Journal of Sex & Marital Therapy ›
Volume 49, 2023 - Issue 4

Open access

Research Articles

The Dutch Protocol for Juvenile Transsexuals: Origins and Evidence

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Pages 348-368 | Published online: 19 Sep 2022

Cite this article https://doi.org/10.1080/0092623X.2022.2121238 Check for updates

Abstract

It has been a quarter of a century since Dutch clinicians proposed puberty suppression as an intervention for “juvenile transsexuals,” which became the international standard for treating gender dysphoria. This paper reviews the history of this intervention and scrutinizes the evidence adduced to support it. The intervention was justified by claims that it was reversible and that it was a tool for diagnosis, but these claims are increasingly implausible. The main evidence for the Dutch protocol came from a longitudinal study of 70 adolescents who had been subjected to puberty suppression followed by cross-sex hormones and surgery. Their outcomes shortly after surgery

small number of observations and incommensurable measures of gender dysphoria. A replication study conducted in Britain found no improvement. While some effects of puberty suppression have been carefully studied, such as on bone density, others have been ignored, like on sexual functioning.

The use of Gonadotropin-Releasing Hormone agonist (GnRHa) drugs to suppress puberty in "juvenile transsexuals" was first proposed in print in the mid-1990s (Gooren & Delemarre-van de Waal, 1996). Developed by three clinicians at Utrecht and Amsterdam, this intervention became known as the Dutch protocol. It rapidly became standard practice in the treatment of adolescents diagnosed with gender dysphoria (HBIGDA, 2001). This intervention has been described in several manifestos by its proponents (e.g. de Vries & Cohen-Kettenis, 2012; Delemarre-van de Waal, 2014; Delemarre-van de Waal & Cohen-Kettenis, 2006) and subjected to brief critical commentaries (Byng et al., 2018; Laidlaw et al., 2019; Levine et al., 2022). The aim of this paper to provide an historical account of the invention of the Dutch protocol and a critical review of the evidence that has accumulated in the quarter of a century since it was proposed.

Before proceeding, some definitions are in order. Gender dysphoria will be used here to describe a persistent desire to become the opposite sex (Zucker, 2010). Medical terminology has changed over time, from "gender identity disorder" and "transsexualism" (both introduced in the *Diagnostic and Statistical Manual of Mental Disorders–III* in 1980) to "gender dysphoria" (as renamed in the 2013 *DSM–5*) and "gender incongruence" (as renamed in the 2019 *International Classification of Diseases–11*). There is no need to dwell on these diagnostic criteria because the condition in practice is defined by the patient's wish for endocrinological and surgical interventions. In the nomenclature of transgender medicine, "puberty blockers" denote GnRHa drugs (alternatively known as Luteinizing Hormone-Releasing Hormone agonists) which stop the production of sex hormones.[1] Drugs in this class include triptorelin (branded

(branded Lupron) in North America. GnRHa drugs are licensed to treat several medical conditions including precocious puberty in children; endometriosis and uterine fibroids in women; and advanced prostate cancer and sexual deviance in men. The drugs have never been licensed as a treatment for gender dysphoria.

The paper begins by describing how puberty suppression was invented, primarily by the psychologist Peggy Cohen-Kettenis, in the 1990s. It reveals the gap between the protocol described in formal manifestos and actual clinical practice. The second section examines the rationale for this intervention, focusing on two claims—that GnRHa is reversible and that it serves as diagnosis—and two omissions—the association between gender dysphoria and homosexuality and the effect of GnRHa on sexual development. The third section traces the international adoption of the Dutch protocol. The fourth section scrutinizes evidence from an early cohort of 70 adolescents subjected to puberty suppression at the Amsterdam clinic (de Vries et al., 2011, 2014). This cohort provides the only significant evidence that GnRHa followed by cross-sex hormones and surgery results in improved psychological function and reduced gender dysphoria. The evidence is less persuasive than it appears: the number of observations was considerably fewer than 70, the reported reduction in gender dysphoria depended on incommensurable scales, and the outcomes omit one patient who died because puberty suppression dictated a riskier vaginoplasty. The fifth section pursues the British study designed to replicate the Dutch one; it was withheld from publication for some years, presumably because puberty suppression in this sample failed to improve gender dysphoria or psychological functioning. The poor quality of American studies is also noted. The final section evaluates evidence for the side effects of GnRHa. The negative effect on the accrual of bone mass is well studied, while there is increasing evidence for negative effects on cognitive and emotional development and on sexual functioning.

Origins of the Dutch protocol

Transsexualism as a concept emerged in the mid-twentieth century, following the discovery of cross-sex hormones and advances in plastic surgery (Hausman, 1995). Novel physical interventions were justified by the new theoretical construct of "gender identity" invented by American psychologists and psychiatrists, most notably John Money (1994). Gender identity was conceived as developing in infancy (e.g. Green, 1968), but physical interventions for transsexuals under the age of 18 were vanishingly rare. Money in 1973 advised a doctor to prescribe testosterone to a 15-year-old girl and even to consider mastectomy—but he was unusually reckless and there is no evidence that his advice was followed (Gill-Peterson, 2018, pp. 163–164). Specialist clinics for children and adolescents with gender identity problems were founded in Toronto in 1975, in Utrecht in 1987, and in London in 1989. They provided counseling. Cross-sex hormones had to wait until the patient was referred to an adult clinic, at an age ranging from 16 to 18 (Bradley & Zucker, 1990). Surgeries were not performed under the age of 18 (Petersen & Dickey, 1995). Referrals of children were rare. The London clinic—the only specialized clinic for children with gender dysphoria in the United Kingdom—over its first decade accepted an annual average of 14 patients (Di Ceglie, 2018). In its first seven years the Utrecht clinic averaged 9 per year (Cohen-Kettenis, 1994).

Lowering the age of intervention was driven by the founder of the Utrecht children's clinic, Peggy Cohen-Kettenis. She had established herself in the field of gender medicine in the 1980s, presenting research to international conferences of the Harry Benjamin International Gender Dysphoria Association (HBIGDA), which had been formed by clinicians and academics. She eventually became professor of psychology in the Department of Child and Adolescent Psychiatry at University Medical Center Utrecht (Everaerd et al., 2014). She was closely connected to clinicians at VU Medical Center Amsterdam (affiliated with Vrije Universiteit Amsterdam), which housed the country's clinic for adult transsexuals.

Cohen-Kettenis believed that transsexuals would experience better outcomes if they started treatment before adulthood. By the mid-1990s, she was referring some patients

sex hormones (Cohen-Kettenis, 1994). Males were given an antiandrogen, cyproterone acetate, which prevented erections and caused breast tissue to grow; females were given progestin to stop menstruation (Gooren & Delemarre-van de Waal, 1996). Johanna, for example, "fulfilled all necessary requirements for early treatment": she did not favor girly things (though neither did her sisters), she was fond of soccer, she never dated in school (perhaps not surprising given that she was homosexual), and her parents discovered her wearing a tight t-shirt to conceal her breasts (Cohen-Kettenis et al., 1998, p. 124). Brought to the clinic at 17, she was prescribed progestin for four months and then testosterone. Within two years Jaap (as Johanna had become) underwent mastectomy, hysterectomy, and oophorectomy, and obtained a new birth certificate. Evidence to support such early treatment came from the first 22 patients from the Utrecht clinic, interviewed in their twenties, from one to five years after surgery (Cohen-Kettenis & van Goozen, 1997; Kuiper & Cohen-Kettenis, 1988). They were compared to a larger group of transsexuals who had transitioned later in adulthood in previous decades (Kuiper and Cohen-Kettenis 1988). Her former patients showed better psychological functioning and "more easily pass in the desired gender role" (Cohen-Kettenis & van Goozen, 1997, p. 270). One problem with the comparison is that they had transitioned in a more tolerant era. Another is the fact that they were still young; most had no sexual partner. Moreover they had not reached an age at which they might regret their inability to conceive children. (This group has not since been followed up.) Cohen-Kettenis' initiative was praised by Money: he singled out her contribution to a conference in London as "the bravest" (1998, p. xviii).

Cohen-Kettenis had two collaborators at Amsterdam. One was Henriette Delemarre-van de Waal, a pediatric endocrinologist. She had expertise using the new GnRHa drugs—developed in the 1980s—to treat precocious puberty and other conditions (e.g. Schroor et al. 1995). The other was Louis Gooren, a psychiatrist and endocrinologist who was installed as the world's first professor of transsexuality in 1989. His inaugural professorial lecture was addressed by Cohen-Kettenis and by Money, who flew over from Johns Hopkins University (Nederlands Tijdschrift voor Geneeskunde 1989). Like the

intersex condition: “there is a contradiction between the genetic, gonadal and genital sex on the one hand, and the brain sex on the other” and therefore “we must provide them with reassignment treatment which meets their needs” (Gooren, 1993, p. 238). This hypothesis was apparently vindicated when he coauthored an article in *Nature* showing that the volume of the central subdivision of the bed nucleus of the stria terminalis in six male-to-female transsexuals was closer to the volume found in females than in males (Zhou et al., 1995). “Unfortunately,” as he recently acknowledged, “the research has never been replicated” (Gooren, 2021, p. 50; see also Kreukels & Burke, 2020).

GnRHa was introduced as a treatment for gender dysphoria in two articles. Gooren and Delemarre-van de Waal (1996) proposed the “Feasibility of Endocrine Interventions in Juvenile Transsexuals.” More influential was a case study of the first “adolescent transsexual” treated with GnRHa (Cohen-Kettenis and van Goozen 1998). From the age of 5, FG “had made it very clear that I was supposed to be a boy” (FG, 2021, p. 131). It later transpired that FG was sexually attracted to women. FG’s father, an Italian with traditional views on gender, disapproved of his daughter’s masculinity, and serious conflict ensued. Extensive psychotherapy did not improve matters; FG wrote a suicide note at the age of 12. When FG was 13, Delemarre-van de Waal prescribed triptorelin.[2] Three years later, around 1990, FG came to the Utrecht gender clinic, and Cohen-Kettenis was impressed by FG’s “boyish appearance” (Cohen-Kettenis, 2021, p. 115). The clinic provided therapy and introduced FG to other adolescent girls who identified as transsexual. (Whether FG was introduced to any adolescents who identified as lesbian is not recorded.) FG’s puberty suppression continued until the age of 18, when testosterone commenced, followed by multiple surgeries: mastectomy, hysterectomy, oophorectomy, and metaidoioplasty. Awaiting the last surgery at the age of 20, FG was “happy with his life” and “never felt any regrets”; gender dysphoria was apparently cured (Cohen-Kettenis & van Goozen, 1998, p. 247).

Puberty suppression remained exceptional for some years. By 2000, GnRHa had been administered to only 7 children under the age of 16 (Cohen-Kettenis et al., 2000). The

Kettenis was appointed professor of medical psychology in 2002, moving with her clinic. The "Dutch protocol" was published in an influential article in 2006, supported financially by Ferring Pharmaceuticals, the manufacturer of triptorelin (Delemarre-van de Waal & Cohen-Kettenis, 2006, p. S137). GnRHa could be administered to transsexuals as young as Tanner stage 2—marked by the first growth of pubic hair and for girls by budding breasts and for boys by growing testicles—as long as they had reached the age of 12. The adolescent would usually then begin "to live permanently in the role of their desired sex" (Delemarre-van de Waal & Cohen-Kettenis, 2006, p. S132). After some years of puberty suppression, the youth would start cross-sex hormones at the age of 16 and then surgeries at the age of 18. Eligibility criteria for puberty suppression appeared strict. First, gender dysphoria should have begun early in childhood, and dysphoria should have worsened with the onset of puberty. Second, the patient should be psychologically stable, and not suffer from other mental health problems. Third, the patient should have support from their family. As the protocol was formalized, the number of children undergoing puberty suppression increased markedly. Between 2000 and 2008, GnRHa was prescribed to 111 children, about one per month (de Vries et al., 2011). One of them was Valentijn de Hingh, the subject of a television documentary (Nietsch, 2007). After a teacher was disconcerted by the boy's passion for dolls, de Hingh at the age of 5 was diagnosed with gender dysphoria by Cohen-Kettenis (de Hingh, 2021). GnRHa was administered from the age of 12 in 2002.

The protocol as published was not always strictly followed by the clinicians. The minimum age of 12 for puberty suppression was not observed in every case (de Vries, 2010, p. 104). De Hingh had regular endocrinological checkups from the age of 10, presumably so that puberty suppression could commence as soon as Tanner stage 2 was reached. Likewise, cross-sex hormones sometimes started before the age of 16, as young as 13.9 years (de Vries et al., 2011, p. 2278). Family support was not essential, as the clinic administered GnRHa to a 14-year-old—who was institutionalized due to a physical handicap—against the parents' objections (Cohen-Kettenis and Pfäfflin 2003). A British television documentary from the mid-1990s provides a glimpse of actual practice

Utrecht, to see transgender medicine at its most advanced. Fredd Foley, aged 13, met Gooren to learn about puberty suppression; this was around the time it was proposed in the medical literature (Gooren and Delemarre-van de Waal 1996). After returning to England and being refused GnRHa by the London clinic, Foley's mother telephoned Gooren who agreed to write a three-month prescription of triptorelin. "If your child knows for sure he is transsexual," he said, "I would not let puberty happen." Gooren's willingness to prescribe drugs for a child in another country, met briefly in front of the cameras, against the wishes of the child's own psychiatrist, hints that the assessment process was not always as rigorous as portrayed in the published literature. As Cohen-Kettenis said in the documentary, "it's very difficult to give exact criteria, in some cases you have the feeling that the adolescent has thought about it and knows pretty well what she or he is doing."

The Dutch protocol scrutinized

The Dutch protocol comprised not just a drug (GnRHa) and a treatment regime (from age 12 or Tanner stage 2) but also two discursive claims. The first was reversibility. The initial article declared GnRHa to be "fully reversible; in other words, no lasting undesired effects are to be expected" (Gooren & Delemarre-van de Waal, 1996, p. 72). The phrasing hinted at the lack of actual evidence. Suppressing puberty for a short time, on the order of months, might be expected to have a negligible effect on a child's development. Yet the Dutch protocol entailed suppression for up to four years (from age 12 to 16); for FG it lasted at least five years (from 13 to 18). It was implausible to claim that suppressing puberty for so many years would have no lasting effect if the child were to stop GnRHa and restart their natal sex hormones. On occasion this was acknowledged, as when Delemarre-van de Waal and Cohen-Kettenis' (2006, p. S137) manifesto stated that "It is not clear yet how pubertal suppression will influence brain development." Ten years later, however, Cohen-Kettenis still claimed that puberty suppression was "completely reversible" (Cohen-Kettenis, 2016; see also de Vries et al., 2016). The postulate of

12 (or below) could give consent to this endocrinological experiment. HBIGDA's Standards of Care warned that cross-sex hormones "are not, or are not readily, reversible" (HBIGDA, 1985, p. 83). By pronouncing GnRHa to be reversible, the Dutch protocol demarcated a boundary between one endocrinological intervention and another.

The second claim was that puberty suppression was a diagnostic tool. The case study of FG described GnRHa as an "aid in diagnosis and treatment" (Cohen-Kettenis & van Goozen, 1998). This echoed the conception of cross-sex hormones as "both therapeutic and diagnostic in that the patient requesting such therapy either reports satisfaction or dissatisfaction regarding the results" (HBIGDA, 1985, p. 85). GnRHa was posited to provide space for therapeutic exploration of gender identity, without the pressure of the physical changes accompanying puberty (Delemarre-van de Waal & Cohen-Kettenis, 2006). This claim was plausible, though it was also plausible that stopping normal cognitive, emotional, and sexual development would impede such exploration. In the event, the Dutch clinicians found that the diagnostic test invariably yielded the same result: "none of the [54] patients who were selected for pubertal suppression has decided to stop taking GnRHa" (Delemarre-van de Waal & Cohen-Kettenis, 2006, p. S136). This might be explained by a rigorous selection process. An alternative explanation is that puberty suppression becomes a self-fulfilling prophecy. Subsequent experience in the Netherlands and in other countries confirms the fact that 96%–98% of children who undergo puberty suppression continue to cross-sex hormones (Brik et al., 2020; Carmichael et al., 2021; Wiepjes et al., 2018).

The framing of GnRHa as diagnostic circumvented a problem recognized in the earliest articles. "Not all children with GID [Gender Identity Disorder] will turn out to be transsexuals after puberty," acknowledged Cohen-Kettenis and Gooren (1999, p. 319). "Prospective studies of GID boys show that this phenomenon is more closely related to later homosexuality than to later transsexualism." They cited three longitudinal studies of feminine boys (Green, 1987; Money & Russo, 1979; Zuger, 1984).[3] The best known is

boys" (Green, 1987, p. 12). After fifteen years, to his surprise, only one out of 44 was contemplating transsexuality, whereas two thirds had become bisexual or homosexual men. Given such studies, Cohen-Kettenis concluded that "most GID children under 12 will not grow up to become transsexuals" (Cohen-Kettenis & van Goozen, 1997, p. 246). These findings were downplayed in subsequent publications; the key manifestos for the Dutch protocol did not mention homosexuality and did not cite any study of feminine boys (Cohen-Kettenis et al., 2008; Delemarre-van de Waal & Cohen-Kettenis, 2006). The assertion that "GID persisting into early puberty appears to be highly persistent" rested on slender evidence (Cohen-Kettenis et al., 2008, p. 1895). The only relevant cited source described adolescents who had been first assessed at ages ranging from 13 to 18, a range extending well beyond early puberty (Smith et al., 2001). This source did not support the hypothesis that the probability of gender dysphoria persisting to adulthood jumped suddenly on the cusp of age 12, from under 50% to virtually 100%. What is known is that most adolescents subjected to puberty suppression were homosexual. Of the first 70 adolescents referred to the Amsterdam clinic from 2000 to 2008 and given GnRHa, 62 were homosexual while only 1 was heterosexual (de Vries et al., 2011).

The crucial advantage of puberty suppression was creating "individuals who more easily pass in to the opposite gender role" (Delemarre-van de Waal & Cohen-Kettenis, 2006, p. 155). The emphasis was on external appearance, especially height.[4] That word appears 23 times in Delemarre-van de Waal's review of puberty suppression (Delemarre-van de Waal, 2014). There is one cursory reference to "loss of fertility." The words orgasm, libido, and sexuality do not appear. This is curious because it was well known that men taking GnRHa for prostate cancer experience complete loss of erotic interest (Marumo et al., 1999). The drug is therefore licensed to chemically castrate men with sexual obsessions. Gooren was an early advocate for this usage. He warned that the side effects "may be very uncomfortable" for men with paraphilias (Gijs & Gooren, 1996, p. 279); no such warning accompanied his recommendation of the same drug for adolescents experiencing gender dysphoria. The Dutch clinicians did not ask whether blocking the normal development of erotic desire would affect their patients'

understanding of their own body and their interest in future sexual and romantic relationships.

One significant disadvantage of puberty suppression for males was not mentioned in the 2006 manifesto for the Dutch protocol, though it had been raised at a conference in the previous year (GIRES, 2005). Stopping sexual development meant the penis did not grow, and so "the genital tissue available for vaginoplasty may be less than optimal" (Cohen-Kettenis et al., 2008, p. 1895). This made it more likely that the orifice would need to be lined with a portion of the patient's intestine rather than the inverted penis (van de Grift et al., 2020). Out of 49 patients at Amsterdam who started GnRHa at Tanner stage 2 or 3, 71% required intestinal vaginoplasty (van der Sluis et al., 2021). This procedure is more invasive, requiring a second surgical site, and it entails greater risk of complications such as rectal fistula. Surgical techniques have been refined so that the "possible occurrence of intestinal discharge could be kept under control" (Bouman, 2021, p. 141), but one quarter of the patients need further corrective surgeries (Bouman et al., 2016).

International adoption of the Dutch protocol

The Dutch protocol immediately attracted interest in other countries. Cohen-Kettenis and Gooren were already prominent in the field of transgender medicine, exemplified by their election to the Board of Directors of HBIGDA (the former served two four-year terms from 1995 and 2003, while the latter served one term from 1999). Puberty suppression soon entered HBIGDA's Standards of Care in the Sixth Version, approved in 2001. It closely followed the Dutch protocol, but did not specify any minimum age. It was "recommended that the adolescent experience the onset of puberty in his or her biologic sex, at least to Tanner stage Two," while also allowing earlier intervention on the recommendation of more than one psychiatrist (HBIGDA, 2001, p. 10). Recall that the published evidence for the benefits of puberty suppression then comprised a single case study of one patient—FG—awaiting final surgery.

In the United States, adoption was led by Norman Spack, a pediatric endocrinologist. More than once he recalled "salivating" at the prospect of treating patients with GnRHa (Hartocollis 2015; Spack 2008, xi). In 2007 he cofounded the Gender Management Service at Boston Children's Hospital, which was the first dedicated clinic for transgender children in America. Its program was based on the Dutch model; the hospital sent a psychologist to Amsterdam to be trained by Cohen-Kettenis (Tishelman et al., 2015). From the outset the Boston clinic offered GnRHa at Tanner stage 2 or 3 with no minimum age (Spack et al. 2012). Spack joined Cohen-Kettenis, Gooren, and Delemarre-van de Waal on the Endocrine Society's committee tasked with writing their first clinical guidelines for "transsexual persons," which recommended GnRHa for children at Tanner stage 2 or 3 (Hembree et al., 2009). "There was an attitudinal shift to be able to say that the Endocrine Society supports this," he later recalled (Ruttimann, 2013, p. 19). The shift is visible in data from 43 children's hospitals on prescriptions of one GnRHa drug (histrelin acetate): it was never prescribed for gender dysphoria between 2004 and 2009 and was then prescribed to 92 patients from 2010 to 2016, most in the final years of the period (Lopez et al., 2018).

Oprah Winfrey Television broadcast the documentary *I Am Jazz: A Family in Transition* in 2011 (Stocks, 2011). Its dramatic structure was similar to *The Wrong Body*, focusing on the looming threat of puberty as Jazz Jennings reached the age of 11. Jennings had been diagnosed with gender dysphoria at the age of 3 and had appeared on national television at the age of 7, when the family created the TransKids Purple Rainbow Foundation (Jennings & Jennings, 2016). The documentary showed the family consulting with a pediatric endocrinologist, who confirmed that Tanner stage 2 had been reached. The denouement was not shown, but Jenning's mother was clear: "you have to kinda nip puberty in the bud, you want to block it" (Stocks, 2011). Jennings did indeed commence puberty suppression some months later. The number of clinics for "gender-nonconforming children and adolescents" multiplied, and within a few years 32 of them advertised puberty blockers (Hsieh & Leininger, 2014).

England provides an example of adoption driven by patients rather than clinicians. *The Wrong Body* had promoted the Dutch approach to 3 million viewers (Nataf, 1999). Dissatisfaction at the cautious policy of the London clinic—still headed by its founder, Domenico Di Ceglie—became increasingly vocal. Sustained pressure came from the parents of children who identified as transgender, organized in the Gender Identity Research and Education Society (GIRES) and Mermaids. GIRES obtained funding from medical charities to organize an international symposium in London in 2005 to develop consensus guidelines for endocrinological intervention, which was attended by Cohen-Kettenis, Delemarre-van de Waal, and Spack. GIRES (2006) warned that "those who can in any way afford to do so have to consider taking their children to the USA." The first was Susie Green, later the chief executive of Mermaids. In 2007 she took her son Jackie, aged 12, to Boston to obtain GnRHa from Spack (Sloan, 2011). A presentation at Mermaids instructed parents in this medical tourism (Mermaids, 2007). Spack treated seven more British children over the next few years (Glass, 2012). The conflict between parents and clinicians climaxed in 2008, with two clashing conferences. The Royal Society of Medicine organized a meeting on adolescent gender dysphoria, which drew criticism for the lack of overseas speakers advocating for puberty blockers, even though it had invited Delemarre-van de Waal. The cofounder of GIRES, whose child had transitioned in their late teens two decades earlier, used the new epithet "transphobic" to describe the cautious clinicians (Groskop, 2008). Richard Green—the author of *Sissy Boys*, then in London as a visiting professor—quickly organized a rival conference to demand puberty suppression (Green, 2008). Speakers included the usual cast of clinicians, including Spack, and also patients and their parents, including two Dutch transgender adolescents. The demand for puberty suppression was becoming irresistible.

Di Ceglie was soon replaced as director of the London clinic (renamed the Gender Identity Development Service and located at the Tavistock and Portman NHS Foundation Trust) by Polly Carmichael, a clinical psychologist. The clinic in 2011 began to offer GnRHa from the age of 12, initially as part of an experimental study (Biggs, 2019b, 2019c). Before any outcomes were published, Carmichael declared success: "Now we've

with it" (Manning and Adams, 2014). She even appeared on BBC Children's Television to promote puberty suppression, in a documentary about a 13-year-old girl who wanted to be a boy, Leo. Carmichael reassured Leo about GnRHa: "the good thing about it is, if you stop the injections, it's like pressing a start button and the body just carries on developing as it would if you hadn't taken the injection" (Niland, 2014). In 2015 the National Health Service adopted a policy of offering GnRHa for adolescents at Tanner stage 2, without age restriction (NHS England, 2015).

Evidence from the Amsterdam clinic

By the mid-2010s, then, the Dutch protocol was established as the standard for transgender medicine. It was apparently vindicated when longitudinal data was published on a cohort of 70 adolescents referred to the clinic between 2000 and 2008 and then subjected to puberty suppression. The lead author, Annelou de Vries, received her doctorate under the supervision of Cohen-Kettenis. Outcomes were initially measured as the patient was transitioning from GnRHa to cross-sex hormones, at ages ranging from 14 to 19. "Behavioral and emotional problems and depressive symptoms decreased, while general functioning improved" (de Vries et al., 2011, p. 2276). Outcomes were subsequently measured soon after the patient's final surgery (vaginoplasty or mastectomy and hysterectomy with oophorectomy), at ages ranging from 19 to 22. The authors concluded that "gender dysphoria had resolved, psychological functioning had steadily improved, and well-being was comparable to same-age peers" (de Vries et al., 2014, p. 696).

When scrutinized, however, the evidence is less persuasive. The sample was small: final outcome measures were available for subsets of patients numbering between 32 and 55. The finding that gender dysphoria had resolved depended on the Utrecht Gender Dysphoria Scale and the Body Image Scale, which have separate questionnaires for each sex. The researchers switched versions over the course of the study (Levine et al., 2022).

baseline before puberty suppression, and then the female versions following surgery—so would be rating agreement with the statement "I hate menstruating because it makes me feel like a girl" (C. Schneider et al., 2016) and satisfaction with "ovaries-uterus" (Lindgren & Pauly, 1975). The inclusion of such meaningless questions compromises the measurement of change in gender dysphoria. The results after surgery exclude eight patients who refused to participate in the follow-up or were ineligible for surgery, and one patient killed by necrotizing fasciitis during vaginoplasty. The authors did not mention the fact that this death was a consequence of puberty suppression: the patient's penis, prevented from developing normally, was too small for the regular vaginoplasty and so surgery was attempted with a portion of the intestine, which became infected (Negenborn et al., 2017). A fatality rate exceeding 1% would surely halt any other experimental treatment on healthy teenagers.

One inevitable limitation of the study was the measurement of results soon after surgery, which repeated the problem with the first study of adolescent transsexuals (Cohen-Kettenis & van Goozen, 1997). As Cohen-Kettenis notes, "a truly proper follow-up needs to span a minimum period of 20 years" (Cohen-Kettenis, 2021, pp. 117–118). A subsequent follow-up of this cohort is in preparation (Bazelon, 2022). The only long-term outcome published in the literature is that of the very first patient, FG, who was followed up again at the age of 35. FG did not regret transition, but scored high on the measure for depression. Owing to "shame about his genital appearance and his feelings of inadequacy in sexual matters," he could not sustain a romantic relationship with a girlfriend (Cohen-Kettenis et al., 2011, p. 845). Ironically, a "strong dislike of one's sexual anatomy" is one of the diagnostic criteria for gender dysphoria in children (according to *DSM*-5), and so in this respect it is not clear how the dysphoria had been resolved. The clinicians were more interested in FG's height, which they compared punctiliously to the Italian as well as the Dutch height distribution. Cohen-Kettenis concluded that "the negative side effects are limited" (Cohen-Kettenis et al., 2011, p. 843). Delemarre-van de Waal's (2014, p. 194) summary was even more optimistic: "He was functioning well psychologically, intellectually, and socially." Now aged 48, FG has given two recent

He describes puberty suppression as “life-saving” in his case (FG, 2021, p. 132) but also recommends that it should require a significant assessment process (Bazelon, 2022). In a recent interview, Valentijn de Hingh, who at the age of 31 now identifies as non-binary, emphasizes that “diagnosis and treatment at a young age were not wrong.” At the same time, de Hingh wonders “wasn’t that very young? To have been seeing a psychologist, having been examined and diagnosed from the age of five” (de Hingh, 2021, p. 182).

Replicating the Dutch results

An international study of puberty suppression—involving London and Boston as well as Amsterdam—was first mooted in 2005 (GIRES, 2005). The Boston clinic dropped out, but eventually an experiment along Dutch lines was begun in London in 2010. The entry criteria were “consistent with the protocol used at the Amsterdam Gender Clinic” (Viner et al., 2010, p. 6) and the outcome measures replicated those used by the Amsterdam longitudinal study (de Vries et al., 2011, 2014). From 2011 to 2014, 44 adolescents aged from 12 to 15 years commenced puberty suppression. Outcomes for all subjects after two years on GnRHa were thus collected by 2016. Preliminary results were presented to the World Professional Association for Transgender Health (as HBIGDA had been renamed) in Amsterdam. In her keynote address, Carmichael observed that “our results have been different to the Dutch” (Carmichael, 2016). According to one presentation, adolescents after one year of GnRHa “report an increase in internalising problems and body dissatisfaction, especially natal girls” (Carmichael et al., 2016). Another presentation was also negative: “Expectations of improvement in functioning and relief of the dysphoria are not as extensive as anticipated, and psychometric indices do not always improve nor does the prevalence of measures of disturbance such as deliberate self harm improve” (Butler, 2016). These conference papers were not published as articles, following the typical fate of medical experiments that fail to produce positive results (Johnson & Dickersin, 2007).

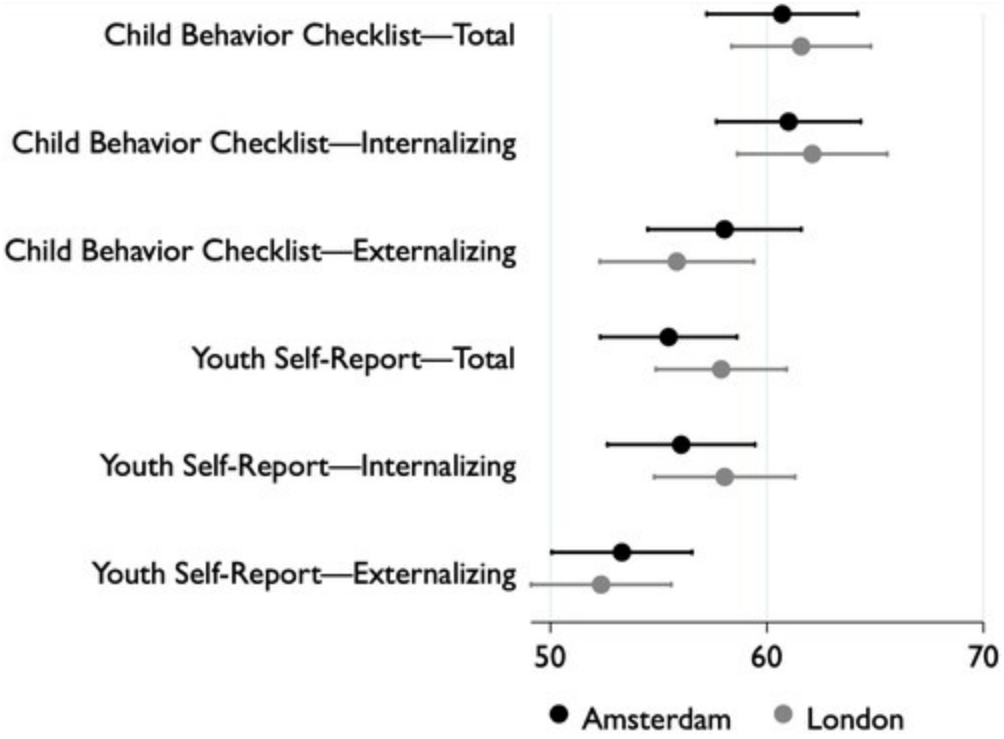
Instead, the London clinic published an article claiming that "adolescents receiving also puberty suppression had significantly better psychosocial functioning after 12 months of GnRHa … compared with when they had received only psychological support" (Costa et al., 2015, p. 2206). The group subjected to puberty suppression were aged between 13 and 17, and must have included some of the 44 experimental subjects. This group comprised 101 adolescents at the outset, diminishing to 35 after twelve months. This high rate of attrition was not explained in the article. Anyway, the data showed no statistically significant difference between the group given GnRHa and counseling and the group given only counseling (Biggs, 2019a).

The full outcomes from the experiment were published following a protracted campaign involving publicity in newspapers and television (e.g. Tominey & Walsh, 2019), complaints to the ethics committee which approved the research (Health Research Authority, 2019), a Parliamentary question (Blackwood of North Oxford, 2019), and a judicial review (Keira Bell and Mrs A v Tavistock NHS Trust, 2020). Out of the 44 subjects in the experiment, all but one transitioned to cross-sex hormones. Outcomes were taken after 12 months of puberty suppression for all patients, and after 24 months for the subset waiting to reach the age of 16 when they could start cross-sex hormones. The headline finding was that "GnRHa treatment brought no measurable benefit nor harm to psychological function in these young people," and gender dysphoria likewise did not improve (Carmichael et al., 2021, p. 20). This is all the more surprising because a placebo response would be expected in patients who had volunteered to pioneer this intervention in Britain (Kirsch, 2019). There was no disaggregation by sex, which is unfortunate because outcomes were evidently worse for natal girls than for boys (Biggs, 2020; Carmichael et al., 2016).

The researchers did not compare their findings to the outcomes from the Amsterdam clinic after puberty suppression (de Vries et al., 2011). Comparison is undertaken here, using available data on two question batteries.[5] The Youth Self-Report (YSR) enables the adolescent to describe their problems, while the Child Behavior Checklist (CBCL)

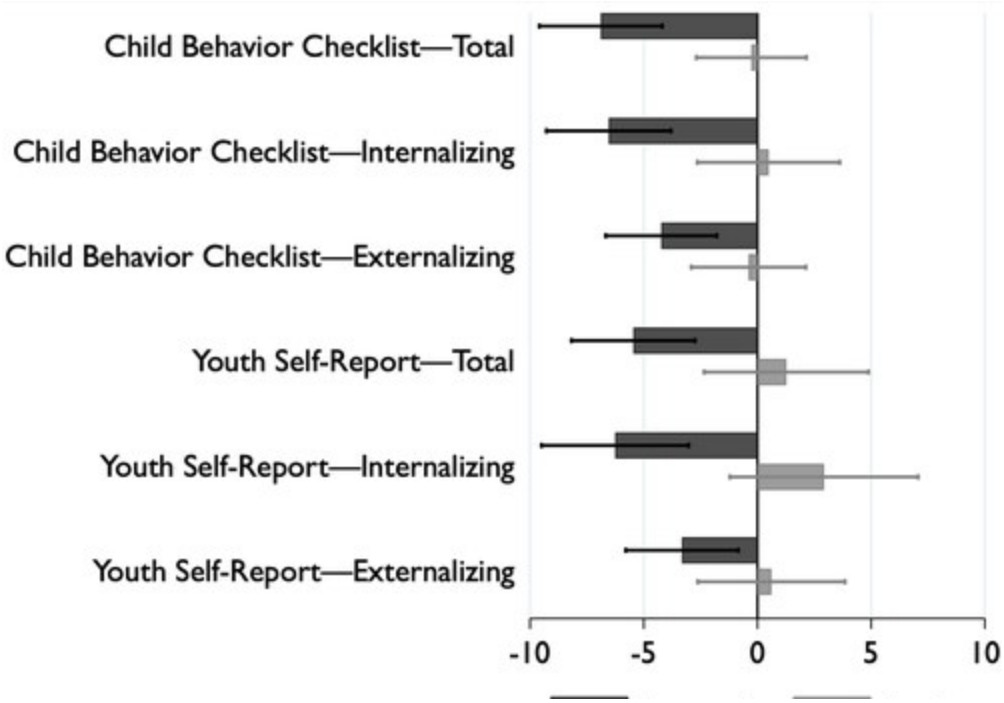
Internalizing Problems like anxiety; one for Externalizing Problems like anger; and a Total Problem score, combining these two along with other problems such as social isolation (Achenbach & Rescorla, 2001). *T*-scores are normalized relative to reference scores (for males and for females aged 12–18), with a mean of 50 and standard deviation of 10. The Amsterdam clinic reported these measures for 54 subjects, compared to 41 for the London clinic. The two samples were similar at the outset of puberty suppression: the mean age at Amsterdam was 14.8, the median at London was 13.6; females comprised 53% of the Amsterdam sample, 43% of the London one. Figure 1 depicts the mean scores at baseline before the commencement of puberty suppression, along with the 95% confidence interval. There was no discernible difference between the Amsterdam and London samples in any component of CBCL or YSR. At the Amsterdam clinic, the subjects completed the questionnaires again when they transitioned to cross-sex hormones, after a mean of 1.9 years. At the London clinic, the questionnaires were completed at 12-month intervals, and so I take the latest available before the end of puberty suppression; the mean duration is 1.4 years. Figure 2 shows how the scores changed since baseline. The Amsterdam sample improved—fewer problems were reported by the subjects and their parents—on all six measures (p = .000004 … .003). The London sample, by contrast, experienced no discernible change (p = .16 … .82). With one exception (YSR Externalizing Problems), the differences between the change in Amsterdam and the change in London are statistically significant (p = .0006 … .03, assuming equal variance).

Figure 1. Psychological functioning before puberty suppression with GnRHa. The circle shows the mean *T*-score at baseline. The line traces the 95% confidence interval. $N = 54$ at Amsterdam, 41 at London. Data from de Vries et al. (2011, Table 2) and Carmichael et al. (2021).



Display full size

Figure 2. Change in psychological functioning after puberty suppression with GnRHa. The bar shows the change in *T*-score from baseline; negative values indicate reduced problems. The line traces the 95% confidence interval. *N* = 54 at Amsterdam, 41 at London. Data reported from de Vries et al. (2011, Table 2) and Carmichael et al. (2021).



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The London clinic's failure to replicate the positive results found by the Amsterdam clinic after puberty suppression demonstrates that the Dutch results cannot be extrapolated to other countries. The reason for the failure to replicate could perhaps lie in the quality of care offered by the clinics or in the characteristics of their patients. Although the two samples had indistinguishable baseline scores on YSR and CBCL, on another measure of psychological functioning—the Children's Global Assessment Scale (CGAS), which is scored by the clinician—the adolescents attending the London clinic were significantly worse at the outset. This fits the general pattern in adolescents referred to European gender clinics: those at Amsterdam have fewer psychological problems and better peer relationships than those at London (de Graaf et al., 2018). The failure to replicate could simply exemplify a general phenomenon in medicine (and science generally): a large effect found in a nonrandomized study with a small sample usually either declines in magnitude or disappears altogether in subsequent studies (e.g. Ioannidis, 2005). Given the London clinic's failure to find favorable results after puberty suppression, it has no incentive to follow up the 43 subjects who transitioned to cross-sex hormones and potential surgery. It loses track of all its patients after the age of 18, blaming "the frequent change in nominal and legal identity, including NHS number in those referred on to adult services" (Butler et al., 2018, p. 635).

One other clinic has published a comparable longitudinal study of puberty suppression. The Hamburg Gender Identity Service followed 11 adolescents who were administered GnRHa for an average of one year, but such a tiny sample provides insufficient statistical power for any conclusions (Becker-Hebly et al., 2021). Three American studies of puberty suppression have been published: from Stony Brook (Achille et al., 2020), Dallas (Kuper et al., 2020), and Seattle (Tordoff et al., 2022).[6] None tried to replicate the Amsterdam and London longitudinal studies, choosing completely different measures, with one exception (BIS is used by Kuper et al., 2020). Each introduced a different set of measures: Quick Inventory of Depressive Symptoms, Screen for Child Anxiety Related Emotional

and Satisfaction Questionnaire, Generalized Anxiety Disorder 7-item scale, and the Patient Health Questionnaire 9-item scale. The last scale was common to two studies, but even they were not comparable: one used the version for teenagers, the other the adult version which the researchers chose to dichotomize. All the samples were tiny: 19, 23 (including an unspecified number of males given anti-androgens and females given medroxyprogesterone rather than GnRHa), and 25. Results were reported inconsistently: sometimes the outcomes for the sample subjected to puberty suppression were combined with a much larger sample on cross-sex hormones; sometimes the parameters of complex multivariate models were reported while the within-subject change during puberty suppression was concealed (Singal, 2022). Finally, some results were vitiated by high—and unexplained—rates of attrition: 47% of the subjects in one study were excluded because they failed to fill in the questionnaires at three points in time (Achille et al., 2020). What is frustrating is that if these researchers had simply followed the methods of de Vries et al. (2011), these three small samples would have contributed to cumulative knowledge. Finally, a large-scale American study recruited 90 subjects for puberty suppression—from Boston, Chicago, Los Angeles, and San Francisco—between 2016 and 2018 (Olson-Kennedy et al., 2019). Outcomes after 24 months have evidently been collected, but only baseline results have been published (Chen et al., 2021).

Evidence on side effects

On the side effects of puberty suppression, there is most evidence on bone density. That GnRHa would cause “an insufficient formation of bone mass” was initially dismissed “of no great concern” (Gooren & Delemarre-van de Waal, 1996, p. 72). Then it was recognized that patients could “end with a decreased bone density, which is associated with a high risk of osteoporosis” (Delemarre-van de Waal & Cohen-Kettenis, 2006, p. S134). The detrimental effect of GnRHa on the accrual of normal bone mass has been documented in several longitudinal studies from the Amsterdam clinic (Klink et al., 2015;

Joseph et al., 2019), and a clinic in Ottawa (Navabi et al., 2021). Less obviously, adolescents who seek GnRHa for gender dysphoria have a lower distribution of bone density compared to the population of the same sex and age (see also Lee et al., 2020). This reflects in part the high prevalence of eating disorders.

Bone mineral density (BMD) is measured by a dual energy X-ray absorptiometry scan over the spine and the hip. The absolute value of BMD is standardized as a *Z*-score, expressing this individual's BMD relative to the population of the same sex and age. BMD can be adjusted for height to derive the volumetric bone mineral apparent density (BMAD), which is likewise standardized as a *Z*-score. A *Z*-score below −2 is considered low; it indicates bone density in the lowest 2.3% of the population. The salience of this threshold is revealed by the London clinic's protocol which required both spine and hip *Z*-scores to exceed −2 to be eligible for GnRHa (Viner et al., 2010). This was subsequently relaxed "in exceptional circumstances" if clinicians "feel that on the balance of risks, pubertal suppression is an appropriate option despite risks of osteoporosis in later adult life" and patients "understand the risks of GnRH analogue treatment for bone density (i.e. risks of later osteoporosis)" (Viner et al., 2012).

Most studies of bone density after puberty suppression summarize the distribution of *Z*-scores by mean and standard deviation; only two provide information on the lower tail of the distribution, which is what matters clinically. At the Amsterdam clinic, 56 transgender adolescents were treated with GnRHa, commencing at ages ranging from 11 to 18, for an average duration of 1.7 years. After puberty suppression, the minimum *Z*-score for spine BMAD was −2.4, and the minimum hip BMAD was −3.4 (Vlot et al., 2017). Normally we would expect to find a *Z*-score below −3 in only 0.13% of the population—1 in 741. At the London clinic, 24 adolescents were treated with GnRHa, commencing at ages ranging from 12 to 14, for a duration of 24 months. After puberty suppression, the hip BMD *Z*-score was below −2 for 7 patients. The spine BMD *Z*-score was below −2 for 7 patients, including 4 patients with *Z*-score below −3; the spine BMAD *Z*-score was below −2 for 8 patients, including 3 with *Z*-score below −3 (Biggs, 2021). Clearly, then, a

suppression. The subsequent administration of cross-sex hormones increases bone mass, but *Z*-scores remain below the baseline recorded at the outset of puberty suppression (Klink et al., 2015; Stoffers et al., 2019; Vlot et al., 2017), with the possible exception of females who take testosterone after starting GnRHa early in puberty (Schagen et al., 2020).

What is not clear is the consequence of abnormally low bone density. Information on fractures, for example, has been published only for adults taking cross-sex hormones who had not undergone puberty suppression (Wiepjes et al., 2020). Anecdotally, a female patient at the London clinic who started GnRHa at age 12 then experienced four broken bones by the age of 16 (Bannerman, 2019). A Swedish television documentary discovered one female who was given GnRHa from age 11 to 15 by the Karolinska University Hospital in Stockholm, and now suffers from severe osteoporosis, including continual skeletal pain (SVT, 2022). This case—along with two others whose puberty suppression was terminated following concerns about bone density—led Sweden to restrict the use of GnRHa for adolescents with gender dysphoria.

The effects of puberty suppression on emotional and cognitive development are more difficult to ascertain, but more consequential as they could potentially affect the capacity to consent to cross-sex hormones and surgery. One case report of puberty suppression commencing just before age of 12 measured a drop in IQ by 10 points after 28 months (M. A. Schneider et al., 2017). A single case is insubstantial, of course, but there are similar findings from children treated with GnRHa for precocious puberty. A study of 25 children measured a drop of 7 points after two years (Mul et al., 2007); another study found a gap of 8 points between 15 treated children and a matched control group (Hayes, 2017; Wojniusz et al., 2016). Unfortunately the Amsterdam clinic's longitudinal study of puberty suppression measured IQ only at baseline and did not measure it again (de Vries et al., 2011, 2014). A small study from the clinic found that 8 adolescent males undergoing puberty suppression performed worse in a test of executive functioning than three control groups; the differences are statistically significant, but the samples

provide evidence of the substantial effects of puberty suppression. In sheep, GnRHa impairs spatial memory, and this effect remains after the treatment is stopped—thus demonstrating the irreversibility of puberty suppression (Hough et al. 2017a; 2017b). Counterintuitively, GnRHa also leads to greater differences between males and females in foraging behavior (Wojniusz et al., 2011). In mice, the effects of GnRHa vary by sex: males develop stronger preference for other males and an increased stress response; females exhibit increased anxiety and despair-like behavior (Anacker et al., 2021).

Even less is known about the effects of puberty suppression on sexual functioning. Jennings, who started on GnRHa at the age of 11, has no libido and cannot orgasm. Jennings' surgeon, Marci Bowers, who has performed over 2,000 vaginoplasties, acknowledges that "every single child … who was truly blocked at Tanner stage 2, has never experienced orgasm. I mean, it's really about zero" (Bowers, 2022). This remark refers to males. The effects of puberty suppression at such an early stage on females is unknown. FG is reportedly able to orgasm (de Vries et al., 2011). One patient at the London clinic who took GnRHa from the age of 12 to 16 but did not continue to cross-sex hormones has experienced no sexual desire in the two years since ceasing GnRHa (Bannerman, 2022). According to de Vries, orgasm is "a very interesting and so far not studied question" (Klotz, 2022).

Conclusion

The use of GnRHa to suppress puberty has proved more popular than could have been envisaged in the mid-1990s. It has become the international standard for treating gender dysphoria and has attracted increasing numbers of patients. Down to 2015, the Amsterdam clinic administered GnRHa to a total of 333 youth aged under the age of 18 (Wiepjes et al., 2018). From 2012 to 2020, the London clinic administered GnRHa to 344 children under the age of 15. Both clinics were overwhelmed by referrals from the mid-2010s, and the lengthening waiting lists provided scope for unscrupulous commercial

a Welsh doctor which will diagnose a 9-year-old with gender dysphoria over video and prescribe GnRHa on the same day (Medical Practitioners Tribunal Service, 2022). The total number of patients subjected to puberty suppression, worldwide, must run to several thousand. The proponents of GnRHa never reassessed the rationale for the intervention as the numbers multiplied. It is one thing to assert that very rare cases of extreme gender dysphoria—one per year in the Netherlands in the late 1990s—should be treated as juvenile transsexuals. It is another to make this claim for numerous adolescents—currently over a hundred a year in the Netherlands. Given the fact that gender dysphoria lacks an objective diagnosis, the potential for puberty suppression is expansive. When a recent survey in one American school district found 7% of students identifying as "gender diverse," the authors urged that all receive "access to gender affirming care," which in effect means giving GnRHa on request (Kidd et al., 2021, p. 3).[7]

Whether the availability of puberty suppression has increased demand is a question that should be raised. Taking GnRHa early in puberty promises a more passable resemblance to the opposite sex, and this is why it proved so fascinating to television audiences. It is no coincidence that media coverage of transgender youth focuses on those who suppressed puberty at a young age, most famously Jennings. Positive media coverage is known to increase referrals to gender clinics, at least over the short term (Indremo et al., 2022; Pang, de Graaf, et al., 2020). Although Dutch clinicians advise against "a complete social transition … before the very early stages of puberty" (de Vries & Cohen-Kettenis, 2012, pp. 308–309), the availability of GnRHa now makes it feasible for parents to treat a young child as the opposite sex, which guarantees that the child will experience the onset of puberty as catastrophic and thus demand endocrinological intervention. For boys, social transition prior to puberty is a powerful predictor of gender dysphoria persisting into adolescence, even controlling for the degree of dysphoria in childhood (Steensma et al., 2013). This pathway is illustrated by interviews with 30 British parents who had started raising their children as the opposite sex between the ages of 3 and 10. According to one parent, "If you don't give a child puberty-blockers there is a consequence—it's not that nothing happens. There's a massive consequence" (Horton,

clinic: “at the end of the day, he’s just gonna say whatever it is, that makes you shut up, so that he can get the blocker” (Horton, 2022, p. 14).

What has happened to the majority of children with gender dysphoria who used to grow up into gay or lesbian adults? The original articles promoting GnRHa (Cohen-Kettenis & van Goozen, 1998; Gooren & Delemarre-van de Waal, 1996) hypothesized that children whose dysphoria persisted to the age of 12 were destined to become transsexual. This arbitrary age threshold was soon forgotten. Outside the Netherlands, GnRHa was adopted with no minimum age, and has been prescribed to children as young as 8 years old.[8] Delemarre-van de Waal eventually advocated for GnRHa to be administered before Tanner stage 2, “right at the onset of puberty,” followed quickly by cross-sex hormones (Delemarre-van de Waal, 2014, p. 202). And of course the transsexual pathway now begins long before puberty, with social transition and psychological diagnosis. As de Hingh observes, “a diagnosis says you’ve got a problem that needs to be treated … The medical process, with pills and protocols, takes over the normal process of identification formation” (de Hingh, 2021, pp. 182–183). Clinicians need to explain how they are sure that some of the adolescents being prescribed GnRHa would not have grown into gay or lesbian adults, with their sexuality and fertility intact.

The article that introduced puberty suppression to the medical literature was accurately titled: this endocrinological intervention is designed for juvenile transsexuals (Gooren & Delemarre-van de Waal, 1996). This fact should not be obscured by claiming that puberty suppression is reversible and diagnostic. It is not diagnostic because over 95% of adolescents given GnRHa will continue to cross-sex hormones, and this fraction has not declined even as the number of youths subjected to GnRHa has multiplied by two orders of magnitude. The claim for reversibility was contradicted from the outset by the unknown effect of puberty suppression on brain development. Irreversibility has now been demonstrated by randomized control trials in nonhuman animals. The central justification for puberty suppression was that it increases outward resemblance to the opposite sex and requires less surgical intervention. Paradoxically, however, early

puberty suppression for males will most likely make subsequent genital surgery more risky—this is what killed one of the initial Dutch cohort—with worse results.

Evidence for the benefits of puberty suppression must be acknowledged as slender. Decisions made by clinicians have prevented the collection of robust evidence. The Dutch proponents of GnRHa chose not to conduct a randomized control trial, giving two reasons (de Vries et al., 2011). Firstly, adolescents would have refused to participate, which does not make sense unless they could have obtained GnRHa from another source. Secondly, it would have been unethical to withhold GnRHa from the control group, because the clinicians believed the treatment to be beneficial—this rationale is circular because discovering whether a treatment is truly beneficial requires a randomized control trial. A lesson can be drawn from the use of GnRHa to pause precocious puberty. This was supposed to mitigate short stature, as was apparently shown by small uncontrolled studies (Hayes, 2016), but this effect was called into question by a randomized control trial (Cassio et al., 1999). When the London clinic designed a study to replicate the findings from Amsterdam, the same reasons for avoiding a randomized control study were repeated, along with an argument that subjects would soon realize whether they were receiving treatment or placebo (Viner et al., 2010). Yet this had been no impediment to the trial for children with early puberty.

The decision to rely on uncontrolled studies was exacerbated by other decisions. The Dutch clinicians chose incommensurable scales to measure gender dysphoria, which calls into question their finding that dysphoria declined following cross-sex hormones and surgery. Worse still, American clinicians eschewed the measures of psychological functioning used by the Amsterdam and London clinics (YSR, CBCL, and CGAS), thus ensuring that their tiny samples could not contribute to cumulative knowledge. One final point to remember in evaluating published studies is that the field of transgender medicine is subject to the same publication bias as every other field: unsuccessful results will not be published. This bias is illustrated by the London clinic's attempt to replicate the Amsterdam clinic's findings: the lack of improvement on GnRHa appeared in print

While the use of GnRHa to suppress puberty helped to create the juvenile transsexual, it could now be creating another "new way of being a person" (Wren, 2020): a sexless adult. This follows from the premise that natal puberty can be a kind of disease, and therefore failure to prevent an "irreversible development of secondary sex characteristics … may be considered unethical" (de Vries et al., 2011, p. 2282). Although the Dutch protocol envisages GnRHa as a preparatory phase before cross-sex hormones—imagined as undergoing puberty of the opposite sex—the logical conclusion is that hormones of either sex can be treated as vectors of disease. An Australian girl, Phoenix, was socially transitioned into a nonbinary identity at the age of 5 and took GnRHa from age 11. Reaching the age of 16, Phoenix refused to take testosterone because "remaining in an androgynous, peripubertal state is the only way their body can truly reflect their non-binary gender identity" (Notini et al., 2020, p. 743). The clinicians agreed to provide perpetual puberty suppression, despite the known deleterious physical effects—most obviously on bone density—and despite the unknown effects on emotional and cognitive development—which would affect Phoenix's capacity to consent. Phoenix is not the only individual seeking indefinite puberty suppression (Pang, Notini, et al., 2020). Such cases are still exceptional. But cases like FG also used to be exceptional.

Acknowledgements

Special thanks are due to Sherena Kranat, Susan Matthews, Ema Abbruzzese, and a Dutch detransitioner.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

Notes

1 The literature sometimes refers to GnRH (or LHRH) analogues, which is a broader classification comprising antagonists as well as agonists.

2 The pediatric endocrinologist was not named in the original article, but her identity is clear from later sources (e.g. Delemarre-van de Waal, 2014). FG is known as "B" in the published literature.

3 Bailey and Zucker (1995) had by then reviewed four additional prospective studies in the same vein as well as numerous retrospective ones. Later prospective studies demonstrated that girls who manifested cross-gender behavior as infants were also more likely to grow up as lesbian, though the association was weaker than for boys (e.g. Li et al., 2017).

4 Pediatric endocrinology's obsession with height has motivated the use of artificial estrogen to accelerate puberty in girls judged as too tall (Cohen & Cosgrove, 2009) and the use of GnRHa to delay puberty in girls judged as too short (Hayes, 2016).

5 A previous comparison (Biggs, 2020) included only 30 subjects from the London clinic and measured outcomes after 12 months. The Stata do-file is posted on Harvard dataverse at https://doi.org/10.7910/DVN/QPRCR1.

6 De Vries (2022) also cites a study from Kansas City (Allen et al., 2019) which includes an unknown number of children subjected to GnRHa before cross-sex hormones, but it took no baseline measure before puberty suppression.

7 The authors calculate the "gender diverse" proportion as 9% because they omit students who skipped the question (Kidd et al., 2021). It is more plausible to include the latter in the denominator, which yields 7%.

8 The London clinic referred a 7-year-old for endocrinological intervention, but it is not known whether GnRHa was actually prescribed before she turned 8 (Butler et al., 2022).

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