

*Presidenza del Consiglio dei Ministri*



**ON THE QUESTION OF AIFA'S REQUEST REGARDING  
THE ETHICALITY OF THE USE OF THE DRUG  
TRIPTORELIN IN THE TREATMENT OF ADOLESCENTS  
WITH GENDER DYSPHORIA**

13 July 2018

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## Presentation

In response to a query from the Italian Medicines Agency (AIFA), the Italian Committee for Bioethics has issued an opinion on the ethicality of the use of the triptorelin drug for the treatment of adolescents with gender dysphoria (GD). Gender dysphoria is frequently accompanied by psychiatric illnesses, emotional and behavioural disorders, with self-harm, and a high incidence of suicidal behaviours. The prescription of this drug for GD is currently possible according to the method of *off label* use for "indications other than those authorised". On the basis of this classification, unless individual local authorities dispose otherwise, the therapeutic decision, the preparation and the obtaining of informed consent are entrusted exclusively to the responsibility of the individual doctor, without an evaluation by an ethical Committee.

The document, after outlining the benefits and risks of its use, without going into the merits of a historical-sociological reconstruction and the philosophical discussion of gender, puts forward several recommendations, inspired by caution and evaluation on a case-by-case basis, as well as recalling that diagnosis and proposed treatment should come from a multidisciplinary and specialized team, that the treatment should be limited to cases where other psychiatric and psychotherapeutic interventions prove ineffective, and that treatment should provide for consent to be freely and voluntarily expressed, with the subject understanding the information received in the specific physical and psychological conditions of the adolescent, the importance of providing adequate training for the paediatrician, the basic social-health network and the educational institutions involved in these issues.

The Committee also recommends the preparation of studies on safety, efficacy and physical-psychic follow-up on the cases treated and the provision of a policy of equitable and homogeneous access to triptorelin.

Lastly, the Committee recommends that AIFA should regulate the particular conditions of administration of the drug in the diagnosis of GD in adolescence. The document was supplemented by the personal remarks of Prof. Assuntina Morresi, published along with the Opinion.

The ICB availed itself of the contributions of experts, with hearings from: Prof. Andrea Lenzi, President of CNBBSV and Professor of Endocrinology, "La Sapienza" University of Rome; Prof. Francesco Lombardo, Associate Professor of Applied Medical Technical Sciences, "La Sapienza" University of Rome; Prof. Stefano Vicari, Head of the Neuroscience and Neurorehabilitation Department of the "Bambino Gesù" Paediatric Hospital in Rome; Dr. Paola Marion, Psychoanalyst of the Italian Psychoanalytic Society; Dr. Jiska Ristori, Psychologist and psychotherapist; Prof. Marco Cappa, Head of UOC of Endocrinology and Diabetology, Department of Paediatric University-Hospital of the Auditorium "Bambino Gesù" Paediatric Hospital in Rome.

The opinion was prepared by Profs. Lorenzo d'Avack and Laura Palazzani, with contributions from Profs. Salvatore Amato, Carlo Caltagirone, Stefano Canestrari, Bruno Dallapiccola, Antonio Da Re, Silvio Garattini, Marianna Gensabella, Maurizio Mori, Assuntina Morresi, Carlo Petrini, Tamar Pitch and Grazia Zuffa.

The document was voted in the plenary session on the 13 July 2018. It was approved by Salvatore Amato, Stefano Canestrari, Cinzia Caporale, Carlo Casonato, Francesco D'Agostino, Antonio Da Re, Lorenzo d'Avack, Mario De

Curtis, Gian Paolo Donzelli, Marianna Gensabella, Maurizio Mori, Laura Palazzani, Tamar Pitch, Lucio Romano, Luca Savarino, Monica Toraldo di Francia, Grazia Zuffa and the consultative members Dott: Maurizio Benato and Amedeo Cesta.

Prof. Assuntina Morresi voted against.

The consultative member, Dr. Carlo Petrini abstained.

Support for the opinion was received from the following members of the Italian Committee for Bioethics who were absent at the time of voting, Professors: Luisella Battaglia, Carlo Caltagirone, Bruno Dallapiccola, Riccardo Di Segni, Silvio Garattini, Mariapia Garavaglia, Massimo Sargiacomo, Lucetta Scaraffia; while the consultative members, Dr. Carla Bernasconi and Prof. Anna Teresa Palamara sent their abstention.

## Introduction

The Italian Committee for Bioethics received a request for an opinion from the Italian Medicines Agency (AIFA) on the 10.04.2018 regarding the ethicality of the use of the drug triptorelin (analogue of gonadotropin-releasing hormone) in the treatment of adolescents with gender dysphoria (GD). The request was substantiated by the fact that when GD occurs during adolescence it may be associated with psychiatric illnesses, emotional and behavioural disorders, with recourse to substance abuse, self-harm, and high incidence of suicide. In addition it was also pointed out that in order to prolong the diagnostic phase and confirm the persistence of the pathology, several scientific Societies – The Italian Society of Endocrinology (SIE), The Italian Society of Medical Andrology and Sexual Medicine (SIAMS), The Italian Society of Paediatric Endocrinology and Diabetology (SIEDP), The National Observatory on Gender Identity (ONIG), have made a request to AIFA for the possible continuous administration of the triptorelin-based drug, in order to interrupt puberty in the adolescent.<sup>1</sup>

## Gender dysphoria (GD) and the use of triptorelin

Gender dysphoria may even occur very early in childhood (at 3-4 years) and adolescence (at 10/13 years) and involves subjects who do not identify with the gender they were assigned at birth, they experience and express a strong desire to change their anatomical sex from male to female and from female to male or even live in a state of sexual ambiguity, given the mismatch between their biological sex and perceived gender identity. This state in adolescence, specifically, can be expressed by the desire, with varying degrees of intensity, to slow down and/or block the development of one's primary sex characteristics and/or secondary sex characteristics in view of the possible acquisition of the primary sexual characteristics and/or secondary sex characteristics of the other gender or of ambiguity between male and female (transgender). GD may be accompanied by internalizing psychological and psychiatric illnesses, often related to stigma and social discrimination: emotional disorders, elevated anxiety, anorexia, self-harm, suicidal tendency, autism, psychosis, body dimorphism, high school *drop-out*.<sup>2</sup>

Triptorelin is generally used with the clinical indication of suspension of pubertal development in cases of precocious puberty (or "pathological puberty") in order to prevent permanent damage (osteoarticular, muscular, metabolic development), it is restricted to girls under 8 years of age and boys under 10 years of age, classed as a Band A drug with note CUF 51, it is therefore included

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<sup>1</sup> Following the request of the above mentioned Societies, on 06.03.2018 AIFA stated that "the Technical-Scientific Advisory Committee (CTS) of AIFA in the session of 12, 13 and 14 February this year, decided to express itself in favour of the inclusion of the drug triptorelin and its off-label use for use in selected cases where puberty is inconsistent with gender identity in the list established pursuant to Law n. 648/1996". It was therefore announced that the procedure for issuing a directive would be activated.

<sup>2</sup> The GD phenomenon, though numerically small, is growing. There is talk of a prevalence of 0.002-0.005% (2-5 cases per 100,000). Some studies in both the Netherlands and Canada indicate that in childhood GD does not necessarily evolve during adolescence; while in cases in which GD remains in the initial phase of puberty (adolescence) it seldom desists and almost all the subjects with GD in adolescence maintain this condition in adulthood.

in the diagnosis and therapeutic plan of specialist structures according to the modality adopted by the individual Regions or Autonomous Provinces.

Extending the use of the drug to adolescents with GD at a precise stage of development, at Stage II of the Tanner scale<sup>3</sup>, to block "physiological puberty"<sup>4</sup>, makes its use in our country an *off label* prescription. On the basis of this classification, unless the individual local authorities dispose otherwise, the therapeutic decision, the preparation and the assumption of informed consent are entrusted exclusively to the responsibility of the individual doctor, without evaluation by an ethical committee.

In general, the potential benefits expected from the use of the drug in GD are indicated as:

1) the possibility for the medical team to "widen the diagnostic window" for a more accurate investigation in order to explore all the issues related to the adolescent's gender identity more serenely as well as allowing for maturation of the subject's awareness, without the discomfort associated with pubertal development;

2) the prevention of irreversible physical changes of puberty, which can be a source of great suffering for the adolescent with GD;

3) the possibility, in the event that the adolescent should subsequently proceed to medically affirming interventions, to avoid physical changes, allowing for a possible inferior use of hormones in future (drugs which have serious negative consequences) at 16 years of age and less invasive surgical interventions at 18 years of age as well as preventing adolescents from resorting to dangerous acts such as the self-administration of drugs purchased online, in the absence of control and specialist monitoring,

In the face of these potential benefits, the potential risks and the medical and ethical perplexities arising from this treatment are contrasting:

1) At present the use of the drug for GD in adolescents is characterized by uncertainty: there are no safety studies and sufficient *follow-up* data able to provide reassurance regarding the lack of short and long-term side effects. So far, it has not been sufficiently proven whether the interruption of physiological puberty may have negative consequences on growth, on the skeletal structure, on the cardio-vascular, neurological-cerebral and metabolic system and on fertility. The available data are anecdotal, observational or narrative in terms of safety and efficacy: a scientific judgment on risks is impossible without appropriate experimental controls.

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<sup>3</sup> The scale of Tanner is a scale of physical development, the II corresponds to the first stage of puberty, different for males (between 11 to 14 years) and females (between 10 and 13 years).

<sup>4</sup> "Puberty is a very delicate physical-psychological maturation process that, in the contextual development of body image and of psychic maturation, leads the subject towards the procreative capacity" (P. Marion).

2) The consequences resulting from blocking sexual development in relation to the emotional-cognitive development which proceeds have not been sufficiently explored.

3) A critical bioethical point is the adolescent's participation and consent to the treatment programme. The particular vulnerability of these adolescents from the psychological and social point of view should be considered in administration of the drug. Therefore, the question arises as to how far the consent of a minor can be taken to be expressed in a truly free and valid manner, without external interference, and with an understanding of the information received, especially in this case and in these conditions, as GD, as already mentioned, is often accompanied by depression, anxiety, suicidal instincts.

## **Recommendations**

The Committee does not intend to reconstruct the issue of gender identity on the historical-sociological and philosophical level, although it is aware that this inevitably remains in the background.

The Committee in comparing and evaluating risks and benefits, typical of *off-label* use, believes that there is an ethical obligation to take into account *in primis* the suffering of adolescents with GD: It involves substantial psychological distress accompanied by a high risk of suicide and self-harm and high levels of depression and anxiety. Therefore, in cases where psychological, psychotherapeutic, psychiatric assistance is not decisive, the use of the drug may be indicated in order to help the adolescent face such a complex situation.

The Committee also notes that some scientific Societies propose its use, as indicated by AIFA, and that some health facilities already treat single cases of adolescents with GD with triptorelin, without any approved protocol of intervention and shared guidelines having been approved.

The NBC believes, therefore, that it is appropriate to justify the use of this drug based on a prudent approach, in carefully selected situations to be evaluated on a case-by-case basis, taking into account the following recommendations:

1. This treatment can be justified on a bioethical basis in particular cases, ascertained, and evaluated, after the diagnosis of GD, if possible, at an early stage, by a multidisciplinary and specialized team composed of at least one specialist in child and neuropsychiatry, one in paediatric endocrinology, one in psychology of the developmental age and one in bioethics. It is recommended that the multidisciplinary team or a specialist GD centre should accompany adolescents and their families over time, in order to make it possible to achieve expectations in the least traumatic way possible and avoid stigmatization and discrimination, having serious repercussions on the adolescents.

2. It is recommended, considering the particular vulnerability of the adolescents, even from a psychological and social point of view, that a protocol should be drawn up defining the diagnostic-therapeutic process in which to use the drug within the context of psychological, psychotherapeutic and psychiatric interventions aimed at removing the causes of suffering induced by social

reasons. All forms of self-medication and treatments not adequately monitored by medical specialists must be avoided due to the high risks involved.

3. With reference to the under 12s, it should be remembered that starting treatment with triptorelin means starting a decisive path for personal identity, which would take place almost entirely - and in any case in its most significant part – while still minors. Through the help of professionals in the sector, it is important to obtain the subject's consent, given freely and voluntarily, with understanding of the information received in the specific physical and mental conditions of the minor. During this process it is of fundamental importance to verify that external expectations, those of parents and society, do not interfere with the acquisition of awareness by the adolescent. The protection of the child's psycho-physical health<sup>5</sup> must be at the centre of these decisions.

4. This is a growing phenomenon, therefore appropriate training on these issues is also recommended for the paediatrician, so that adolescents and families may be guided towards the competent multi-specialist centres equipped for GD. Training must also be provided for the basic social-health network and educational institutions attended by adolescents with GD.

5. Effective safety studies and physical-psychological follow-up on the treated cases are recommended. Given the rarity of the condition and the consequent small number of cases, adequate extensive experimentation will not be possible, however, there should, at least, be the study of outcomes.

6. It is recommended that, given the cost and the prolonged duration of therapy, the NHS should, as already recommended by the Italian Committee for Bioethics for other drugs<sup>6</sup>, provide a policy for equitable and homogeneous access to triptorelin at national level, in order to ensure equal distribution.

7. The Committee, as previously noted, in conclusion recommends a specific directive by AIFA to clarify the particular conditions for administration of the drug in the diagnosis and treatment of GD in adolescence. Currently, we are still far from a form of combined approach by a multidisciplinary team and there is no guarantee that the information given to parents and the informed consent of the minor are submitted with the necessary accuracy. The question of reimbursement and related inclusion in the list established pursuant to Law 648/96 does not solve any of these problems, because it limits itself to stabilizing the use of the drug in economic terms, leaving open the relevant ethical problems explained in this document.

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<sup>5</sup> The law 219/2017 (article 3) has provided for medical treatments that, in the case of minors, even if they do not have full legal capacity, their opinion should be considered as an increasingly important factor in the decision-making process in proportion to their age, their degree of maturity and discernment, so that their abilities of understanding and decision are valued. The law establishes in the choices the priority of the psycho-physical protection of the minor.

<sup>6</sup> ICB, *For a fair access policy to innovative drugs with high efficacy for serious diseases: price reduction and cost containment by the NHS and citizens*, 2017; *Orphan drugs for persons affected by rare diseases*, 2011.



## **Personal remark**

### ***A personal remark signed by Prof. Assuntina Morresi***

I note with satisfaction that the response of the ICB to AIFA's query regarding the use of triptorelin (TRP) for gender dysphoria (GD) is determined by a prudent use of the product whereas the inclusion of TRP in the list of *off-label* products reimbursable by the NHS, as is AIFA's manifest intention, is liable to promote its use, currently already regulated only *off-label*.

However, I can not fully agree with the approved document, on the grounds of some objections, first of all on a scientific level. According to the information currently available, in fact, there is no evidence of the efficacy of TRP in the treatment of GD in children during adolescence, on the contrary, the expert hearings and the literature of the sector have exposed serious doubts and perplexities, which, when brought to the attention of the ICB and that of the experts during hearings found no answer or place in the final document.

Therefore I believe it is useful to reaffirm my perplexities, already expressed during the discussion of the document, perplexities which concern: the consistency of the scientific literature in support of its use (of which there is a marked paucity, in my opinion); the same rationale of the method (the criterion of "gender neutrality") and finally the bioethical profile (the informed consent of the minor).

## **The scientific standpoint**

The ICB has acknowledged the uncertainty of the data in relevant existing literature, but several clarifications should have been made explicit, for a proper assessment of these uncertainties.

As mentioned in the document, the authorized use of TPR is primarily for precocious puberty, i.e. to interrupt "pathological puberty" (for example for very young children, 7-9 years), while *off label* use for GD is to interrupt "physiological puberty" (for preadolescents, around 12). The efficacy of TRP for GD, should NOT therefore be evaluated in relation to the interruption of puberty, but in relation to GD itself, i.e. the non-conformity of the "perceived" gender with the one assigned at birth. This effectiveness should be "measured" as it is functional in the achievement of self-acceptance for the established/consolidated gender, at the end of what might be called "the process of verification of one's gender identity" and subsequently, during the course of life. This also implies determining how to measure "self-acceptance", in order to assess whether this is indeed satisfactory.

Consequently, it is not correct to assume the results of studies concerning the suppression of "pathological" puberty by means of TRP (for which there is ample scientific literature) as being valid also in the case of "physiological" puberty, as is often reported in the literature of the sector.

For example: interruption of early puberty may allow for a more serene comparison between peers - ex. a 7-year-old girl will not develop breasts, like her peers - while the interruption of physiological puberty can make it much more problematic - ex. a 14-year-old girl who has not developed secondary sexual

characteristics is much more easily "different" from her peers. And if it is true that in preadolescents with GD peer comparison is often very problematic in itself<sup>7</sup>, it is not clear how the increase in differences, blocking body development while continuing cognitive development, can reduce this complexity. The differences from the clinical/biological point of view should then be assessed: for example, is interrupting bone development in "pathological" puberty at 7 years of age equivalent from the clinical/biological point of view to interrupting the same development if it is "physiological" at 12 years of age?

As for the correct evaluation of TRP, i.e. in relation to GD, scientific literature quotes a single case, with a follow-up after twenty-two years from treatment<sup>8</sup>. The other follow-up available in literature is a Dutch study of 55 transgender youths, at least one year after surgery.<sup>9</sup> The same authors, while judging the results obtained very positively, are aware of the complexities in the field and reiterate that these are preliminary data<sup>10</sup>. In these conditions it is not possible to speak of scientific evidence.

- The use of the TRP for GD implies the possibility that, even at a young age, treated adolescents can start a transition to the other gender; despite the paucity of literature, it is clear that almost all of the adolescents treated actually take this path.

Effectiveness should therefore be judged only at the end, even more so when started in minors, compared to the same process undertaken at an older age, (and therefore without the use of TRP). For now, the existing data on the outcome of SRS (Sex Reassignment Surgery) record a loss in follow up of 70% of those treated<sup>11</sup>, and in any case those available show that death rates from all causes - including suicide - are generally much higher than those of the general population.<sup>12</sup>

The phenomenon of so-called *detransitioners* also begins to emerge, that is to say, those who, after a process of gender change, surgical and/or hormonal, see fit to return to their initial gender.<sup>13</sup> It is a phenomenon that is increasing in visibility, in parallel with the number of people who undertake the path of gender change, both within the binary model and in the "genderfluid"/transgender model,

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<sup>7</sup> Dr. Paola Marion's hearing.

<sup>8</sup> P.T. COHEN-KETTENIS, S.E.E. SCHAGEN, T.D. STEENSMA, A.L.C. DE VRIES, H.A. DELEMARRE-VAN DE WAAL, *Puberty suppression in a Gender-Dysphoric Adolescent: a 22-year follow up*, Arch. Sex Behav., 2011 Aug, 40 (4): 843-7.

<sup>9</sup> A.L. DE VRIES, J.K. MCGUIRE, T.D. STEENSMA, E.C. WAGENAAR, T.A. DORELEIJERS, P.T. COHEN-KETTENIS, *Young adult psychological outcome after puberty suppression and gender reassignment*, in "Pediatrics", 2014 Oct, 134 (4): 696-704. Started in 2000, 196 minors examined in eight years, 140 considered suitable for medical intervention, 29 of which were immediately prescribed cross-sex hormones while for the other 111 the blocking of puberty began, of these the first 70 became part of an observational study with reported outcomes shortly before starting treatment with cross-sex hormones, and in turn, for 55 of these it was possible to perform a follow-up after at least one year after surgery.

<sup>10</sup> S.B. LEVINE, *Ethical concerns about emerging treatment paradigms for gender dysphoria*, in "J. of Sex & Marital Ter.", 2018 Jan, 44 (1): 29-44.

<sup>11</sup> S.B. LEVINE, *Reflections on the legal battles over prisoners with Gender Dysphoria*, in "J. Am. Acad. Psychiatry Law", 2016 Jun, 44 (2): 236-45.

<sup>12</sup> S.B. LEVINE, *Transitioning back to maleness*, Arch. Sex. Behav., 2018 May, 47 (4): 1295-1300 and refs therein.

<sup>13</sup> See for example The Atlantic, *When children say they're transgender*, July/August 2018.

so as to provide a specially dedicated section in the Eighth edition of the WPATH (World Professional Association for Transgender Health) Standards of Care.

- Given this lack of scientific evidence, the suggestion in the text (Recommendation 6) to equitable and homogeneous access to TRP is surprising, above all in reference to the opinions of the ICB "For a fair access policy to innovative drugs with high efficacy for serious diseases: price reduction and cost containment by the NHS and citizens, 2017"; "Orphan drugs for persons affected by rare diseases, 2011", both concern drugs whose efficacy is recognized (the first in particular, dedicated to innovative drugs for Hepatitis C). Secondly, the cited opinions deal with undoubtedly, serious pathological situations, while the tendency of the main international organizations of reference is the de-pathologization of "gender incongruence"<sup>14</sup>.

- Regarding the administration of TRP, the ICB recommends a "prudence approach, in carefully selected situations to be evaluated on a case-by-case basis"; the recommendations listed above demonstrate, as already mentioned, a prudential mode, but they do not, obviously, specify the appropriate filter for the selection of cases, and then again, how could they, given the lack of scientific data on the basis of which to select the above cases. The prudent approach, although insufficient for the writer, is appreciable, given that also - but not only - the data of the above mentioned Dutch study show a far from rare use of TRP (out of 196 minors examined it was scheduled for 111 of these).

- The main motivation for the ICB's being in favor of administering TRP is the suffering of the child with GD, first and foremost because of the fear of self-injurious behaviour and suicidal intentions. But there is no scientific evidence that administration of TRP is the treatment of choice in these situations.

### **The rationale of the method and its implications**

- In the decision to make the text synthetic, the ICB devotes only two lines to the problem of the misalignment that is created between cognitive development and physical development in children treated with TRP, however this point should have been given much closer attention.

- According to the literature on the subject, this use of TRP leads to a "limbo in which they can explore their gender without the stress of developing a body in which they perceive themselves as aliens", "the body remains in a neutral state of pre-puberty"<sup>15</sup>

How is it possible in these conditions of not belonging to any gender, "to explore one's gender identity"? With respect to which hypothesis can this occur and be explored, in the absence of a sexed body, that is in the absence of the physical expression of one's gender identity, if not an imaginary one? And what

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<sup>14</sup> [www.who.int/news-room/detail/18-06-2018-who-releases-new-international-classification-of-diseases-\(icd-11\)](http://www.who.int/news-room/detail/18-06-2018-who-releases-new-international-classification-of-diseases-(icd-11)).

<sup>15</sup> A.D. FISHER, J. RISTORI, E. BANDINI, S. GIORDANO, M. MOSCONI, E.A. JANNINI, N.A. GREGGIO, A. GODANO, C. MANIERI, C. MERIGGIOLA, V. RICCA, Italian GnRh Analogs study ONIG group, D. DETTORE, M. MAGGI, *Medical treatment in gender dysphoric adolescents endorsed by SIAMS-SIE-SIEDP-ONIG*, in "J. Endocrinol. Invest", 2014 Jul, 37 (7): 675-87.

about the typical experiences of adolescent love? Does the suppression of puberty not prevent one from having the first, typical romantic and sexual experiences related to this age (12-16 years)?

In the ICB opinion on Sexual differentiation disorders in minors<sup>16</sup>, in the case of uncertain sexual attribution of the born child, it was recommended that there should, however, be determination of the infant's sex at birth, defining as "the pre-eminent interest of the child to be brought up as male or female". In other words: is it possible to embark in a process of awareness of self-identity, in an experience of "neutral" sexual identity (which can last up to four years)?

- From the ongoing debate within LGBT communities, there has been concern regarding the possibility of the treatment of transition covering/censoring an issue related more with the sexual orientation of the child: the perception of self and its incongruence with the gender assigned at birth could instead depend on sexual orientation of a homosexual type, and not on one's gender identity<sup>17</sup>. If so, this would be nothing short of an attempt to "cure/modify" a homosexual orientation through a process of gender transition, interfering with the development of sexual orientation: an objection also raised by some scholars.<sup>18</sup>

- There is a high rate of co-morbidity associated with GD. How is it possible to establish the relationship between cause and effect, if one does not proceed to cure at least the co-morbidities (e.g. depression, anxiety, suicidal instincts, autism spectrum disorders, etc.), in order to identify with reasonable certainty GD as the primary cause? The problem arises because GD is often presented as a "feeling of being in the wrong body", assuming therefore the perception of self and one's gender identity to be correct: the use of TRP works on this hypothesis. The opposite possibility must be excluded, that is, the perception of self as being inadequate: that is to say, that at the basis there is a wider or different problem concerning one's own identity, while the body is "right". Given the choice of the ICB to open to TRP, explaining this aspect as a basic criterion for its administration would have been appropriate.

### **The bioethical point of view**

- The ICB has rightly pointed out the difficulties of informed consent. However, it did not mention one essential aspect: the need to inform the minor and the minor's family about the consequences on fertility.

First of all, we should recall that the data on the long-term effect of TRP on fertility are only known in relation to its use in "pathological" puberty and not "physiological" puberty, and therefore there is currently no evidence on the effective full restoration of fertility in the case of withdrawal from treatment and keeping the gender assigned at birth.

Instead, in cases in which there is the desire to continue the process of transition - as seems to happen for the great majority of those who opt for the blocking of puberty – they head towards certain sterility unless there is the

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<sup>16</sup> ICB, *Minor's sexual differentiation disorders: bioethical aspects*, 2010.

<sup>17</sup> E.G. CAMERTONI, D. DANNA, C. GRAMOLINI for ArciLesbica, in <https://www.facebook.com/Arcilesbica/posts/1572271469547982>.

<sup>18</sup> A. KORTE, D. GOECKER, H. KRUDE, U. LEHMUL, A. GRUTERS-KIESLICH, K.M. BEIER, *Gender Identity Disorders in Childhood and Adolescence*, in "Dtsch. Arztebl. International", 2008.

preservation of fertility through cryopreservation of gametes, once pubertal development is achieved and allows for it. The minor and the minor's family must be informed that, depending on the level of physical development achieved, there is the opportunity to maintain their own procreative potential by the prior freezing of male semen or oocytes<sup>19</sup>, and therefore in future, possibly be, at the same time, a biological/genetic mother (literature also reports gestational cases<sup>20</sup>) and a social/legal father - in the case of FtM (Female to Male transition) - or vice versa a biological father and a social/legal mother- in the case of MtF (Male to Female transition).

We must ask ourselves to what extent a minor with GD and his family can consciously and freely evaluate all this.

It is well-known that preadolescents (12 years), as well as teenagers (16 years old), have little awareness of their own procreative potential. It should also be remembered as pointed out by the American Psychological Association, "Adolescents can be intensely focused on their immediate desires, manifesting as a result frustration and resentment in the face of any delay in receiving medical treatment from which they feel they will benefit, and to which they feel entitled" and that "this intense focus on immediate needs. can create problems in ensuring that adolescents are cognitively and emotionally capable of making life-changing decisions, changing their gender names or markers, initiating hormone therapy (which can affect fertility) or proceeding with surgery"<sup>21</sup>.

Finally, considering the co-morbidity that often accompanies GD in minors (anxiety, depression, autism spectrum disorders, suicidal intentions), it is almost inevitable that consent in these conditions is reduced to a purely formal act.

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<sup>19</sup> See for example D. CHEN, L. SIMONS, E.K. JOHNSON, B.A. LOCKART, C. FINLAYSON, *Fertility preservation for transgender adolescents*, in "J. Adolesc. Health", 2017 Jul, 61 (1): 120-3; Australian Standards of Care and Treatment Guidelines for Trans and Gender Diverse Children and Adolescents, in "Med. J. Aust.", 2018, June 18.

<sup>20</sup> A.D. LIGHT, J. OBEDIN MALIVER, J.M. SEVELIUS, J.L. KERNS, *Transgender men who experienced pregnancy after female-to-male gender transitioning*, in "Obstet. Gynecol.", 2014 Dec, 124 (6): 1120-7.

<sup>21</sup> American Psychological Association, Guidelines for Psychological Practice with Transgender and Gender Nonconforming People, in "Am. Psychol.", 2015, 70, 832-64.

The Italian Medicines Agency  
**AIFA**

Rome 10/04/2019

Attn. Prof. Lorenzo d'Avack  
President Italian Committee  
for Bioethics  
comitatonazbioetica@pec.governo.it

**Re: Request for an Opinion on the drug Triptorelin in the treatment of adolescents with gender dysphoria**

Dear President

I am writing to request the opinion of the Italian Committee for Bioethics, for which you hold the Chair, regarding the ethicality of the possible use of the drug Triptorelin in the treatment of adolescents with Gender dysphoria.

Gender dysphoria occurs when there is an incongruence between the gender identity of an individual, child or adolescent, and the person's biological sex. When this occurs in adolescence, Gender dysphoria may be associated with psychiatric illnesses, emotional and behavioural disorders, with recourse to substance abuse, self-harm, and high incidence of suicide. In order to prolong the diagnostic phase and confirm the persistence of the pathology, the scientific societies – The Italian Society of Endocrinology (SIE), The *Italian Society of Medical Andrology and Sexual Medicine (SIAMS)*, The *Italian Society of Paediatric Endocrinology and Diabetology (SIEDP)*, The *National Observatory on Gender Identity (ONIG)*, have made a request to AIFA for the possible continuous administration of the Triptorelin-based drug, (*analogue of gonadotropin-releasing hormone*) for puberty suppression.

In this regard the aforementioned scientific societies have presented a scientific report (enclosed) that includes references to clinical studies and International Guidelines on the use of Triptorelin.

I remain at your disposal for any further clarification that may be needed.

Awaiting your reply, I would like to take this opportunity to extend my kindest regards.

**General Director**  
*Mario Melazzini*