, and further investigations are needed to better understand the benefits and risks associated with the therapy.

2. Puberty suppression

Hypothalamic blockers have been used in the treatment of children and adolescents with central precocious puberty since 1981. Empirical studies demonstrate the efficacy and long-term safety of similar drugs, such as gonadotropin-releasing hormone (GnRH) [8]. In 2009, the Endocrine Society published guidelines for the treatment of adolescents with gender dysphoria, recommending suppression of puberty with hypothalamic blocking drugs for patients who have reached Tanner stages 2–3 (Table 6 and Table 7 in the appendix) and who meet the eligibility criteria (further detailed below), assigning pediatricians to care for children with gender dysphoria [6]. The World Professional Association for Transgender Health also follows the Endocrine Society guidelines for the treatment of children and adolescents, and published the seventh edition of the Standards of Care [7]. Adolescents with gender dysphoria often consider the physical changes associated with puberty to be unsustainable [6, 9]. Girls experience breast appearance, followed by an increase in breast volume and fat mass. Breast growth is also associated with accelerated height development, with menarche usually occurring 2 years later. In boys, the first physical change is the growth of the testicles that reach a volume of at least 4 ml. Starting from a testicular volume of 10 ml, daily testosterone levels increase, resulting in virilization of the physical appearance. Physical changes in pubertal development are the consequence of the maturation of the hypothalamus-pituitary-gonadal axis and the development of secondary sexual characteristics [10]. According to clinical practice guidelines, transgender and gender non-conforming (TGNC) young people can undergo puberty suspension procedures, with the administration of the synthetic hormones GnRH analogues that have the effect of suppressing the endogenous production of sex hormones [6, 7, 11, 12]. The suppression of the functioning of the gonads can be effectively achieved with the inhibition of gonadotropic secretion with

GnRH analogues and antagonists [6]. While similar drugs achieve this effect after a short period of administration, the antagonists immediately block pituitary secretions. Since long-acting antagonists are not available for use in pharmacotherapy, long-acting agonist analogues are the best treatment option.

2.1 Eligibility criteria for treatment with gonadotropin-releasing hormone GnRH analogues

According to the indications provided in the Standards of Care, withdrawal therapy can only be started at the beginning of puberty, which coincides with Tanner stages 2–3 [7], and a detectable presence of steroid sex hormones in the blood [5]. The treatment eligibility criteria proposed in the Standards of Care are shown in **Table 1** [7].

2.2 Pharmacology of GnRH analogues

GnRH is a decapeptide produced by the GnRH-secreting neuronal system, located in the preoptic area of the anterior hypothalamus and the mid-basal hypothalamus [13]. The axons of GnRH secreting neurons send projections to different areas of the nervous system. Some of these terminate in a ganglion of vascular buttons in the median eminence of the primary portal vessel, which releases GnRH into gonadotropic cells. GnRH reaches the anterior pituitary via the portal system and activates specific receptors, stimulating the production of gonadotropins, such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The gonadotropins thus synthesized regulate the activity of the gonads (reproductive organs), responsible for the production of gametes and female and male steroids. If GnRH is administered it results in rapid production of LH and less secretion of FSH. Since GnRH is a decapeptide, it is made up of a chain of 10 amino acids, joined together by a peptide bond. The amino acids of GnRH with crucial functions are found at positions 1, 2, 3, 6, and 10. A large number of analogues with agonistic or antagonistic properties have been synthesized, obtained by modifications of the amino acid chain. Triptorelin in GnRH analogue is mostly used to treat adolescents with gender dysphoria.

2.3 Pharmacodynamics

The single administration of GnRH agonists causes the secretion of LH and FSH in the pituitary cells, with the consequent regulation of the activity of the gonads

-
- The adolescent showed an intense and lasting pattern of gender non-compliance, or gender dysphoria (repressed or expressed);
-
- Gender dysphoria emerged or worsened at the onset of puberty;
-
- Any other coexisting psychological, social, medical problem (which could interfere with treatment) has been resolved, and the situation and functioning of the adolescent are sufficiently stable to be able to start therapy;
-
- The adolescent has provided informed consent, and especially when the patient has not reached the age to consent to medical procedures, the parents, or other caregivers or guardians, have consented to the treatment and/or are committed to offering support throughout the duration of the treatment process.
-

Table 1.
Eligibility criteria for treatment with GnRH analogues [7].

(stimulating or flare-up effect), [13]. Repeated administrations, on the other hand, result in the desensitization of gonadotropic cells and a reduction in the number of GnRH receptors on the membranes (down-regulation), with the effect of inhibiting the production of the hormones LH and FSH. The result is the blocking of the synthesis of androgens, estrogens, and male and female gametes. The mechanism of action of the antagonists is different since they act by blocking the pituitary receptors for endogenous GnRH and exogenous agonists, blocking access. Levels of LH and FSH decrease rapidly a few hours after administration. The drugs are effective in suppressing gonadotropic production, however, long-acting formulations have not yet been synthesized.

3. Criticism of pharmacological therapy

There are potential risks concerning the use of similar GnRH drugs, in relation to the effects that they can generate in the critical time interval for the development of the adolescent brain and bone mass. Although the therapy is safe in patients with central precocious puberty, these data are not generalizable to transsexual adolescents. For them, the treatment, in addition to starting later in development and continuing until the age of 15–16, is not followed by a process of inducing puberty of the biological sex, but of the opposite sex to that of birth [11]. These practices may also expose individuals to greater psychosocial difficulties as they remain physically prepubertal as peers reach puberty [5]. Therapy can thus contribute to more and more socially isolating transsexual adolescents, further increasing the risk of being victims of discrimination and bullying. Furthermore, adolescents could interpret the administration of hypothalamic blockers as a guarantee for future surgical sex reassignment, without engaging in other reflections on the matter [14]. They may risk feeling trapped in a certain life trajectory once puberty suppression therapy has begun, because family members and healthcare professionals, albeit in a benevolent way, may inadvertently reinforce a specific gender identity [12]. Furthermore, GnRH analogues are very expensive and not always reimbursed by health insurers [6, 9]. Progestins represent a less effective but more affordable alternative: they suppress gonadotropic secretion and exert a mild peripheral anti-androgen effect in boys; in girls, they suppress ovulation and progesterone production for long periods of time, with variable estrogen residues [15]. However, side effects such as disruption of adrenal functioning and bone growth are frequent at these doses of administration [6]. Therefore, when the patient can bear the costs of the therapy, the guidelines recommend proceeding with the administration of GnRH analogues, as they are safer and more effective [7].

4. Benefits of treatment with GnRH analogues

Empirical studies demonstrate the efficacy of GnRH analogue therapy in suppressing puberty in transgender adolescents. Schagen and colleagues found the efficacy of GnRH analogue therapy in suppressing puberty in trans adolescents: after 12 months of therapy, in 49 trans assigned female at birth (AFAB, mean age 13.6 years) adolescents, testicular development was halted with a reduction in volume, in 67 trans assigned male at birth (AMAB) adolescents, (mean age 14.2 years), menstruation was blocked and breast development regressed [16]. They share the belief that therapy is a way to allow patients to buy time in which they can mature

cognitively and emotionally, in order to better manage gender variance [17]. In addition, the timeliness of the intervention is fundamental: hypothalamic blockers are less effective in reducing secondary sexual attributes when taken when puberty is already advanced (Tanner stage 4 or 5), [18]. If administered in prepuberty, drugs reduce the number of operations required in the future for gender reassignment, including breast removal in MtoF transsexual individuals, facial and voice feminization procedures in FtoM individuals [9, 19]. The cartilage of the nose, jaw, and larynx (Adam's apple) is also less developed after treatment [9, 20]. Those who are in favor of early treatment emphasize the suffering of patients who have been treated as adults, the advantage of buying time in the diagnostic phase, and having a physical appearance more conforming to that of the desired gender [11]. Also in Italy, a group of psychologists and endocrinologists expert in gender identity issues has begun to question the use of analogous GnRH drugs, coming to the conclusion that they do not cause any sex change, which temporarily suspends the formation of secondary sexual characteristics and have reversible effects [21]. Early therapy does not initiate the transition phase, but allows the adolescent to explore their gender identity, preventing, in the case of "desistant" young people in whom gender dysphoria would tend to regress naturally, the possibility of undergoing treatments more irreversible such as therapies with gender-affirming hormones (GAH) [9, 18, 19]. Adolescents have the opportunity to explore their gender identity in greater tranquility, without having to worry about the development of secondary sexual attributes [22]. Therapy with hypothalamic blockers can be considered a diagnostic tool since it allows a greater understanding of the degree and persistence of adolescent distress [23] and improves the accuracy of the diagnosis itself [20].

Another advantage of the use of GnRH analogues is the reversibility of the treatment: when the patient, after having explored the role consistent with gender identity, no longer wishes to undergo sex reassignment therapies, therapy with GnRH analogues can be interrupted and normal pubertal physiological development resumes [6, 19]. Furthermore, in adolescents who are already biologically mature but are undecided about cross-sex hormone therapy, hypothalamic blockers can inhibit those physiological functions that are perceived as unpleasant, such as menstruation in girls and erections in boys, in the intervening period, until the actual decision [11]. Regarding the efficacy of the drugs, the suppression of the activation of the hypothalamic-pituitary-gonadal axis has been demonstrated, with a reduction in testicular volume, in the levels of gonadotropins and prepubertal steroid sex hormones [23].

4.1 Psychological effects of the drug

Some international scientific societies, such as the World Professional Association for Transgender Health-WPATH; the European Society of Endocrinology-ESE; the European Society for Pediatric Endocrinology-ESPE; and the Lawson Wilkins Pediatric Endocrine Society-LWPES, recommend treatment with blockers that can improve children's quality of life and social relationships since gender-variant adolescents can experience severe distress that can lead to suicide [21]. Studies showing an association between the suspension of puberty and a reduction in depression and anxiety are encouraging in this regard [11, 12]. A better psychosocial adaptation seems to be related to early intervention, as the physical aspect more conforming to that of the experienced gender, allows one to be better accepted as a member of the other sex than those who start treatment in adulthood [20, 24]. Two longitudinal

studies conducted by researchers from the medical centre of VU University in Amsterdam investigated the effectiveness of drug therapy with similar GnRH, in terms of psychological effects and drug tolerance. The first survey involved 70 transsexual adolescents [25]. The initiation of treatment was associated with reduced emotional and behavioral problems and an improvement in general functioning. However, the feelings of anger and anxiety remained stable even in a second measurement time before the start of cross-sex hormone therapy. The second research with 55 young transsexuals evaluated the long-term efficacy of the treatment protocol in subsequent times: before the start of therapy with GnRH analogues, at the time of induction of puberty with cross-sex hormones, 1 year after gender reassignment surgery [26]. By investigating psychological functioning and general well-being in areas such as social interactions and education or quality of life, the researchers showed that among young adults, gender dysphoria was attenuated, with improved psychological functioning following the beginning of gender-affirming medical interventions. Greater satisfaction with one's physical appearance was noted: the therapy had allowed an anatomical development that conformed to and not in contrast with one's gender identity. Furthermore, the psychological well-being level of the population was equal to or greater than that of the general population [26]. The results suggest that the origin of psychiatric symptoms may not be primarily psychiatric, but secondary to gender dysphoria, in particular, due to the development of secondary sexual attributes in the pubertal phase [26]. These results were replicated by a study conducted with young patients with gender dysphoria at Boston hospital [18]. Costa and colleagues [27] have evaluated the psychological functioning, measured with CGAS, in a sample of adolescents with gender dysphoria at different stages of care: after 6 months of psychological support; after 12 months of psychological support and six of treatment with similar GnRH; after 18 months of psychological support and 12 months of treatment with GnRH analogues using the Children's Global Assessment Scale (CGAS). The sample was divided into a group immediately eligible for treatment, and a group not immediately eligible for treatment. Young people immediately eligible for treatment had higher psychological functioning scores at the start of management and showed no significant improvement after 6 months of psychological support. Psychological functioning improved significantly after 12 months of treatment with GnRH analogues in young people immediately eligible for treatment, with results similar to those found in a sample of adolescents without psychological or psychiatric symptoms. On the other hand, in the group not immediately eligible for treatment, there was an improvement in functioning already after 6 months of psychological support. A 2011 study by the Dutch group evaluated psychological functioning by administering the Minnesota Multiphasic Inventory-2 (MMPI-2) and Minnesota Multiphasic Inventory-Adolescent (MMPI-A) in a group of adults and adolescents requiring reassignment of type. Compared to adolescents, a higher percentage of adults were in the clinically significant range of scores on the Paranoia scale (49.8% vs. 18.1%, $\chi^2(1) = 26.641$, $pb0.001$) and the Psychasthenia scale (36.9% vs. 13.3%, $\chi^2(1) = 16.662$, $pb0.001$), [28].

When adolescents and adults were compared for the number of total MMPI scales for which they achieved scores in the range of clinical significance, most adults (62.8%) had clinical relevance scores for two or more scales. Instead, most adolescents (67.5%) had clinical relevance scores for none or only one of the subscales ($\chi^2(2) = 24.198$, $pb0.001$). The authors speculate that the better functioning observed in adolescents compared to adults may also be associated with the timing of the assessment since they had not yet developed secondary sexual characteristics.

4.2 Negative psychosocial outcomes of untreated gender dysphoria in adolescence

Brain development patterns during puberty increase the likelihood of adopting risky behaviors, a typical characteristic of adolescents [29]. However, the decision to undertake a reassignment process is not immediate and usually derives from a deep-rooted desire already present years before the young person turns to specialized centres. Furthermore, given the presence of this variable of impulsivity, adolescents with gender dysphoria could react to the omission of care by adopting risky behaviors, such as prostitution [30] and self-harming behaviors, even going so far as to attempt suicide [31].

4.2.1 Harm reduction model

The Harm Reduction Model is configured as an alternative to the moral model and the disease model, focusing on the consequences of deviant behavior [30]. When it is no longer possible to work preventively and the young transsexual has already adopted risky behaviors, he is encouraged to reduce them by the mental health professional who provides him with information on the pros and cons of each type of conduct, in order to protect his health [30, 32].

4.2.2 Autolesionism, suicides' ideations and attempts

For many professionals who treat developmental gender dysphoria, the decision to administer GnRH analogues is based on the fear of a possible increased risk of suicide in untreated adolescents. In the literature, there is a greater risk of suicidal ideation and attempts among young transsexuals [31, 33–35]. Studies investigating suicidal risk factors in transgender and gender non-conforming youth (TGNC) have identified gender dysphoria, parental physical and verbal abuse, and body image concerns as predictors [36]. Research conducted in Europe and America shows that young people with gender dysphoria are more likely to have other coexisting mental health problems, resulting in anxiety, depression, and suicidal tendencies [12]. GnRH analogue therapy has been shown to reduce psychological distress in transsexual adolescents [25, 26], so it could be hypothesized that the administration of hypothalamic blockers can actually prevent the adoption of suicidal behaviors in the adolescent with gender dysphoria. Spack and colleagues (2012) examined a sample of 97 adolescents with gender dysphoria from the Gender Management Service (GeMS) between January 1998 and February 2010 [18]. The data collected indicate that among young people: 44.3% had a history of psychiatric diagnoses; 37.1% took psychiatric drugs; 21.6% had a history of self-injurious behavior. Specifically, 20 patients reported self-mutilation episodes, and nine had attempted suicide at least once. The authors found an improvement in psychological functioning after medical intervention, suggesting that the patient's psychiatric symptoms may be secondary to gender dysphoria. Grossman and D'Augelli investigated the ideas and suicide attempts in a group of 55 adolescents with gender dysphoria [31]. The results obtained indicate an association between suicidal risk and two aspects related to self-esteem: body weight and the perception of one's physical appearance by others. Transsexual people strive to change their bodies in order to be perceived externally in a way that is congruent with their gender identity [37]. The use of hypothalamic blockers to nullify the inconsistency between perceived gender and the development of secondary sexual attributes reduces the stress associated with gender role transition and provides the opportunity

to socially present oneself as a member of the opposite sex [38]. However, most adolescents with gender dysphoria do not have access to the care and resources to be able to achieve this state of self-congruence and satisfaction for their own bodies [31]. Therefore, age-appropriate medical treatment with GnRH analogues and hormones could prevent self-harming behaviors, ideas, and suicide attempts in young transsexuals. Indeed, when adequate treatment cannot be offered, some adolescents may react by making suicide attempts [30].

4.2.3 Automedication

Adolescents often prefer to buy hormones and blockers illegally rather than go to a specialized clinic, especially if the professional requires the fulfillment of many criteria to be able to administer the therapy [30]. If the doctor refuses to prescribe the therapy or to correct the dosage and way of taking it, young transsexuals will probably continue to obtain the drugs in unconventional ways. The risk of psychological, social, and behavioral complications is greater if the administration is not guided by a specialist [30]. The injection of potentially toxic, low-quality drugs without medical supervision could expose the adolescent to unsatisfactory physical outcomes and health-threatening medical conditions, such as HIV, AIDS, and hepatitis. Teens may also be given silicone injections, increasing the risk of infections or other complications (discolouration of surrounding tissues, inflammation and silicone-induced pulmonary embolism). Furthermore, involvement in illegal buying practices can have judicial consequences for young people, with repercussions in terms of social stigma and further involvement in the criminal justice system in adulthood [12, 39]. Those who come from geographic areas where gender adjustment treatments are not available often need to emigrate in order to receive appropriate medical treatment [39]. Often these are young illegal immigrants for whom prostitution remains the only option available to earn the money needed to pay for healthcare [40]. Baltieri and colleagues report two case reports of adolescents with gender dysphoria in Brazil who engaged in prostitution to obtain enough money to illegally buy cross-sex hormones, after being denied treatment because they were not reaching age, minimum sufficient [30]. Hormonal drugs were not given as there are no laws in Brazil regulating the medical treatment of young trans people.

4.2.4 Psychological issues

Denial of treatment has irreversible psychological effects on the psychosexual development of the adolescent since he will never be able to experience puberty in line with his own gender identity. Transsexual adolescents often suffer more from not being able to experience puberty of the desired sex than from the inability to experience puberty of the sex assigned at birth in case of treatment with similar GnRH [24]. Retrospective studies conducted with transsexual adults indicate that psychological problems, such as anxiety and depression, often emerge during puberty as a consequence of the distress associated with the development of secondary sexual attributes [24]. Psychopathologies secondary to gender dysphoria can, therefore, be prevented if we intervene in time [28]. Unfavorable outcomes of surgical gender reassignment in adults appear to be associated with late treatment rather than early intervention [41, 42]. Studies evaluating the psychological functioning of adults and transsexual adolescents from the same clinic also found improved functioning among adolescents who had been treated early with hormone therapy [28, 38, 43]. The poorer

psychological functioning in adults may result in part from the constant and lasting distress they have experienced throughout their lives. In fact, the omission of treatment can result in long-term psychosocial outcomes such as stigmatization and social isolation [24].

5. Atypical development with GnRH analogues

Given the effects of drugs on the body during treatment, the guidelines recommend monitoring the adolescent with auxological clinical evaluations (weight, height, body mass index, blood pressure, and Tanner stage) every 3–6 months, and evaluation hormones (LH, FSH, estradiol, testosterone, prolactin, and 25-OH vitamin D) to be repeated every 6–12 months for the first year of therapy [5].

5.1 Short-term collateral effects

Hypothalamic blockers are generally well tolerated, with the exception of possible hot flashes [23], fatigue, migraine, mood changes, injection pain, and abscesses [5]. Some cases of arterial hypertension following the administration of Triptorelin were observed in three male transsexual adolescents in a sample of 138 subjects [5, 44]; and in two treated patients, with complications in one out of two patients related to increased intracranial pressure, which resulted in a temporary interruption of treatment [45]. The increase in intracranial pressure is a very rare side effect, usually associated only with the analogue GnRH drug Leuprolide [46]. The consequences that the use of similar GnRH drugs can have on blood pressure require further investigation [11].

5.2 Long-term collateral effects

5.2.1 Fertility

From the available literature, it is noted that treatment with analogous GnRH has no negative effects on the fertility of younger patients who are treated before the age of 7 [47], indeed it seems to have a protective effect in patients with central precocious puberty [48]. In young male (biological sex) adolescents with gender dysphoria undergoing GnRH analogue therapy, sperm production and development of the reproductive system is insufficient for sperm cryopreservation [6]. However, sperm production can be induced by a spontaneous recovery in gonadotropin production after cessation of GnRH analogues, or by gonadotropin-stimulating treatment (associated with physical manifestations of testosterone production), [6].

5.2.2 Nervous system effects

The physiological reorganization of the central nervous system occurs during puberty, in particular the executive functions located in the prefrontal cortex develop [49]. What emerges from the studies conducted so far is that there are no undesirable effects on brain development for adolescents undergoing therapy with GnRH analogues and GAF: the brain functioning of young patients seems to replicate that of the general population [24]. No negative effects on executive function emerged in research [50]. However, further long-term investigations are needed to arrive at more conclusive data [11].

5.2.3 Effects on bones development

During puberty, bone mass increases, reaching its maximum density around 20–30 years of age [11]. Suspension of puberty in adolescence is associated with reduced bone mineral density (BMD) in adult men [6]. Some studies do not detect changes in BMD values during the period of administration of GnRH analogues [6]. Other data report stable values of bone mineral density during therapy, but with a decrease in zeta scores, and a resumption of bone mass accumulation at the start of cross-sex hormone therapy [23]. When BMD was assessed in the same adult sample, a delay in reaching peak bone mass was detected, since the loss of zeta scores was still partially present at the age of 22. William Malone, an American endocrinologist interested in puberty blockers, affirms that the drugs seem to halt the rapid increase in bone density, the expected rise that takes place typically in adolescence is delayed [51]. Van Coverden and colleagues observed an increase in bone mass in the long-term treatment of adolescents with gender dysphoria: during the administration of gender-affirming hormones (GAF) there is a recovery in bone mass accumulation following normal physiological development [52]. Therapy with GnRH analogues appears to initially reduce BMD, with a future normalization after the induction of puberty with cross-sex hormones. Dutch studies report a reduction of BMD during puberty suppression, with a subsequent increase at the start of GAH therapy and achieving a final BMD no different than that observed before initiating analogue [44, 53].

5.2.4 Metabolical effects

The first data on early hormone therapy in adolescents with gender dysphoria revealed an increase in fat mass and a decrease in lean mass, only during the first year of treatment with Triptorelin, followed by a restoration of normal values with the administration of GAF [23]. Effects on lipid and carbohydrate metabolism were absent in the sample examined. Evidence shows an increase in body mass index (BMI) [54], an increase in fat mass, and a reduction in lean mass [16] in trans adolescents taking GnRH analogues.

5.2.5 Effects on growth

Suppression of puberty can impair growth in trans adolescents AFAB and AMAB [6, 55]. Schagen and colleagues found a reduction in the rate of growth rate in the sample of trans adolescents analyzed [16]. This can be an advantage for trans AMAB adolescents, who are more likely to reach a height similar to the average female population. Growth reduction can also have side effects on bone development and metabolism [56]. Subsequent therapy with cross-sex hormones allows for manipulation of growth and the achievement of an almost normal height [23]. Since the expected height for trans AMAB adolescents is greater than the female average, it is possible to increase the dose of estrogen administered during therapy with GAF, to reduce the final height. On the contrary, for trans AFAB adolescents, treatment with GnRH analogues must be longer, before being able to administer androgens at the age of 16 [55]. To achieve maximum height, a slow introduction of androgens mimics an acceleration of growth typical of puberty, or one can proceed with the administration of oxandrolone, a growth-stimulating anabolic steroid [6].

5.2.6 Effects on venous circulation

Despite the lack of clear results, venous thromboembolism can be a complication of drugs, so early screening for thrombophilia is appropriate for those with a personal or family history of venous thromboembolism [6].

6. Ethical aspects

The biomedical ethics model, theorized by Beauchamp and Childress, is the main point of reference for the management of ethical problems in the clinical setting [57]. According to the authors, there are four prerequisites that healthcare and health professionals must abide by in clinical practice, which are autonomy, non-maleficence, beneficence, and justice.

6.1 Autonomy

Hormonal treatment in puberty is justified as it aims to satisfy the desire of adolescents who want to align biological sex with their gender identity. Respect for the autonomy of the young person and the decision to undergo therapy should be emphasized, as the same results are not achievable if the drugs are administered in adulthood, except with invasive operations [20]. Furthermore, to fully respect the autonomy of the child, it is essential to educate him to know the different treatment options for gender dysphoria, in order to allow an informed decision, regardless of geographic location or socioeconomic status. The exercise of autonomy in the decision-making process is based on the recognition of children's rights and the informed consent expressed by the adolescent and the family [58].

6.2 Non-maleficence

The principle of non-maleficence imposes the obligation not to inflict harm on the patient. Hypothalamic blockers are classified as a reversible treatment since they appear to be free of long-term side effects. The doctor who respects the principle of non-maleficence adopts a more holistic approach and considers not only the possible damage to the body but also any negative consequences on the emotional, social, and spiritual values. For many adolescents, the ability to reduce the distress associated with developing secondary sexual attributes is far more important than drug-induced fertility deprivation. In general, the arguments against the use of blockers are based on the concern that gender dysphoria in childhood may go into remission in adolescence [59, 60]; on the impossibility of making a certain diagnosis of gender dysphoria in developmental age given the variability of gender identity in childhood and adolescence [17, 33]; and on the lack of knowledge of the long-term effects on the organism and psychological functioning [60, 61]. Furthermore, therapy can inhibit the spontaneous formation of a compliant gender identity, which sometimes develops through the "gender crisis" [62], and reduce libido, negatively affecting the adolescent's sexual experiences and limiting exploration of one's sexual orientation [17, 33]. Finally, for trans adolescents AMAB, the arrest of the development of the penis and testicles reduces the amount of skin tissue needed to perform a better vaginoplasty [63]. According to Giordano, the ethics of puberty suppression therapy

depend not only on the balance of risks and benefits of the treatment but also on the evaluation of the consequences of the omission of treatment [39]. Health professionals must consider the long-term implications on the body (invasiveness of surgery), and the psychological and social/relational risks (self-loathing, social integration, and suicide risk).

6.3 Beneficence

Given the variability in the persistence of gender dysphoria from childhood to adulthood, it is not easy to establish how the specialist can operate in such a way as to respect the principle of beneficence. The health professional makes some choices also influenced by personal belief systems and theoretical orientation that can influence the future of the adolescent, in both cases of treatment with similar GnRH and abstention from therapy [64]. The Standards of Care authorizes specialists to adapt the guidelines according to the needs and wishes of the individual patient [7]. The choice of prescribing blockers is ethical when the doctor believes that the patient will benefit from the treatment. If, after conducting the appropriate assessments, the physician concludes that refusal of treatment is the riskiest option because gender dysphoria is likely to persist into adolescence and adulthood, then early treatment is found to be in the best interests of the patient. Child [19]. The doctor's responsibility is to help the child or adolescent consider the possible consequences of each choice.

6.4 Justice

According to the principle of justice of Beauchamp and Childress, health services must be equally distributed among the population. Gender-dysphoric young people seeking assistance face a variety of barriers due to socioeconomic status and geographic location. There are disparities in access to care between gender-variant adolescents and cisgender peers, due to the stigma that prevents them from seeking and obtaining adequate treatments [12]. The social and structural stigma experienced by gender non-conforming young people reduces accessibility to care from a structural, interpersonal, and individual point of view [65]. The structural stigma implies a reduction in available resources and health coverage; the medicalization of atypical expressions of gender identity; electronic registers with only two options for gender identification; the lack of knowledge and research on the health of trans people [65]. Stigma in social relationships at school and in the family also represents a barrier to access to specialized medical services for atypical gender identity [66]. Young people, inserted in a stigmatizing social context, are increasingly reluctant to reveal their atypical gender identity. The tendency to hide associated with the fear of being judged as different reduces the likelihood for young gender-variant people to seek and receive assistance [67]. Furthermore, the services are not equally distributed throughout the territory, so there are few clinics with specialized professionals who are used to treat problems related to gender identity, generating inequalities in access to care due to geographic location. The shortage of adequately trained and competent personnel can lead to inappropriate or even harmful medical care for patients [68]. Gender-variant young people often have difficulty accessing other forms of assistance [69].

7. Conclusion

The experience of biological puberty is an undesirable condition for adolescents with gender dysphoria who find themselves living in a body they do not recognize as their own. Actionable interventions for gender dysphoria are classified in the Standards of Care as fully reversible, partially reversible, and irreversible interventions [7]. Suppression of puberty is a reversible treatment that involves the administration of similar drugs of gonadotropin-releasing hormone (GnRH). The analogue agonist most frequently used with adolescents with gender dysphoria is Triptorelin, administered by the intramuscular or subcutaneous route. This intervenes to arrest the development of secondary sexual attributes and associated physiological functions in adolescents with gender dysphoria. After the suppression of puberty, if gender dysphoria persists, the induction of puberty of gender identification can be carried out by administering GAF [11]. Regarding drug safety, GnRH analogues appear to be well tolerated in the short term, with the exception of hot flashes [23], fatigue, migraine, mood swings, pain from injection, and abscesses [5]. Even in the long term, there do not seem to be any significant side effects on the body, but the knowledge is still uncertain [11]. The issue of fertility is particularly delicate, since, if the gender adjustment process is continued, it remains irremediably compromised for adolescents who have not resorted to the preservation of sexual gametes. This aspect represents an element to be evaluated when defining the decision-making capacity of the minor who chooses to undergo medical treatment for gender dysphoria [24]. When the young person has not yet reached the age of majority, the request for the gender adjustment process should be accompanied by parental approval. However, there is no agreement on the minimum age for adolescents to express consent. Furthermore, it seems useless to establish an age threshold: the International Covenant on the Rights of the Child focuses on the capacity for judgment, whereby the adolescent can express consent when he has reached sufficient emotional and cognitive maturity to understand the implications of therapy, including possible side effects and risks that may occur [12]. Since puberty suppression therapy is partly experimental, consent cannot be fully informed, because the professionals themselves are not aware of all the long-term outcomes of drugs on the body [19]. The candidate can undertake treatment if he meets the eligibility criteria for treatment, whereby the professional assesses whether the adolescent is able to understand and provide consent; and was informed of the expected outcomes, possible disadvantages, potential loss of fertility, and opportunities for preserving fertility [5].

Parents have the right to make decisions for their children only when they do not hinder the “best interests” of young people [12]. The choice of the clinician should not be based only on parental opinion, because parents do not always know what their children’s wishes are, and there is a risk of limiting the child’s right to autonomy [17]. Gender dysphoria implies a strong inconsistency between assigned sex and experienced gender, with a rejection of one’s sexual attributes leading to clinically significant suffering and impaired individual functioning in daily life [4]. This condition is also associated with problems of a psychological and psychiatric nature, such as depression and anxiety [70]; suicide ideas and attempts [18, 31, 35]; an intense dissatisfaction with one’s body image [71, 72].

The negative psychosocial consequences of untreated gender dysphoria in adolescence are now well known. First of all, the young person can experience the omission

of treatment as psychological torture and interpret it as a denial of the possibility of experiencing puberty of the kind of identification. Faced with this suffering, the adolescent who reacts with impulsiveness can adopt behaviors that are risky to health [30]. The anguish can be so intense that it leads to suicidal ideas and attempts. Suicidal behaviors are more frequent in the transgender population than in the rest of the population [31, 33–35]. Unfavorable outcomes of surgical gender reassignment in adults appear to be associated with late treatment rather than early intervention [41]. Poorer psychological functioning in adults could be due to the distress experienced due to a prolonged inconsistency between gender identity and physical appearance that exposes to stigmatization and social isolation [24]. On the other hand, timely treatment with similar GnRH not only allows to prevent negative outcomes but also bring benefits to the young person. The same effects cannot be obtained if therapy is started later in puberty, as blockers are less effective in reducing secondary sexual attributes when they are already formed [18, 20], for which it will be necessary to expose themselves to invasive surgical removal operations in the future. Suppression of puberty can be considered a diagnostic tool, as it saves time for both the adolescent, who can explore their gender identity without worrying about the development of secondary sexual attributes [22], and to the clinician, who can better understand the nature and intensity of adolescent distress [23] to arrive at a more precise diagnosis [20]. Many studies have found an improvement in functioning and psychological well-being after treatment with GnRH analogues [25–38]. When, on the other hand, therapy is denied, and the adolescent resorts to self-medication, he is no longer followed by professionals in the sector, with the foreseeable physical and psychological repercussions that follow (wrong methods and dosages of administration, possible infections due to injections that do not comply with appropriate hygiene standards), [12, 39]. Involvement in prostitution exposes adolescents to situations that are risky for their life and sexual health since they could be victims of abuse or contract infections and diseases if they do not use the appropriate precautions [71]. The advantages that can be brought by GnRH analogue therapy cannot be underestimated, which are arresting in the development of secondary sexual attributes and greater satisfaction with body image; preventing a series of risky behaviors for health, in particular suicidal ideations and attempts. The right of the adolescent emerges to a future in which life opportunities are maximized, whereby the possibility of living the puberty experience of gender identification is offered, preventing the need to undergo invasive gender affirmation surgeries in future [73–75]. The importance of respecting the right of the child to exercise personal autonomy in the decision-making process is noted, so his/her opinion must be considered by the professional when making a therapeutic choice [17, 76, 77]. Whether parents not only deny consent but adopt abusive attitudes towards the gender-variant child, then the possibility of intervention to protect the minor is evaluated [78]. Since the prevalence of gender in adolescence is progressively increasing in the population [24], this issue cannot be underestimated, and it is important to convey the right therapeutic tools for young people afferent to health services [79]. It is clear that denial of therapy is not a neutral option, and the health professional cannot omit the intervention, thus thinking of not harming the patient. This type of action can harm young people in two ways: it does not respect the principle of non-maleficence as they can adopt risk behaviors that compromise their health; does not respect the principle of beneficence as it does not bring benefit. The studies cited highlight the importance of evaluating for each case which therapeutic option is that can improve the well-being and quality of life of the minor, without focusing on rigid and a priori beliefs, but keeping the multiple possibilities of treatment open.

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