5. Butler G, De Graaf N, Wren B, Carmichael P. Assessment and support of children and adolescents with gender dysphoria. Arch Dis Child. 2018; 103(7):631–6. Epub 2018/04/14. https://doi.org/10.1136/archdischild-2018-314992 PMID: 29650510.

6. Turban JL, Ehrensaft D. Research Review: Gender identity in youth: treatment paradigms and controversies. J Child Psychol Psychiatry. 2018; 59(12):1228–43. Epub 2017/10/27. https://doi.org/10.1111/jcpp.12833 PMID: 29071722.

7. Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. J Am Acad Child Adolesc Psychiatry. 2013; 52(6):582–90. Epub 2013/05/25. https://doi.org/10.1016/j.jaac.2013.03.016 PMID: 23702447.

8. Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017; 102(11):3869–903. Epub 2017/09/26. https://doi.org/10.1210/jc.2017-01658 PMID: 28945902.

9. Oliphant J, Veale J, Macdonald J, Carroll R, Johnson R, Harte M, et al. Guidelines for Gender Affirming Healthcare for Gender Diverse and Transgender Children, Young People and Adults in Aotearoa, New Zealand. N Z Med J. 2018; 131(1487):86–96. Epub 2018/12/14. PMID: 30543615.

10. Telfer MM, Tollit MA, Pace CC, Pang KC. Australian standards of care and treatment guidelines for transgender and gender diverse children and adolescents. Med J Aust. 2018; 209(3):132–6. Epub 2018/06/16. https://doi.org/10.5694/mja17.01044 PMID: 29902964.

11. Rafferty J. Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents. Pediatrics. 2018; 142(4). Epub 2018/09/19. https://doi.org/10.1542/peds.2018-2162 PMID: 30224363.

12. Skordis N, Butler G, de Vries MC, Main K, Hannema SE. ESPE and PES International Survey of Centers and Clinicians Delivering Specialist Care for Children and Adolescents with Gender Dysphoria. Hormone research in paediatrics. 2018; 90(5):326–31. Epub 2019/01/30. https://doi.org/10.1159/000496115 PMID: 30695784.

13. Agana MG, Greydanus DE, Indyk JA, Calles JL Jr., Kushner J, Leibowitz S, et al. Caring for the transgender adolescent and young adult: Current concepts of an evolving process in the 21st century. Dis Mon. 2019; 65(9):303–56. Epub 2019/08/14. https://doi.org/10.1016/j.disamonth.2019.07.004 PMID: 31405516.

14. Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. J Clin Endocrinol Metab. 2015; 100(2):E270–5. Epub 2014/11/27. https://doi.org/10.1210/jc.2014-2439 PMID: 25427144.

15. Cohen-Kettenis PT, Schagen SE, Steensma TD, de Vries AL, Delemarre-van de Waal HA. Puberty suppression in a gender-dysphoric adolescent: a 22-year follow-up. Arch Sex Behav. 2011; 40(4):843–7. Epub 2011/04/20. https://doi.org/10.1007/s10508-011-9758-9 PMID: 21503817.

16. Schagen SE, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE. Efficacy and Safety of Gonadotropin-Releasing Hormone Agonist Treatment to Suppress Puberty in Gender Dysphoric Adolescents. J Sex Med. 2016; 13(7):1125–32. Epub 2016/06/19. https://doi.org/10.1016/j.jsxm.2016.05.004 PMID: 27318023.

17. Kuper LE, Stewart S, Preston S, Lau M, Lopez X. Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. Pediatrics. 2020; 145(4). Epub 2020/03/30. https://doi.org/10.1542/peds.2019-3006 PMID: 32220906.

18. Achille C, Taggart T, Eaton NR, Osipoff J, Tafuri K, Lane A, et al. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results. International Journal of Pediatric Endocrinology. 2020; 2020(1):8. https://doi.org/10.1186/s13633-020-00078-2 PMID: 32368216

19. Brik T, Vrouenraets L, de Vries MC, Hannema SE. Trajectories of Adolescents Treated with Gonadotropin-Releasing Hormone Analogues for Gender Dysphoria. Arch Sex Behav. 2020; 49(7):2611–8. Epub 2020/03/11. https://doi.org/10.1007/s10508-020-01660-8 PMID: 32152785.

20. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2009; 94(9):3132–54. Epub 2009/06/11. https://doi.org/10.1210/jc.2009-0345 PMID: 19509099.

21. Spack NP, Edwards-Leeper L, Feldman HA, Leibowitz S, Mandel F, Diamond DA, et al. Children and adolescents with gender identity disorder referred to a pediatric medical center. Pediatrics. 2012; 129(3):418–25. Epub 2012/02/22. https://doi.org/10.1542/peds.2011-0907 PMID: 22351896.

22. Meyer WJ 3rd. Gender identity disorder: an emerging problem for pediatricians. Pediatrics. 2012; 129 (3):571–3. Epub 2012/02/22. https://doi.org/10.1542/peds.2011-3696 PMID: 22351880.

23. Hewitt JK, Paul C, Kasiannan P, Grover SR, Newman LK, Warne GL. Hormone treatment of gender identity disorder in a cohort of children and adolescents. Med J Aust. 2012; 196(9):578–81. Epub 2012/05/25. https://doi.org/10.5694/mja12.10222 PMID: 22621149.

24. de Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. J Sex Med. 2011; 8(8):2276–83. Epub 2010/07/22. https://doi.org/10.1111/j.1743-6109.2010.01943.x PMID: 20646177.

25. Cole TJ, Freeman JV, Preece MA. Body mass index reference curves for the UK, 1990. Arch Dis Child. 1995; 73(1):25–9. https://doi.org/10.1136/adc.73.1.25 PMID: 7639544

26. Kalkwarf HJ, Zemel BS, Gilsanz V, Lappe JM, Horlick M, Oberfield S, et al. The bone mineral density in childhood study: bone mineral content and density according to age, sex, and race. J Clin Endocrinol Metab. 2007; 92(6):2087–99. Epub 2007/02/22. https://doi.org/10.1210/jc.2006-2553 PMID: 17311856.

27. Zemel BS, Leonard MB, Kelly A, Lappe JM, Gilsanz V, Oberfield S, et al. Height adjustment in assessing dual energy x-ray absorptiometry measurements of bone mass and density in children. J Clin Endocrinol Metab. 2010; 95(3):1265–73. Epub 2010/01/28. https://doi.org/10.1210/jc.2009-2057 PMID: 20103654.

28. Crijnen AA, Achenbach TM, Verhulst FC. Comparisons of problems reported by parents of children in 12 cultures: total problems, externalizing, and internalizing. J Am Acad Child Adolesc Psychiatry. 1997; 36(9):1269–77. Epub 1997/09/18. https://doi.org/10.1097/00004583-199709000-00020 PMID: 9291729.

29. Verhulst FC, Achenbach TM, van der Ende J, Erol N, Lambert MC, Leung PW, et al. Comparisons of problems reported by youths from seven countries. Am J Psychiatry. 2003; 160(8):1479–85. Epub 2003/08/06. https://doi.org/10.1176/appi.ajp.160.8.1479 PMID: 12900311.

30. Aitken M, VanderLaan DP, Wasserman L, Stojanovski S, Zucker KJ. Self-Harm and Suicidality in Children Referred for Gender Dysphoria. J Am Acad Child Adolesc Psychiatry. 2016; 55(6):513–20. Epub 2016/05/31. https://doi.org/10.1016/j.jaac.2016.04.001 PMID: 27238070.

31. Van Meter AR, Algorta GP, Youngstrom EA, Lechtman Y, Youngstrom JK, Feeny NC, et al. Assessing for suicidal behavior in youth using the Achenbach System of Empirically Based Assessment. Eur Child Adolesc Psychiatry. 2018; 27(2):159–69. Epub 2017/07/28. https://doi.org/10.1007/s00787-017-1030-y PMID: 28748484.

32. Deutz MH, Geeraerts SB, van Baar AL, Dekovic M, Prinzie P. The Dysregulation Profile in middle childhood and adolescence across reporters: factor structure, measurement invariance, and links with self-harm and suicidal ideation. Eur Child Adolesc Psychiatry. 2016; 25(4):431–42. Epub 2015/08/01. https://doi.org/10.1007/s00787-015-0745-x PMID: 26226917.

33. Ravens-Sieberer U, Gosch A, Rajmil L, Erhart M, Bruil J, Power M, et al. The KIDSCREEN-52 quality of life measure for children and adolescents: psychometric results from a cross-cultural survey in 13 European countries. Value Health. 2008; 11(4):645–58. Epub 2008/01/09. https://doi.org/10.1111/j.1524-4733.2007.00291.x PMID: 18179669.

34. Lindgren TW, Pauly IB. A body image scale for evaluating transsexuals. Arch Sex Behav. 1975; 4 (6):639–56. Epub 1975/11/01. https://doi.org/10.1007/BF01544272 PMID: 1212093.

35. Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, et al. A children's global assessment scale (CGAS). Arch Gen Psychiatry. 1983; 40(11):1228–31. Epub 1983/11/01. https://doi.org/10.1001/archpsyc.1983.01790100074010 PMID: 6639293.

36. Viner RM, Clark C, Taylor S, Bhui K, Klineberg E, Head J, et al. Risk factors for persistent fatigue in adolescents: A population-based study. Journal of Adolescent Health. 2006; 38(2):113–4. https://doi.org/10.1016/j.jadohealth.2005.11.080

37. Krogh AB, Larsson B, Linde M. Prevalence and disability of headache among Norwegian adolescents: A cross-sectional school-based study. Cephalalgia. 2015; 35(13):1181–91. Epub 2015/02/28. https://doi.org/10.1177/0333102415573512 PMID: 25720767.

38. Ghelani R, Lim C, Brain C, Fewtrell M, Butler G. Sudden sex hormone withdrawal and the effects on body composition in late pubertal adolescents with gender dysphoria. J Pediatr Endocrinol Metab. 2019. Epub 2019/12/14. https://doi.org/10.1515/jpem-2019-0045 PMID: 31834861.

39. Vlot MC, Klink DT, den Heijer M, Blankenstein MA, Rotteveel J, Heijboer AC. Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. Bone. 2017; 95:11–9. Epub 2016/11/16. https://doi.org/10.1016/j.bone.2016.11.008 PMID: 27845262.

40. Joseph T, Ting J, Butler G. The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort. J Pediatr Endocrinol Metab. 2019; 32(10):1077–81. Epub 2019/09/01. https://doi.org/10.1515/jpem-2019-0046 PMID: 31472062.

41. Rothman MS, Iwamoto SJ. Bone Health in the Transgender Population. Clin Rev Bone Miner Metab. 2019; 17(2):77–85. Epub 2019/08/28. https://doi.org/10.1007/s12018-019-09261-3 PMID: 31452648.

42. Panagiotakopoulos L. Transgender medicine—puberty suppression. Rev Endocr Metab Disord. 2018; 19(3):221–5. Epub 2018/08/17. https://doi.org/10.1007/s11154-018-9457-0 PMID: 30112593.

43. Skagerberg E, Davidson S, Carmichael P. Internalizing and Externalizing Behaviors in a Group of Young People with Gender Dysphoria. Int J Transgenderism. 2013; 13(3):105–12. https://doi.org/10.1080/15532739.2013.822340

44. Zucker KJ. Adolescents with Gender Dysphoria: Reflections on Some Contemporary Clinical and Research Issues. Arch Sex Behav. 2019; 48(7):1983–92. Epub 2019/07/20. https://doi.org/10.1007/s10508-019-01518-8 PMID: 31321594.

45. Zucker KJ, Bradley SJ, Owen-Anderson A, Kibblewhite SJ, Wood H, Singh D, et al. Demographics, behavior problems, and psychosexual characteristics of adolescents with gender identity disorder or transvestic fetishism. J Sex Marital Ther. 2012; 38(2):151–89. Epub 2012/03/07. https://doi.org/10.1080/0092623X.2011.611219 PMID: 22390530.

46. Levitan N, Barkmann C, Richter-Appelt H, Schulte-Markwort M, Becker-Hebly I. Risk factors for psychological functioning in German adolescents with gender dysphoria: poor peer relations and general family functioning. Eur Child Adolesc Psychiatry. 2019; 28(11):1487–98. Epub 2019/03/17. https://doi.org/10.1007/s00787-019-01308-6 PMID: 30877477.

47. Becerra-Culqui TA, Liu Y, Nash R, Cromwell L, Flanders WD, Getahun D, et al. Mental Health of Transgender and Gender Nonconforming Youth Compared With Their Peers. Pediatrics. 2018; 141(5). Epub 2018/04/18. https://doi.org/10.1542/peds.2017-3845 PMID: 29661941.

48. Taliaferro LA, McMorris BJ, Rider GN, Eisenberg ME. Risk and Protective Factors for Self-Harm in a Population-Based Sample of Transgender Youth. Arch Suicide Res. 2019; 23(2):203–21. Epub 2018/02/21. https://doi.org/10.1080/13811118.2018.1430639 PMID: 29461934.

49. Costa R, Dunsford M, Skagerberg E, Holt V, Carmichael P, Colizzi M. Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria. J Sex Med. 2015; 12(11):2206–14. Epub 2015/11/12. https://doi.org/10.1111/jsm.13034 PMID: 26556015.

50. Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. Pediatrics. 2020. Epub 2020/01/25. https://doi.org/10.1542/peds.2019-1725 PMID: 31974216.

51. Goedegebuure WJ, van der Steen M, de With JL, Hokken-Koelega A. Cognition, Health-Related Quality of Life, and Psychosocial Functioning After GH/GnRHa Treatment in Young Adults Born SGA. J Clin Endocrinol Metab. 2018; 103(11):3931–8. Epub 2018/08/24. https://doi.org/10.1210/jc.2018-01463 PMID: 30137415.

52. de Graaf NM, Cohen-Kettenis PT, Carmichael P, de Vries ALC, Dhondt K, Laridaen J, et al. Psychological functioning in adolescents referred to specialist gender identity clinics across Europe: a clinical comparison study between four clinics. Eur Child Adolesc Psychiatry. 2018; 27(7):909–19. Epub 2017/12/20. https://doi.org/10.1007/s00787-017-1098-4 PMID: 29256158.

53. Nock MK, Green JG, Hwang I, McLaughlin KA, Sampson NA, Zaslavsky AM, et al. Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: results from the National Comorbidity Survey Replication Adolescent Supplement. JAMA Psychiatry. 2013; 70(3):300–10. Epub 2013/01/11. https://doi.org/10.1001/2013.jamapsychiatry.55 PMID: 23303463.

54. Jung KY, Kim T, Hwang SY, Lee TR, Yoon H, Shin TG, et al. Deliberate Self-harm among Young People Begins to Increase at the Very Early Age: a Nationwide Study. Journal of Korean medical science. 2018; 33(30):e191. Epub 2018/07/24. https://doi.org/10.3346/jkms.2018.33.e191 PMID: 30034304.

55. Morey Y, Mellon D, Dailami N, Verne J, Tapp A. Adolescent self-harm in the community: an update on prevalence using a self-report survey of adolescents aged 13–18 in England. J Public Health (Oxf). 2017; 39(1):58–64. Epub 2016/02/20. https://doi.org/10.1093/pubmed/fdw010 PMID: 26892623.

56. Stallard P, Spears M, Montgomery AA, Phillips R, Sayal K. Self-harm in young adolescents (12–16 years): onset and short-term continuation in a community sample. BMC psychiatry. 2013; 13:328. Epub 2013/12/04. https://doi.org/10.1186/1471-244X-13-328 PMID: 24294921.

57. Becker I, Auer M, Barkmann C, Fuss J, Moller B, Nieder TO, et al. A Cross-Sectional Multicenter Study of Multidimensional Body Image in Adolescents and Adults with Gender Dysphoria Before and After Transition-Related Medical Interventions. Arch Sex Behav. 2018; 47(8):2335–47. Epub 2018/08/09. https://doi.org/10.1007/s10508-018-1278-4 PMID: 30088234.

58. Biggs M. Gender Dysphoria and Psychological Functioning in Adolescents Treated with GnRHa: Comparing Dutch and English Prospective Studies. Arch Sex Behav. 2020; 49(7):2231–6. Epub 2020/07/01. https://doi.org/10.1007/s10508-020-01764-1 PMID: 32594279.

59. Vandenbroucke JP. What is the best evidence for determining harms of medical treatment? CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne. 2006; 174 (5):645–6. Epub 2006/03/01. https://doi.org/10.1503/cmaj.051484 PMID: 16505461.

60. Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. The Cochrane database of systematic reviews. 2014;(4):MR000034. Epub 2014/05/02. https://doi.org/10.1002/14651858.MR000034.pub2 PMID: 24782322.

61. Golder S, Loke YK, Bland M. Meta-analyses of adverse effects data derived from randomised controlled trials as compared to observational studies: methodological overview. PLoS Med. 2011; 8(5): e1001026. Epub 2011/05/12. https://doi.org/10.1371/journal.pmed.1001026 PMID: 21559325.

62. Olson-Kennedy J, Chan YM, Rosenthal S, Hidalgo MA, Chen D, Clark L, et al. Creating the Trans Youth Research Network: A Collaborative Research Endeavor. Transgend Health. 2019; 4(1):304–12. Epub 2019/11/09. https://doi.org/10.1089/trgh.2019.0024 PMID: 31701011.

63. Olson J, Chan Y-M, Garofalo R, Spack NP, Chen D, Clark L, et al. Impact of Early Medical Treatment for Transgender Youth: Protocol for the Longitudinal, Observational Trans Youth Care Study. JMIR research protocols. 2019; 8(7):e14434. https://doi.org/10.2196/14434 PMID: 31290407

Socialstyrelsen
THE NATIONAL BOARD OF HEALTH AND WELFARE

Care of children and adolescents with gender dysphoria

Summary

Summary

The National Board of Health and Welfare (NBHW) has been commissioned by the Swedish government to update the national guidelines on care of children and adolescents with gender dysphoria, first published in 2015 [1]. Guidelines chapters are updated stepwise and this report contains revised guidance on psychosocial support and diagnostic assessment, and on puberty suppressing treatment with GnRH-analogues and gender-affirming hormonal treatment. This report thus replaces the corresponding chapters in the publication from 2015. Remaining chapters and the updated guidelines as a whole will be published later in 2022. In response to comments received during external review, two new chapters have been added, named *New recommendations on hormonal treatment – their reasons and consequences and Non-binary gender identity – current knowledge and a need for clarification*. Another difference compared to the guidelines from 2015 [1] is that the term "gender incongruence" is used alongside the term "gender dysphoria". For explanations of terms and abbreviations, see Appendix 2. For a description of the scientific evidence and clinical experience underlying the recommendations and the work process, see Appendices 3 and 4.

The guidelines apply to children and adolescents, i.e. people under 18 years of age. In the medical text sections, the term children (barn) refers to persons who have not yet entered puberty, while the term adolescents (ungdomar) refers to people whose puberty has started. In the text sections relating to juridical regulations, only the term children (barn) is used and denotes people younger than 18 years of age. Finally, the term "young people" (unga) is sometimes used in text sections addressing both children and adolescents.

Introductory comment

The summary that follows and the introductory chapter describe that the updated recommendations for puberty suppression with GnRH-analogues and gender-affirming hormonal treatment have become more restrictive compared to 2015, and the reasons that they have changed. The new recommendations entail that a larger

proportion than before, among adolescents with gender incongruence referred for diagnostic assessment of gender dysphoria, will need to be offered other care than hormonal treatments. Questions on how to ensure that all young people suffering from gender dysphoria be taken seriously and confirmed in their gender identity, well received and offered adequate care are becoming increasingly relevant, and will need to be answered during the ongoing restructuring of certain care for gender dysphoria into three national specialised medical care services (NBHW decision in December 2020). The care for children, adolescents and adults with gender dysphoria in these three national specialised units aims to improve equality in care, coordination and dialogue, and may enhance the implementation of national guidelines.

Recommendations and criteria for hormonal treatment

For adolescents with gender incongruence, the NBHW deems that the risks of puberty suppressing treatment with GnRH-analogues and gender-affirming hormonal treatment currently outweigh the possible benefits, and that the treatments should be offered only in exceptional cases. This judgement is based mainly on three factors: the continued lack of reliable scientific evidence concerning the efficacy and the safety of both treatments [2], the new knowledge that detransition occurs among young adults [3], and the uncertainty that follows from the yet unexplained increase in the number of care seekers, an increase particularly large among adolescents registered as females at birth [4].

A systematic review published in 2022 by the Swedish Agency for Health Technology Assessment and Assessment of Social Services [2] shows that the state of knowledge largely remains unchanged compared to 2015. High quality trials such as RCTs are still lacking and the evidence on treatment efficacy and safety is still insufficient and inconclusive for all reported outcomes. Further, it is not possible to determine how common it is for adolescents who undergo gender-affirming treatment to later change their perception of their gender identity or interrupt an ongoing treatment. An important difference compared to 2015 however, is that the occurrence of

detransition among young adults is now documented [3], meaning that the uncertain evidence that indicates a low prevalence of treatment interruptions or any aspects of regret is no longer unchallenged. Although the prevalence of detransition is still unknown, the knowledge that it occurs and that genderconfirming treatment thus may lead to a deteriorating of health and quality of life (i.e. harm), is important for the overall judgement and recommendation.

To minimize the risk that a young person with gender incongruence later will regret a gender-affirming treatment, the NBHW deems that the criteria for offering GnRH-analogue and gender-affirming hormones should link more closely to those used in the Dutch protocol, where the duration of gender incongruence over time is emphasized [5-7]. Accordingly, an early (childhood) onset of gender incongruence, persistence of gender incongruence until puberty and a marked psychological strain in response to pubertal development is among the recommended criteria. The publications that describe these criteria and the treatment outcomes when given in accordance [5, 6, 8] consitute the best available knowledge and should be used as guidance.

To ensure that new knowledge is gathered, the NBHW further deems that treatment with GnRH-analogues and sex hormones for young people should be provided within a research context, which does not necessarily imply the use of randomized controlled trials (RCTs). As in other healthcare areas where it is difficult to conduct RCTs while retaining sufficient internal validity, it is also important that other prospective study designs are considered for ethical review and that register studies are made possible. Until a research study is in place, the NBHW deems that treatment with GnRH-analogues and sex hormones may be given in exceptional cases, in accordance with the updated recommendations and criteria described in the guidelines. The complex multidisciplinary assessments will eventually be carried out in the three national units that are granted permission to provide highly specialized care services.

In accordance with the DSM-5, the recommendations in the guidelines from 2015 applied to young people with gender dysphoria in general, i.e. also young people with a non-binary gender identity. Another criterion within the Dutch protocol is that the child has had a binary ("cross-gender") gender identity since childhood [5, 6].

It has emerged during the review process, that the clinical experience and documentation of puberty-suppressing and hormonal treatment for young people with non-binary gender identity is lacking, and also that it is limited for adults. The NBHW still considers that gender dysphoria rather than gender identity should determine access to care and treatment. An urgent work thus remains, to clarify criteria under which adolescents with non-binary gender identity may be offered puberty-suppressing and gender-affirming hormonal treatment within a research framework.

References

1. Socialstyrelsen. God vård av barn och ungdomar med könsdysfori. Nationellt kunskapsstöd. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2015-4-6.pdf; 2015.
2. Statens beredning för medicinsk och social utvärdering. Hormonbehandling vid könsdysfori - barn och unga. En systematisk översikt och utvärdering av medicinska aspekter: SBU; 2022.
3. Littman L. Individuals Treated for Gender Dysphoria with Medical and/or Surgical Transition Who Subsequently Detransitioned: A Survey of 100 Detransitioners. Arch Sex Behav. 2021; 50(8):3353-69.
4. Socialstyrelsen. Utvecklingen av diagnosen könsdysfori - förekomst, samtidiga psykiatriska diagnoser och dödlighet i suicid. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/ovrigt/2020-2-6600.pdf.; 2020.
5. Cohen-Kettenis PT, van Goozen SH. Sex reassignment of adolescent transsexuals: a follow-up study. J Am Acad Child Adolesc Psychiatry. 1997; 36(2):263-71.
6. Smith YL, van Goozen SH, Cohen-Kettenis PT. Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. J Am Acad Child Adolesc Psychiatry. 2001; 40(4):472-81.
7. Delemarre-van de Waal H, Cohen-Kettenis P. Clinical management of gender identity disorder in adolescents: a protocol on

psychological and paediatric endocrinology aspects. European Journal of Endocrinology. 2006; 155:S131-7.

8. Schagen SE, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE. Efficacy and Safety of Gonadotropin-Releasing Hormone Agonist Treatment to Suppress Puberty in Gender Dysphoric Adolescents. J Sex Med. 2016; 13(7):1125-32.

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ORIGINAL PAPER

Trajectories of Adolescents Treated with Gonadotropin-Releasing Hormone Analogues for Gender Dysphoria

Tessa Brik[1] · Lieke J. J. J. Vrouenraets[2,3] · Martine C. de Vries[1,3] · Sabine E. Hannema[1,4]

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Abstract
Gonadotropin-releasing hormone analogues (GnRHa) are recommended as initial treatment for adolescents diagnosed with gender dysphoria, providing time to follow gender identity development and consider further treatment wishes without distress caused by unwanted pubertal changes. This has been described as an extended diagnostic phase. However, there are also concerns about the physical, neurocognitive, and psychosocial effects of this treatment. In this retrospective study, we document trajectories after the initiation of GnRHa and explore reasons for extended use and discontinuation of GnRHa. Treatment was considered appropriate in 143 (67%) of the 214 adolescents eligible for GnRHa treatment by virtue of their age/pubertal status, and all started GnRHa (38 transgirls, 105 transboys; median age, 15.0 years [range, 11.1–18.6] and 16.1 years [range, 10.1–17.9]). After a median duration of 0.8 years (0.3–3.8) on GnRHa, 125 (87%) started gender-affirming hormones (GAH). Nine (6%) discontinued GnRHa, five of whom no longer wished gender-affirming treatment. Thirteen had used GnRHa for longer than required by protocol for reasons other than logistics and regularly met with a mental health professional during this time, supporting the use of GnRHa treatment as an extended diagnostic phase. In conclusion, the vast majority who started GnRHa proceeded to GAH, possibly due to eligibility criteria that select those highly likely to pursue further gender-affirming treatment. Due to the observational character of the study, it is not possible to say if GnRHa treatment itself influenced the outcome. Few individuals discontinued GnRHa, and only 3.5% no longer wished gender-affirming treatment.

Keywords Gender dysphoria · Transgender · Gonadotropin-releasing hormone analogues · Hormone treatment · Gender identity

Introduction

Increasing numbers of young people diagnosed with gender dysphoria are seen by pediatric endocrinologists. Gender dysphoria is the persistent feeling of incongruence between gender identity (sense of being a man, woman, or other) and the sex assigned at birth. The diagnosis gender dysphoria can be made if the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) criteria are met (American Psychiatric Association, 2013). The prevalence of gender dysphoria among Dutch adolescents aged 12–18 years was recently estimated to be 1 in 6300 based on numbers of adolescents seeking medical treatment, with a ratio of transboys (assigned female at birth) to transgirls (assigned male at birth) of 1.9:1 (Wiepjes et al., 2018). Genetic, hormonal, psychological, and social factors may play a role, but the exact etiology of gender dysphoria remains unknown (de Vries & Cohen-Kettenis, 2012; Hembree et al., 2017; Martinerie et al., 2018).

Gender dysphoria in prepubertal children can be expressed by dislike of their physical sex characteristics and gender incongruent behavior. In many children, gender dysphoria will not persist, but if the gender dysphoric feelings intensify during puberty, they are thought to be unlikely to subside (de Vries & Cohen-Kettenis, 2012; Hembree et al., 2017; Zucker et al., 2011). When puberty starts (Tanner genital/breast stage

✉ Sabine E. Hannema
s.e.hannema@lumc.nl

[1] Department of Pediatrics, Leiden University Medical Centre, P.O. Box 9600, 2300 RC Leiden, The Netherlands

[2] Department of Pediatric and Adolescent Psychiatry, Curium-Leiden University Medical Centre, Leiden, The Netherlands

[3] Department of Medical Ethics and Health Law, Leiden University Medical Centre, Leiden, The Netherlands

[4] Department of Paediatric Endocrinology, Sophia Children's Hospital, Erasmus Medical Centre, Rotterdam, The Netherlands

2) and gender dysphoria persists, adolescents are eligible to start with puberty suppression using gonadotropin-releasing hormone analogues (GnRHa) (Coleman et al., 2011; Hembree et al., 2017). GnRHa treatment aims to give the adolescent the opportunity to explore their gender identity and time to consider if they wish to pursue gender-affirming treatment while development of unwanted secondary sex characteristics is suppressed in order to reduce distress (Hembree et al., 2017; Zucker et al., 2011). Effects of GnRHa on pubertal development are reversible. This is in contrast to gender-affirming hormones which have largely irreversible effects on secondary sex characteristics and may compromise fertility after prolonged use (De Roo, Tilleman, T'Sjoen, & De Sutter, 2016; Hembree et al., 2017).

Short-term adverse effects of GnRHa are hot flushes at the start of the treatment and sometimes mood alterations and fatigue (Delemarre-van de Waal & Cohen-Kettenis, 2006; Hembree et al., 2017; Schagen, Cohen-Kettenis, Delemarre-van de Waal, & Hannema, 2016). Few data are available on long-term adverse effects. Bone mineral density may be affected (Klink, Caris, Heijboer, van, & Rotteveel, 2015; Vlot et al., 2017), and since puberty is an important period for brain development (Sisk & Zehr, 2005), puberty suppression with GnRHa might also influence brain development. There is a lack of studies investigating effects of GnRHa on the brain. One study examined executive function and concluded that GnRHa treatment had no detrimental effects on performance (Staphorsius et al., 2015). However, a longitudinal study among 25 adopted girls treated with GnRHa for early puberty reported a decrease in IQ from 100.2 ± 12.7 to 93.1 ± 10.5 with a significant decline of performance score during treatment, but it was concluded that the decrease in IQ was not clinically relevant (Mul et al., 2001). A limitation of the study was the lack of a control group. A second small cross-sectional study of girls treated with GnRHa because of precocious puberty found no significant difference in cognitive functioning, behavioral, and social problems compared to healthy age-matched controls, but the study did not have enough power to detect differences smaller than one standard deviation (Wojniusz et al., 2016). Wojniusz et al. did report that emotional reactivity was possibly higher in girls treated with GnRHa although these results were not conclusive. Girls with early or precocious puberty are treated at a younger age so it is unclear to what extent these results apply to adolescents treated with GnRHa for gender dysphoria. Further studies are needed to assess if and what effects GnRHa have on various aspects of brain development in adolescence.

Opinions about the use of GnRHa vary (Vrouenraets, Fredriks, Hannema, Cohen-Kettenis, & de Vries, 2015). Arguments for the use of GnRHa that have been brought forward are the benefit of early treatment with GnRHa for mental health and quality of life (de Vries, Steensma, Doreleijers, & Cohen-Kettenis, 2011). Furthermore, it gives the adolescent and treatment team more time to explore the adolescent's gender identity and treatment wishes (Hembree et al., 2017). If the adolescent pursues gender-affirming treatment, some surgeries may not be necessary or less invasive as secondary sex characteristics are less developed. Early treatment is correlated with better postsurgical outcomes, possibly because of a physical appearance more in line with the affirmed gender (Cohen-Kettenis & van Goozen, 1997; Leibowitz & de Vries, 2016). However, this may not be of equal importance to all adolescents and early puberty suppression also precludes certain surgeries such as penile inversion vaginoplasty by limiting penile growth. Some have argued that puberty-blocking treatment prevents devastating psychological and physical harms including suicide and that adolescents should therefore be able to access this treatment even without parental approval (Dembroff, 2019; Priest, 2019), but others have underscored that there is no evidence that puberty suppression prevents suicide and that the risk of suicide, although high, should not be overstated and should be seen in comparison with a clinical comparison group rather than the general population (Antommaria, Shapiro, & Conard, 2019; Baker, 2019; Zucker, 2019).

Arguments against the use of GnRHa that have been raised include possible long-term adverse effects on health, psychological, and sexual functioning (Laidlaw, Cretella, & Donovan, 2019; Richards, Maxwell, & McCune, 2019; Vrouenraets et al., 2015). Some state that adolescents may be unable to make far-reaching decisions at a young age, especially in the presence of comorbid psychiatric conditions, which are common among youth with gender dysphoria (Korte et al., 2008; Laidlaw et al., 2019; Vrouenraets et al., 2015). Furthermore, gender identity develops and may change during adolescence. Concerns have been raised that the use of GnRHa may influence this process and might increase the likelihood of persistence of gender dysphoria (Korte et al., 2008; Laidlaw et al., 2019; Richards et al., 2019; Stein, 2012; Vrouenraets et al., 2015). It is unknown if the use of GnRHa prevents resolution of gender dysphoria (Korte et al., 2008). Many prepubertal children with gender dysphoria no longer experience gender dysphoria in adolescence, and the experience of romantic and sexual attraction is thought to play an important role in this process (Steensma, Biemond, de Boer, & Cohen-Kettenis, 2011). Some may come to understand themselves as homosexual or bisexual (Steensma et al., 2011). GnRHa, by blocking sexual development, might interfere with this process (Korte et al., 2008). Another concern is that although GnRHa treatment is to be used as an extended diagnostic phase, the start of it may lead the adolescents and parents to assume that transgender outcome is the only possible outcome which may prevent exploration of other possibilities (Leibowitz & de Vries, 2016).

To gain more insight into the use of GnRHa in adolescents with gender dysphoria, the current study aims to document trajectories after the initiation of GnRHa, i.e., discontinuation

of GnRHa, prolonged use of GnRHa, and initiation of gender-affirming hormones; to investigate the duration of GnRHa treatment; and to explore reasons for extended use and discontinuation of GnRHa.

Method

Participants

This is a single-center retrospective study. Out of 269 children and adolescents registered at the Curium-Leiden University Medical Centre gender clinic in Leiden, the Netherlands, 214 were pubertal and within the appropriate age range for treatment at our pediatric clinic. Out of these, 143 (67%) had started GnRHa treatment between November 2010 (when the clinic first started) and January 1, 2018. The study population consisted of these 143 adolescents (38 transgirls, 105 transboys). Not included in the study were children and adolescents in whom gender dysphoria was not diagnosed ($n = 39$), those who had coexisting problems that interfered with the diagnostic process and/or might interfere with successful treatment ($n = 9$), those that did not wish hormonal treatment ($n = 4$), those in whom the diagnostic evaluation was still ongoing ($n = 10$), and those who had stopped to attend appointments ($n = 9$).

Of adolescents who had started GnRHa, treatment status as of 1 July 2019 was reviewed. If they had used GnRHa monotherapy for more than 3 months longer than minimally required before the start of gender-affirming hormones according to the local protocol (see below for description of the treatment protocol), the reason for this was noted. The 3 months was chosen to select those who may have had a prolonged diagnostic phase rather than those in whom gender-affirming hormone therapy started slightly later due to logistical issues such as rescheduling of an appointment. Adolescents who had started GnRHa treatment and had stopped this treatment were included in a detailed review. Baseline characteristics such as age and gender and data on the start, duration, and discontinuation of treatment were recorded from the medical files, as well as reasons given for the discontinuation of GnRHa treatment and the adolescents' and parents' views on the treatment.

Procedure

Before the start of GnRHa treatment, all adolescents had a diagnostic evaluation by a pediatric endocrinologist and mental health professional (MHP) to confirm the diagnosis of gender dysphoria according to the DSM-5 criteria (American Psychiatric Association, 2013), to assess the presence of any medical, psychiatric, or psychosocial problems that might interfere with treatment, to assess if the adolescent was able to give informed consent for the treatment and to confirm that puberty had started, as recommended by current guidelines (Hembree et al., 2017). This evaluation usually consisted of approximately six visits (more if necessary) of the adolescent with an MHP in 6–12 months in addition to interviews with parents/guardians. All adolescents gave written informed consent for the treatment. Informed consent from parents/guardians was also required if the adolescent was < 16 years old. After the start of GnRHa treatment, follow-up visits were scheduled with the pediatric endocrinologist and MHP, usually every 3 months in the first year and every 3–6 months thereafter, to evaluate satisfaction with the treatment, adequacy of puberty suppression, and any side effects. In the case of mental health issues (psychiatric morbidity but also issues such as difficulty to express oneself and doubts about one's gender identity), adolescents were either seen more frequently by the psychologist of the gender team or referred to a local MHP for therapy.

According to the local protocol, adolescents were eligible for gender-affirming hormone treatment from the age of 16 years and after at least 6 months of GnRHa treatment. No maximum time of use of GnRHa was defined in the protocol. From 2016, adolescents who had already been treated with GnRHa for at least 3 years were eligible for gender-affirming hormone treatment from the age of 15 years. From 2017, those who had been treated with GnRHa for at least 2 years and were 15 years old were eligible. Before the start of gender-affirming hormones, evaluation by a MHP and pediatric endocrinologist took place to assess the indication, any contraindications, and ability to give informed consent for this treatment. If adolescents had discontinued GnRHa treatment, there was a follow-up appointment at which adolescents and parents were asked about current feelings regarding gender identity and how they looked back on the treatment.

Results

During the study period, 143 adolescents started GnRHa treatment (38 transgirls, 105 transboys). Median age at the start of treatment was 15.0 years (range, 11.1–18.6 years) in transgirls and 16.1 years (range, 10.1–17.9 years) in transboys. Of these adolescents, 125 (87%, 36 transgirls, 89 transboys) subsequently started treatment with gender-affirming hormones after 1.0 (0.5–3.8) and 0.8 (0.3–3.7) years of GnRHa treatment (see Fig. 1). Median age at the start of gender-affirming hormones was 16.2 years (range, 14.5–18.6 years) in transgirls and 17.1 years (range, 14.9–18.8 years) in transboys. Five adolescents who used GnRHa had not started gender-affirming hormones at the time of data collection, because they were not yet eligible for this treatment due to their age. At the time of data collection, they had used GnRHa for a median duration of 2.1 years (1.6–2.8). Six adolescents had been referred to a gender clinic elsewhere for further treatment. One of these was

17 years old and eligible for gender-affirming hormones but initially indicated he needed more time to decide about testosterone treatment and subsequently stated that he wished to delay the start of this treatment until after his school examinations. The other five were not eligible yet due to their age at the time of referral. Nine had discontinued GnRHa treatment (see below), one of whom restarted GnRHa after 5 months. This individual and two others subsequently started gender-affirming hormone treatment (Fig. 1).

Prolonged Use of GnRHa

Twenty adolescents (3 transgirls and 17 transboys) had used GnRHa for longer than minimally required by protocol. One was the transboy mentioned above who needed more time to decide about testosterone treatment. He had used GnRHa for 2.5 years when he was referred from the pediatric clinic to a clinic for adults elsewhere. The other 19 adolescents had subsequently started gender-affirming hormones. The median duration of GnRHa monotherapy in these 19 adolescents was 1.0 year (0.8–2.4). Reasons for prolonged use of GnRHa were (sometimes there was more than one reason): unstable situation due to family issues such as lack of parental support and/or acceptance of gender dysphoria ($n=6$) or social problems such as lack of a safe home, excessive school absenteeism ($n=5$); (psychiatric) comorbidity ($n=8$) such as autism or depression; more time needed for decision about gender-affirming hormone treatment by the adolescent ($n=1$) or for further diagnostics by the gender team ($n=1$, because of non-binary aspects); and logistic issues such as missed/rescheduled appointments ($n=8$; in 7 this was the only reason). The 11 adolescents who received prolonged GnRHa treatment because of mental health and/or psychosocial problems had regular (approximately monthly on average) appointments with a psychologist at the gender clinic ($n=5$) and/or received support from a local MHP ($n=9$) during this period.

Discontinuation of GnRHa Treatment

From the 143 adolescents who started GnRHa treatment, nine (6%; one transgirl, eight transboys) stopped this treatment after a median duration of 0.8 years (0.1–3.0), at a median age of 15.0 years (13.4–18.9). Four individuals discontinued although they did wish further endocrine treatment because of gender dysphoria. One stopped treatment because of an increase in mood problems and suicidal thoughts and confusion attributed to GnRHa treatment and restarted treatment (gender-affirming hormone treatment) at an adult gender clinic elsewhere. He later indicated: "I was already fully matured when I started GnRHa, menstruations were already suppressed by contraceptives. For me, it had no added value" (transboy, age 19 years).

Another transboy experienced hot flushes, an increase in migraine, and had fear of injections in addition to stress due to problems at school and unrelated medical issues and therefore wished to temporarily discontinue GnRHa treatment after 4 months. He restarted 5 months later and subsequently started testosterone treatment. A third transboy experienced mood swings starting 4 months after he had begun GnRHa treatment. A year later, he started to frequently feel unwell and miss school. After 2.2 years, he developed severe nausea and rapid weight loss for which no cause was identified. Because of this deterioration of his general condition, he wished to discontinue GnRHa treatment after 2.4 years. He gradually recovered over the next 2 years. He subsequently started lynestrenol and testosterone treatment. The last adolescent had stopped GnRHa because his parents were unable to regularly collect medication from the pharmacy and take him to appointments for the injections. He subsequently started lynestrenol to suppress menses; he is not eligible yet for testosterone treatment.

The five others (3.5%) no longer wished gender-affirming treatment. One adolescent had been very distressed about breast development at the start of GnRHa. She later thought

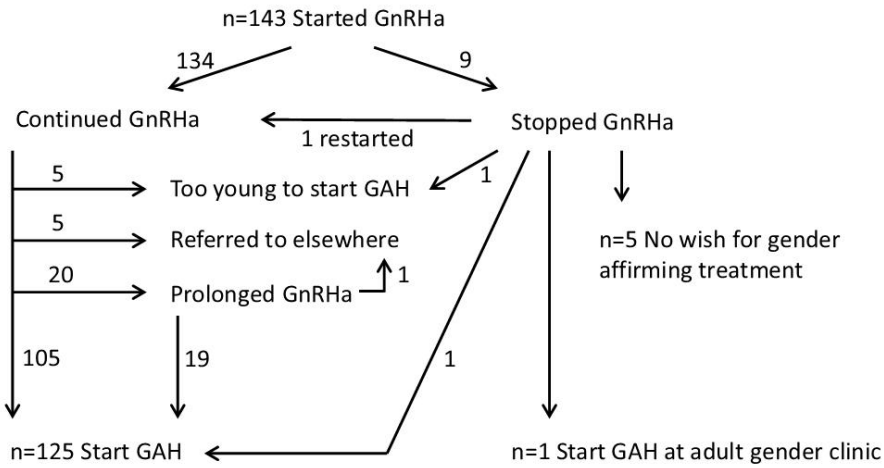

Fig. 1 Flow chart showing the trajectories of adolescents who started GnRH analogue (GnRHa) treatment. *GAH* gender-affirming hormone treatment

that she might want to live as a woman without breasts. She did not want to live as a boy and did not wish testosterone treatment and decided to discontinue GnRHa although she dreaded breast development and menstruation. Another adolescent had concurrent psychosocial problems interfering with the exploration of gender identity and did not currently wish treatment. When looking back on GnRHa treatment this individual said: "The decision to stop GnRHa to my mind was made by the gender team, because they did not think gender dysphoria was the right diagnosis. I do still feel like a man, but for me it is okay to be just me instead of a he or a she, so for now I do not want any further treatment" (adolescent assigned female sex at birth, age 16 years).

One adolescent felt more in between man and woman and therefore did not wish to continue treatment: "At the moment, I feel more like 'I am' instead of 'I am a woman' or 'I am a man'" (adolescent assigned female sex at birth, age 16 years).

Another individual made a social transition while using GnRHa and shortly afterward decided to discontinue treatment. He indicated that he had fallen in love with a girl and had never had such feelings, which made him question his gender identity. At subsequent visits, he indicated that he was happy living as a man.

The last adolescent stated: "After using GnRHa for the first time, I could feel who I was without the female hormones, this gave me peace of mind to think about my future. It was an inner feeling that said I am a woman" (adolescent assigned female sex at birth, age 18 years).

The adolescents and parents were also asked about their views on GnRHa in the treatment protocol for gender dysphoria. All of them saw it as the first step in treatment, but it was also clear that it was used as an extended diagnostic phase. They all felt free to stop GnRHa. They had varying visions on the role of GnRHa in the treatment of gender dysphoria. Some stated it gave them time to think and feel who they were and what they wanted in the future and felt that without GnRHa treatment they would not have been able to make these decisions. Others stated that GnRHa should not be routinely offered before the start of gender-affirming hormones when adolescents are already fully matured, because of the lack of physical benefits. Instead, a consideration time of 6 months with psychological follow-up was suggested.

Discussion

The great majority of adolescents who started GnRHa subsequently started gender-affirming hormones as soon as they were eligible for this treatment. Very few discontinued treatment, although slightly more than in previous studies in which cohorts of transgender adolescents were described. Out of 333 adolescents that had started puberty suppression at the VUmc gender clinic in the Netherlands up until December 2015, 1.9% stopped; reasons for discontinuation of GnRHa were not reported (Wiepjes et al., 2018). In the Canadian study by Khatchadourian, Amed, and Metzger (2014), one of 27 individuals who started GnRHa stopped the treatment due to emotional lability, not because the wish to pursue transition had subsided. In the current study, 6% of those who started GnRHa discontinued and 3.5% no longer wished gender-affirming treatment.

Several studies reviewed by Ristori and Steensma (2016) have found that much higher percentages (61–98%) of prepubertal children no longer experience gender dysphoria ("desist") as adolescents. The period between 10 and 13 years seems to be a crucial period in which social changes (for example starting secondary school), the physical changes of puberty, and first romantic and sexual experiences may lead to either an increase or a decrease/resolution of gender dysphoria (Steensma et al., 2011). The adolescents that start GnRHa treatment have entered puberty and are mostly older than 13 years and may be past this critical period so that gender dysphoria may be more likely to persist. This may explain the lower percentage of resolution of gender dysphoria found in the studies of treated adolescents. In addition, the groups that started treatment in previous studies and in the current study consisted of selected adolescents that had had an extensive diagnostic process to establish if they met the eligibility criteria for treatment as well as the diagnostic criteria for gender dysphoria (Wiepjes et al., 2018). Alternatively, concerns have been raised that GnRHa treatment itself may increase the chances of persistence of gender dysphoria (Korte et al., 2008; Richards et al., 2019; Stein, 2012; Vrouenraets et al., 2015). Whether or not GnRHa treatment influenced gender identity development cannot be concluded from the current study due to its observational nature. The study does show that gender identity development was not suppressed in all, as a few adolescents discontinued GnRHa because they no longer experienced gender dysphoria, but it is unknown if gender dysphoria would have subsided in more adolescents in the absence of GnRHa treatment.

For one adolescent, the experience of falling in love made him doubt whether he was transgender. This is in line with previous findings that the first romantic experiences and the awareness of one's sexual attraction play an important role in the resolution of gender dysphoria in adolescents (Steensma et al., 2011). This emphasizes the importance of this topic in the diagnostic evaluation. However, some adolescents may not have had any romantic or sexual experiences, especially if they present at an early age. In addition, transgender adolescents were shown to be less experienced, both sexually and romantically, compared to peers from the general population (Bungener, Steensma, Cohen-Kettenis, & de Vries, 2017). GnRHa treatment prevents the physical changes of puberty and is known to negatively affect sexual desire (Plosker & Brogden, 1994). Puberty suppression might thus decrease the chances of adolescents having romantic and sexual

experiences which might in turn influence gender identity development (Korte et al., 2008). This was not true for the adolescent in the current study who fell in love while using GnRHa and then decided to discontinue treatment, but it is uncertain if more adolescents would have had such experiences if they had not used GnRHa.

Two individuals who discontinued GnRHa indicated that they did not feel either male or female. A non-binary gender identity appears to be becoming more common among adolescents presenting at gender clinics (Butler, De Graaf, Wren, & Carmichael, 2018). For these adolescents, it may be more difficult to find out and understand their own gender identity and it is unclear what constitutes optimal care for this group.

Experienced side effects played a role in the decision to discontinue GnRHa treatment in three adolescents. However, for none of the adolescents who stopped GnRHa in the current study, were potential long-term side effects a reason to decline or discontinue GnRHa treatment. Lack of information about long-term effects of GnRHa use was not considered an important problem by interviewed adolescents with gender dysphoria in the study by Vrouenraets, Fredriks, Hannema, Cohen-Kettenis, and de Vries (2016), but is seen as a major problem by many professionals (Vrouenraets et al., 2015).

In the current study, 13 adolescents who were eligible for gender-affirming hormone treatment used GnRHa monotherapy for longer than the minimum time required by protocol for reasons other than logistics. During this time, they received mental health support from a local MHP or from a psychologist from the gender team. This supports the idea that the time on GnRHa is used as an extended diagnostic phase where the adolescents can further explore their gender identity and treatment wishes and work on issues that might interfere with successful treatment. The great majority started gender-affirming hormones as soon as was possible within the treatment protocol, after a median duration of approximately one year. This does not mean that for them this time was not used as an extended diagnostic phase. Those who were youngest at the start of GnRHa were treated the longest, up to 3.8 years, with visits to the clinic every 3–6 months. In this period of growing up, becoming more independent, and discovering oneself, their development was followed by the team and discussed in relation to the treatment. Older adolescents, who presented after age 16 years, were often treated with GnRHa for the minimum period of 6 months. Generally, they were more mature than the younger adolescents at the start of the diagnostic process and many already had clear ideas about their treatment wishes. In adults, gender-affirming hormones are usually started directly after the diagnostic phase (Wiepjes et al., 2018).

The period of puberty suppression used in adolescents is considered worthwhile by some of the adolescents, as the individual in the current study who indicated it gave peace of mind to think about the future. On the other hand, some postpubertal adolescents perceived little benefit of the treatment, as stated by one transboy who discontinued GnRHa in the current study. A possible benefit of GnRHa treatment for fully matured transgender boys may be the suppression of menstrual bleeding. Alternative methods may be used to achieve this, although GnRHa are more effective than progestins to immediately and fully suppress menstruation (Tack et al., 2016). Furthermore, many adolescents do not wish to use continuous oral contraceptives because of the fact that they contain "female" hormones and because of fear that breast size may increase. Adolescents should be counseled on all available treatment options and their (side) effects so that they can make an informed choice.

The relatively small size of the cohort that was described is a limitation of the current study as well as its retrospective character. The duration of follow-up was limited, and in some of the adolescents who stopped GnRHa treatment because they no longer experienced gender dysphoria, gender dysphoria might recur later in life. The observational design does not allow conclusions about any possible effect of GnRHa treatment on gender identity development. A randomized controlled trial in adolescents presenting with gender dysphoria, comparing groups with and without GnRHa treatment, could theoretically shed light on the effect of GnRHa treatment on gender identity development. However, many would consider a trial where the control group is withheld treatment unethical, as the treatment has been used since the nineties and outcome studies although limited have been positive (de Vries et al., 2014; Smith, van Goozen, & Cohen-Kettenis, 2001). In addition, it is likely that adolescents will not want to participate in such a trial if this means they will not receive treatment that is available at other centers. Mul et al. (2001) experienced this problem and were unable to include a control group in their study on GnRHa treatment in adopted girls with early puberty because all that were randomized to the control group refused further participation. An alternative approach that has been suggested to gain more insight into the effect of treatment on gender identity development is to collect baseline data at the time of referral from adolescents who are on a long waiting list for diagnostic evaluation and treatment and compare the percentage of these adolescents in whom gender dysphoria is still present after a certain period of time to that in adolescents on GnRHa treatment (Zucker, 2019).

In conclusion, this study shows that a small number of adolescents discontinued GnRHa treatment because they no longer wished gender-affirming treatment. This indicates that not all adolescents and parents assume that transgender outcome is the only possible outcome and shows that gender identity can still fluctuate when using GnRHa, at least in some adolescents. However, gender dysphoria subsided in a small number of adolescents and it is uncertain if this would have been different without GnRHa treatment. Some

adolescents used GnRHa for a prolonged period before starting gender-affirming hormones while regularly meeting with an MHP which is consistent with the use of GnRHa treatment as an extended diagnostic phase. The great majority who had started GnRHa treatment continued with gender-affirming hormones. It is important to take this into account when counseling adolescents who consider this treatment and their parents.

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Compliance with Ethical Standards

Conflict of interest MC de Vries and SE Hannema have received a lecture fee from Ferring. The other authors have nothing to declare.

Ethical Approval The study is part of an observational study on the effects of hormonal treatment in adolescents with gender dysphoria which was approved by the local medical ethical committee.

Informed Consent Adolescents who were included in the detailed review gave informed consent for the use of their data for this study, as well as their parents/guardians for adolescents younger than 16 years.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Press.

Antommaria, A. H. M., Shapiro, R. A., & Conard, L. A. E. (2019). Psychological maltreatment and medical neglect of transgender adolescents: The need for recognition and individualized assessment. *American Journal of Bioethics, 19*(2), 72–74. https://doi.org/10.1080/15265161.2018.1557286.

Baker, L. L. (2019). True autonomy/false dichotomies? Genderqueer kids and the myth of the quick fix. *American Journal of Bioethics, 19*(2), 63–65. https://doi.org/10.1080/15265161.2018.1557281.

Bungener, S. L., Steensma, T. D., Cohen-Kettenis, P. T., & de Vries, A. L. C. (2017). Sexual and romantic experiences of transgender youth before gender-affirmative treatment. *Pediatrics, 139*(3), e20162283. https://doi.org/10.1542/peds.2016-2283.

Butler, G., De Graaf, N., Wren, B., & Carmichael, P. (2018). Assessment and support of children and adolescents with gender dysphoria. *Archives of Disease in Childhood, 103*(7), 631–636. https://doi.org/10.1136/archdischild-2018-314992.

Cohen-Kettenis, P. T., & van Goozen, S. H. (1997). Sex reassignment of adolescent transsexuals: A follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*(2), 263–271. https://doi.org/10.1097/00004583-199702000-00017.

Coleman, E., Bockting, W., Botzer, M., Cohen-Kettenis, P., DeCuypere, G., Feldman, J., … Zucker, K. (2011). Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. *International Journal of Transgenderism, 13*(4), 165–232.

De Roo, C., Tilleman, K., T'Sjoen, G., & De Sutter, P. (2016). Fertility options in transgender people. *International Review of Psychiatry, 28*(1), 112–119. https://doi.org/10.3109/09540261.2015.1084275.

de Vries, A. L. C., & Cohen-Kettenis, P. T. (2012). Clinical management of gender dysphoria in children and adolescents: The Dutch approach. *Journal of Homosexuality, 59*(3), 301–320. https://doi.org/10.1080/00918369.2012.653300.

de Vries, A. L. C., McGuire, J. K., Steensma, T. D., Wagenaar, E. C., Doreleijers, T. A., & Cohen-Kettenis, P. T. (2014). Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics, 134*(4), 696–704. https://doi.org/10.1542/peds.2013-2958.

de Vries, A. L. C., Steensma, T. D., Doreleijers, T. A., & Cohen-Kettenis, P. T. (2011). Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. *Journal of Sexual Medicine, 8*(8), 2276–2283. https://doi.org/10.1111/j.1743-6109.2010.01943.x.

Delemarre-van de Waal, H. A., & Cohen-Kettenis, P. T. (2006). Clinical management of gender identity disorder in adolescents: A protocol on psychological and paediatric endocrinology aspects. *European Journal of Endocrinology, 155*(suppl 1), S131–S137. https://doi.org/10.1530/eje.1.02231.

Dembroff, R. (2019). Moving beyond mismatch. *American Journal of Bioethics, 19*(2), 60–63. https://doi.org/10.1080/15265161.2018.1557293.

Hembree, W. C., Cohen-Kettenis, P. T., Gooren, L., Hannema, S. E., Meyer, W. J., Murad, M. H., … T'Sjoen, G. G. (2017). Endocrine treatment of gender-dysphoric/gender-incongruent persons: An Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism, 102*(11), 3869–3903. https://doi.org/10.1210/jc.2017-01658.

Khatchadourian, K., Amed, S., & Metzger, D. L. (2014). Clinical management of youth with gender dysphoria in Vancouver. *Journal of Pediatrics, 164*(4), 906–911. https://doi.org/10.1016/j.jpeds.2013.10.068.

Klink, D., Caris, M., Heijboer, A., van Trotsenburg, M., & Rotteveel, J. (2015). Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. *Journal of Clinical Endocrinology and Metabolism, 100*(2), E270–E275. https://doi.org/10.1210/jc.2014-2439.

Korte, A., Lehmkuhl, U., Goecker, D., Beier, K. M., Krude, H., & Gruters-Kieslich, A. (2008). Gender identity disorders in childhood and adolescence: Currently debated concepts and treatment strategies. *Deutsches Ärzteblatt International, 105*(48), 834–841. https://doi.org/10.3238/arztebl.2008.0834.

Laidlaw, M., Cretella, M., & Donovan, G. K. (2019). The right to best care for children does not include the right to medical transition. *American Journal of Bioethics, 19*(2), 75–77. https://doi.org/10.1080/15265161.2018.1557288.

Leibowitz, S., & de Vries, A. L. C. (2016). Gender dysphoria in adolescence. *International Review of Psychiatry, 28*(1), 21–35. https://doi.org/10.3109/09540261.2015.1124844.

Martinerie, L., Condat, A., Bargiacchi, A., Bremont-Weill, C., de Vries, M. C., & Hannema, S. E. (2018). Management of endocrine disease: Approach to the management of children and adolescents with gender dysphoria. *European Journal of*

Endocrinology, 179(5), R219–R237. https://doi.org/10.1530/EJE-18-0227.

Mul, D., Versluis-den Bieman, H. J., Slijper, F. M., Oostdijk, W., Waelkens, J. J., & Drop, S. L. (2001). Psychological assessments before and after treatment of early puberty in adopted children. *Acta Paediatrica, 90*(9), 965–971.

Plosker, G. L., & Brogden, R. N. (1994). Leuprorelin. A review of its pharmacology and therapeutic use in prostatic cancer, endometriosis and other sex hormone-related disorders. *Drugs, 48*(6), 930–967. https://doi.org/10.2165/00003495-199448060-00008.

Priest, M. (2019). Transgender children and the right to transition: Medical ethics when parents mean well but cause harm. *American Journal of Bioethics, 19*(2), 45–59. https://doi.org/10.1080/15265161.2018.1557276.

Richards, C., Maxwell, J., & McCune, N. (2019). Use of puberty blockers for gender dysphoria: A momentous step in the dark. *Archives of Disease in Childhood, 104*(6), 611–612. https://doi.org/10.1136/archdischild-2018-315881.

Ristori, J., & Steensma, T. D. (2016). Gender dysphoria in childhood. *International Review of Psychiatry, 28*(1), 13–20. https://doi.org/10.3109/09540261.2015.1115754.

Schagen, S. E., Cohen-Kettenis, P. T., Delemarre-van de Waal, H. A., & Hannema, S. E. (2016). Efficacy and safety of gonadotropin-releasing hormone agonist treatment to suppress puberty in gender dysphoric adolescents. *Journal of Sexual Medicine, 13*(7), 1125–1132. https://doi.org/10.1016/j.jsxm.2016.05.004.

Sisk, C. L., & Zehr, J. L. (2005). Pubertal hormones organize the adolescent brain and behavior. *Frontiers in Neuroendocrinology, 26*(3–4), 163–174. https://doi.org/10.1016/j.yfrne.2005.10.003.

Smith, Y. L. S., van Goozen, S. H. M., & Cohen-Kettenis, P. T. (2001). Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: A prospective follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry, 40*(4), 472–481. https://doi.org/10.1097/00004583-200104000-00017.

Staphorsius, A. S., Kreukels, B. P., Cohen-Kettenis, P. T., Veltman, D. J., Burke, S. M., Schagen, S. E., … Bakker, J. (2015). Puberty suppression and executive functioning: An fMRI-study in adolescents with gender dysphoria. *Psychoneuroendocrinology, 56*, 190–199. https://doi.org/10.1016/j.psyneuen.2015.03.007.

Steensma, T. D., Biemond, R., de Boer, F., & Cohen-Kettenis, P. T. (2011). Desisting and persisting gender dysphoria after childhood: A qualitative follow-up study. *Clinical Child Psychology and Psychiatry, 16*(4), 499–516. https://doi.org/10.1177/1359104510378303.

Stein, E. (2012). Commentary on the treatment of gender variant and gender dysphoric children and adolescents: Common themes and ethical reflections. *Journal of Homosexuality, 59*(3), 480–500. https://doi.org/10.1080/00918369.2012.653316.

Tack, L. J., Craen, M., Dhondt, K., Vanden Bossche, H., Laridaen, J., & Cools, M. (2016). Consecutive lynestrenol and cross-sex hormone treatment in biological female adolescents with gender dysphoria: A retrospective analysis. *Biology of Sex Differences, 7,* 14. https://doi.org/10.1186/s13293-016-0067-9.

Vlot, M. C., Klink, D. T., den Heijer, M., Blankenstein, M. A., Rotteveel, J., & Heijboer, A. C. (2017). Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. *Bone, 95,* 11–19. https://doi.org/10.1016/j.bone.2016.11.008.

Vrouenraets, L. J., Fredriks, A. M., Hannema, S. E., Cohen-Kettenis, P. T., & de Vries, M. C. (2015). Early medical treatment of children and adolescents with gender dysphoria: An empirical ethical study. *Journal of Adolescent Health, 57*(4), 367–373. https://doi.org/10.1016/j.jadohealth.2015.04.004.

Vrouenraets, L. J., Fredriks, A. M., Hannema, S. E., Cohen-Kettenis, P. T., & de Vries, M. C. (2016). Perceptions of sex, gender, and puberty suppression: A qualitative analysis of transgender youth. *Archives of Sexual Behavior, 45*(7), 1697–1703. https://doi.org/10.1007/s10508-016-0764-9.

Wiepjes, C. M., Nota, N. M., de Blok, C. J., Klaver, M., de Vries, A. L., Wensing-Kruger, S. A., … Gooren, L. J. (2018). The Amsterdam Cohort of Gender Dysphoria Study (1972–2015): Trends in prevalence, treatment, and regrets. *Journal of Sexual Medicine, 15*(4), 582–590. https://doi.org/10.1016/j.jsxm.2018.01.016.

Wojniusz, S., Callens, N., Sütterlin, S., Andersson, S., De Schepper, J., Gies, I., … Vögele, C. (2016). Cognitive, emotional, and psychosocial functioning of girls treated with pharmacological puberty blockage for idiopathic central precocious puberty. *Frontiers in Psychology, 7,* 1053. https://doi.org/10.3389/fpsyg.2016.01053.

Zucker, K. J. (2019). Adolescents with gender dysphoria: Reflections on some contemporary clinical and research issues. *Archives of Sexual Behavior, 48*(7), 1983–1992. https://doi.org/10.1007/s10508-019-01518-8.

Zucker, K. J., Bradley, S. J., Owen-Anderson, A., Singh, D., Blanchard, R., & Bain, J. (2011). Puberty-blocking hormonal therapy for adolescents with gender identity disorder: A descriptive clinical study. *Journal of Gay & Lesbian Mental Health, 15*(1), 58–82. https://doi.org/10.1080/19359705.2011.530574.

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TRANSGENDER HEALTH

The Amsterdam Cohort of Gender Dysphoria Study (1972–2015): Trends in Prevalence, Treatment, and Regrets

Chantal M. Wiepjes,[1,2] Nienke M. Nota,[1,2] Christel J. M. de Blok,[1,2] Maartje Klaver,[1,2] Annelou L. C. de Vries,[2,3] S. Annelijn Wensing-Kruger,[2,4] Renate T. de Jongh,[1] Mark-Bram Bouman,[2,5] Thomas D. Steensma,[2,4] Peggy Cohen-Kettenis,[2,4] Louis J. G. Gooren,[1,2] Baudewijntje P. C. Kreukels,[2,4] and Martin den Heijer, MD, PhD[1,2]

ABSTRACT

Background: Over the past decade, the number of people referred to gender identity clinics has rapidly increased. This raises several questions, especially concerning the frequency of performing gender-affirming treatments with irreversible effects and regret from such interventions.

Aim: To study the current prevalence of gender dysphoria, how frequently gender-affirming treatments are performed, and the number of people experiencing regret of this treatment.

Methods: The medical files of all people who attended our gender identity clinic from 1972 to 2015 were reviewed retrospectively.

Outcomes: The number of (and change in) people who applied for transgender health care, the percentage of people starting with gender-affirming hormonal treatment (HT), the estimated prevalence of transgender people receiving gender-affirming treatment, the percentage of people who underwent gonadectomy, and the percentage of people who regretted gonadectomy, specified separately for each year.

Results: 6,793 people (4,432 birth-assigned male, 2,361 birth-assigned female) visited our gender identity clinic from 1972 through 2015. The number of people assessed per year increased 20-fold from 34 in 1980 to 686 in 2015. The estimated prevalence in the Netherlands in 2015 was 1:3,800 for men (transwomen) and 1:5,200 for women (transmen). The percentage of people who started HT within 5 years after the 1st visit decreased over time, with almost 90% in 1980 to 65% in 2010. The percentage of people who underwent gonadectomy within 5 years after starting HT remained stable over time (74.7% of transwomen and 83.8% of transmen). Only 0.6% of transwomen and 0.3% of transmen who underwent gonadectomy were identified as experiencing regret.

Clinical Implications: Because the transgender population is growing, a larger availability of transgender health care is needed. Other health care providers should familiarize themselves with transgender health care, because HT can influence diseases and interact with medication. Because not all people apply for the classic treatment approach, special attention should be given to those who choose less common forms of treatment.

Strengths and Limitations: This study was performed in the largest Dutch gender identity clinic, which treats more than 95% of the transgender population in the Netherlands. Because of the retrospective design, some data could be missing.

Conclusion: The number of people with gender identity issues seeking professional help increased dramatically in recent decades. The percentage of people who regretted gonadectomy remained small and did not show a tendency to increase. **Wiepjes CM, Nota NM, de Blok CJM, et al. The Amsterdam Cohort of Gender Dysphoria Study (1972–2015): Trends in Prevalence, Treatment, and Regrets. J Sex Med 2018;15:582–590.**

Key Words: Transgender; Prevalence; Regret; Gender-Affirming Hormones; Gender-Affirming Surgery

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[1]Department of Endocrinology, VU University Medical Center, Amsterdam, the Netherlands;

[2]Center of Expertise on Gender Dysphoria, VU University Medical Center, Amsterdam, the Netherlands;

[3]Department of Child and Adolescent Psychiatry, VU University Medical Center, Amsterdam, the Netherlands;

[4]Department of Medical Psychology, VU University Medical Center, Amsterdam, the Netherlands;

[5]Department of Plastic, Reconstructive, and Hand Surgery, VU University Medical Center, Amsterdam, the Netherlands

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INTRODUCTION

Gender dysphoria (GD) refers to the distress related to a marked incongruence between one's assigned sex at birth and the experienced gender later in life.[1] In this study, we define transwomen as having a male birth assignment and transmen as having a female birth assignment who might receive medical treatment to adapt their physical characteristics to their experienced gender. This treatment can include puberty suppression (PS), gender-affirming hormonal treatment (HT), and gender-affirming surgery.

It has been widely observed that the transgender population is growing and broadening.[2,3] This increase in the transgender population raises several questions, especially concerning the frequency of performing gender-affirming treatments with irreversible effects and regret from such interventions.

There are no reliable estimations of the current prevalence of transgender people who actually have received gender-affirming treatment (including HT), because most recent studies are based on questionnaires[4,5] or data about gender-affirming surgery only.[6,7] In most countries transgender care is performed by multiple health care providers (eg, university clinics or general practitioners), which makes it difficult to provide these numbers. In contrast, in the Netherlands, more than 95% of the transgender population has received treatment in only 1 center, the gender identity clinic at the VU University Medical Center (VUmc; Amsterdam, the Netherlands), currently known as the Center of Expertise on Gender Dysphoria.[8–10] This center started treating adults in 1972. From 1987 to 2002, children and adolescents were seen by a mental health specialist in the Utrecht University Medical Center (Utrecht, the Netherlands). After they were considered eligible, they could receive medical treatment in the VUmc, which consisted of PS (usually by gonadotropin-releasing hormone analogues), followed by HT (see Kreukels and Cohen-Kettenis[11] for the treatment protocol for adolescents diagnosed with GD). After 2002, the Utrecht clinic stopped seeing adolescents and the diagnostics were performed in the VUmc. Adult people are referred to a psychologist or psychiatrist for the diagnostic phase after an initial screening. People diagnosed with GD can start HT if they are considered eligible. HT consists of testosterone for transmen and estrogens, often combined with antiandrogens, for transwomen. In the 1st year of HT, checkups are performed every 3 months. After a minimum of 12 months of HT, gender-affirming surgery can be performed, including mastectomy and hysterectomy with oophorectomy in transmen and breast augmentation and vaginoplasty (including orchiectomy) in transwomen. After gonadectomy (oophorectomy or orchiectomy), people are usually seen every 1 to 2 years for clinical follow-up.

In the present study we included the complete population seen at the gender identity clinic of the VUmc from 1972 through December 2015 to assess the current prevalence of transgender people who received medical treatment, the frequency of specific medical treatments performed, and the numbers of people who received HT in line with their sex assigned at birth because they regretted undergoing gonadectomy.

METHODS

Study Design and Patient Selection

After approval of the local ethics committee, a retrospective medical record review was performed to identify all people seen in our gender identity clinic from 1972 until December 2015. Data were collected from the hospital registries of the VUmc. The total study population was defined as people who had been diagnosed with 1 of the following *International Classification of Diseases* diagnoses: 302.5 (transsexualism), 302.6 (gender identity disorder not otherwise specified), or 302.85 (gender identity disorder in adolescent or adult) according to the 9th edition or F64 (gender identity disorders) according to the 10th edition.[12] In addition, the administrative employees of our gender identity clinic registered everyone who was referred to our gender identity clinic since the early 1970s. People reported on this list also were included in the study population. Some people of this study population have been described in previous studies.[9,13–18] People were excluded from the study if they had been registered at our gender identity clinic but had actually never visited the clinic or if they had presented with other complaints than gender identity issues. Because of the retrospective design and the large study population, necessity for informed consent was waived by our local ethics committee.

Hospital Registries

The hospital registries store clinical data obtained during regular patient care performed in our center, including medical diagnoses (since 1985), medication prescriptions (since 2000), surgical interventions (since 2006), laboratory test results (since 2004), radiology results (since 1993), and visit dates (since 2007). The 1st visit was defined as the 1st appointment with the psychologist, psychiatrist, pediatrician, endocrinologist, or gynecologist for health care related to gender identity.

Clinical Data Collection

Not all data were available from the hospital registries, particularly older data or surgeries performed in other centers. To generate the most reliable results, the medical records of all people who composed the study population were checked. All people were classified as transwomen or transmen (based on the sex assigned at birth), and date of birth and death were noted. The following categories were included: the individual was in the diagnostic stage, the individual did not start HT, or the individual was on HT. Start of HT was defined as the 1st date gender-affirming hormones were prescribed by a physician in our gender identity clinic after a confirmed GD diagnosis, irrespective of previous gender-affirming hormone use. Of the people who started HT, baseline and follow-up data, including

1st visit, medical history, medication use, prior gender-affirming hormone use, start date and type of PS and HT, and date of gonadectomy, were collected. Some people regretted the interventions they had undergone. Transwomen who started testosterone treatment after vaginoplasty or transmen who started estrogen treatment after oophorectomy and expressed regret were categorized as those who experienced regret. Reasons for regret as reported in their medical records were noted. Dates were set to the 1st of the month and personal identification data were removed from the research database.

Statistical Analysis

The total number of people visiting the clinic each year and their median age were reported separately for transwomen and transmen and were stratified for age at the 1st visit: children were younger than 12 years, adolescents were 12 to 18 years old, and adults were at least 18 years old. The percentage of people who started HT within 5 years after the 1st visit was reported for each year. The prevalence was calculated for people at least 12, at least 16, 12 to 18, 18 to 30, 30 to 50, and at least 50 years old by using the total number of people in these age groups who received medical treatment in our center until 2015, excluding deceased people. The total populations of these age groups in the Netherlands in 2015 were provided by the Central Bureau of Statistics of the Netherlands. The percentage of people who underwent gonadectomy within 5 years after starting HT was reported. For calculation of the total percentage of the study population who had undergone gonadectomy, only people at least 18 years old who used HT for at least 1.5 years were included, because these were requirements for surgery. People who regretted their medical transition are reported as the percentage of the total population of transwomen and transmen who underwent gonadectomy. In adults, time from 1st visit to start of HT or gonadectomy, if applicable, are expressed as median days with interquartile range (IQR). Total follow-up time was calculated for every individual who started HT and was expressed as years from the 1st visit to the last visit. Prevalence with 95% CI was calculated using OpenEpi.[19] All other analyses were performed using STATA 13.1 (StataCorp, College Station, TX, USA).

RESULTS

1st Visit

6,793 people presented for gender-affirming treatment, with more transwomen (65.2%) than transmen (34.8%; Table 1). The number of people attending the gender identity clinic increased over time (Table 2), whereas the median age of adults at the time of their 1st visit decreased (Figure 1). The median age at the 1st visit was younger for adult transmen (25 years; IQR = 21–35 years) than for adult transwomen (33 years; IQR = 25–42 years). Although historically more transwomen than transmen presented for treatment, more transmen than

Table 1. Treatment patterns of total study population, stratified for age groups and for transwomen and transmen*

	Transwomen	Transmen	Total	Ratio of transwomen to transmen
Total study population, N (%)	4,432 (65.2)	2,361 (34.8)	6,793 (100)	1.9:1
Adults (≥18 y)	3,809	1,624	5,433	2.3:1
Age (y)†, median (IQR; max)	33 (25–42; 81)	25 (21–35; 73)	31 (23–41; 81)	
Started HT§, %	68.9	72.9	69.9	
Underwent gonadectomy‖, %	75.3	83.8	77.7	
Adolescents (12–18 y)	330	482	812	0.7:1
Age (y)†, median (IQR)	16 (15–17)	16 (15–17)	16 (15–17)	
Started PS‡, %	28.7	50.8	41.0	
Stopped PS, %	4.1	0.7	1.9	
Started HT§ without PS, %	33.9	30.8	32.2	
Underwent gonadectomy‖, %	79.5	77.2	78.2	
Children (<12 y)	293	255	548	1.1:1
Age (y)†, median (IQR)	8 (7–10)	9 (8–11)	9 (7–10)	
Started PS‡,¶, %	33.6	49.1	40.3	
Regret#, % (n)	0.6 (11)	0.3 (3)	0.5 (14)	2.0:1

HT = gender-affirming hormonal therapy; IQR = interquartile range; max = maximum; PS = puberty suppression.
*From 1987 through 2002, children and adolescents were seen at the Utrecht University Medical Center and then at the VU University Medical Center only if they could begin medical treatment.
†Age is defined as the age at the 1st visit to the VU University Medical Center, Amsterdam.
‡Only those who reached the age of eligibility (usually ≥12 years old) could undergo PS.
§Only in people at least 16 years old.
‖Only people treated with gender-affirming hormones for at least 1.5 years and at least 18 years old (orchiectomy in transwomen and oophorectomy in transmen).
¶Those who were too old (≥18 years) after the diagnostic phase for PS could begin directly with HT.
#Only those people who underwent gonadectomy.

Table 2. Description of adult study population for every 5-year cohort

	1st visit, n	Started HT*, %	Age (y) at start of HT, median (IQR)	Previous HT, %	Underwent gonadectomy†, %
Transwomen (≥18 y)					
1972–1979	119	89.9	33 (26–40)	16.8	79.4
1980–1984	189	88.4	33 (25–40)	12.6	71.9
1985–1989	319	75.9	31 (25–39)	15.3	76.5
1990–1994	392	65.8	30 (25–41)	20.5	76.7
1995–1999	522	65.5	34 (27–41)	26.6	78.7
2000–2004	605	56.0	38 (30–45)	29.2	67.3
2005–2009	476	61.6	39 (29–47)	22.9	68.6
2010–2014	926 (138‡)	60.9‡	32 (23–42)‡	29.8‡	NA
Transmen (≥18 y)					
1972–1979	30	96.7	24 (21–30)	10.3	72.4
1980–1984	69	84.1	24 (21–32)	3.5	82.8
1985–1989	105	84.8	24 (21–30)	1.1	79.8
1990–1994	142	69.0	27 (21–33)	7.1	88.8
1995–1999	177	65.0	29 (24–37)	7.0	88.7
2000–2004	207	63.3	32 (26–39)	5.3	87.0
2005–2009	185	63.8	29 (23–37)	3.4	81.4
2010–2014	518 (70‡)	71.4‡	24 (21–37)‡	0‡	NA

HT = gender-affirming hormonal therapy; IQR = interquartile range; NA = not applicable.
*People who started HT within 5 years after the 1st visit.
†People who had this procedure within 5 years after the start of HT.
‡Only in people who had their 1st visit 5 years before December 31, 2015 (n = 138 transwomen; n = 70 transmen).

transwomen applied for treatment in 2015. This change in sex ratio was mainly due to the increase in adolescent transgender boys, because the ratio of transwomen to transmen in adults remained stable over time.

Prevalence and Treatment

At the end of 2015, 3,838 transgender people at least 16 years old had received medical treatment and were not deceased. Because the total population of people at least 16 years old in the Netherlands in 2015 was 13,870,426, the prevalence was 27.7 per 100,000 people (95% CI = 26.8–28.6), or 1:3,600. Stratification for transwomen and transmen showed a prevalence of 36.4 (95% CI = 35.0–37.8) per 100,000 people (or 1:2,800) for men (transwomen) and 19.3 (95% CI = 18.3–20.3) per 100,000 people (or 1:5,200) for women (transmen). The calculation of prevalence numbers of people at least 12 years old and specific age groups are presented in Table 3.

The percentage of adult people who started HT within 5 years after the 1st visit decreased over time, whereas the percentage of people who underwent gonadectomy within 5 years after starting HT remained stable (Figure 2). Of the total study population at least 18 years old treated with HT for at least 1.5 years, 75.6% of transwomen (n = 1,742) and 82.4% of transmen (n = 885) underwent gonadectomy. The median time from the 1st visit to the start of HT for adults was 327 days (IQR = 36–570 days) and from the 1st visit to gonadectomy was 1,029 days (IQR = 679–1,465 days). The median follow-up time for people treated with HT was 6.4 years (range = 0.4–41.6 years).

Of adolescents, 41.0% started PS, whereas only 1.9% of these adolescents stopped PS and did not start HT (Table 1). 32.2% of adolescents started directly with HT, because they were too old (≥18 years) to start with PS after the diagnostic phase.

Regret

Regret was identified in 0.6% of transwomen and 0.3% of transmen who underwent gonadectomy. The characteristics of these people are presented in Table 4. Their ages at start of HT ranged from 25 to 54 years, and they expressed their regrets 46 to 271 months after initiation of HT. Reasons for regret were divided into social regret, true regret, or feeling non-binary. Transwomen who were classified as having social regret still identified as women, but reported reasons such as "ignored by surroundings" or "the loss of relatives is a large sacrifice" for returning to the male role. People who were classified as having true regret reported that they thought gender-affirming treatment would be a "solution" for, for example, homosexuality or personal acceptance, but, in retrospect, regretted the diagnosis and treatment.

DISCUSSION

The aim of this study was to generate a dataset of all individuals who presented to our clinic for gender-affirming care from 1972 to 2015. We found that the number of people with

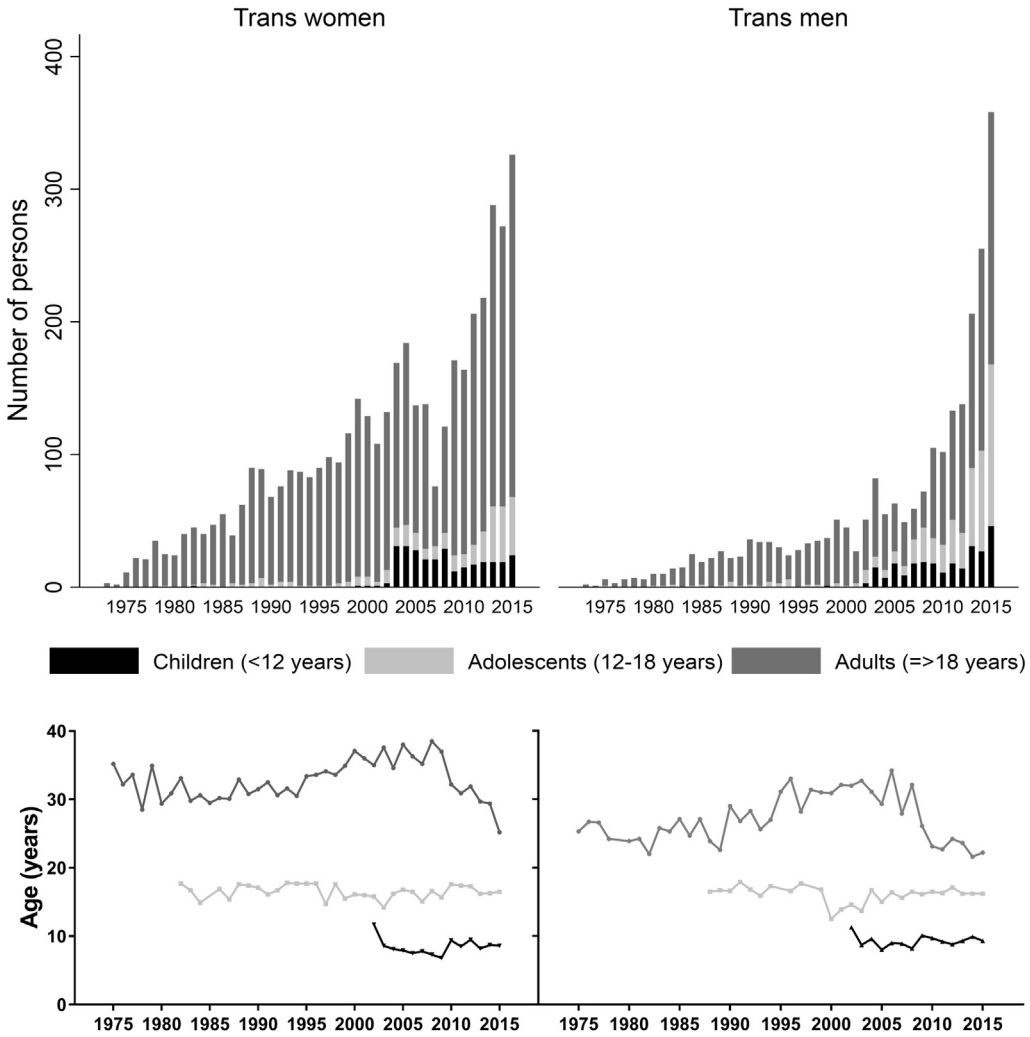

Figure 1. Number of people and median age for each year, stratified for transwomen and transmen and for children (<12 years), adolescents (12–18 years), and adults (≥18 years). Age is defined as age at the 1st visit to the VU University Medical Center, Amsterdam. From 1987 through 2002, children and adolescents were seen at the Utrecht University Medical Center and then at the VU University Medical Center only if they could begin medical treatment.

gender identity issues who sought professional help increased dramatically in recent decades and that the median age of adults at presentation decreased. The ratio of transwomen to transmen remained stable over the years for adults, whereas in adolescents the population of transgender boys increased compared with the population of transgender girls. Currently, more transgender boys than transgender girls are seen. This phenomenon also has been described by Aitken et al.[17] The age at the 1st visit was

Table 3. Prevalence numbers, specified for different age groups*

	Total population		Male sex assigned at birth (transwomen)		Female sex assigned at birth (transmen)	
Age (y)	Per 100,000	1 per	Per 100,000	1 per	Per 100,000	1 per
≥12	26.9 (26.1–27.8)	3,700	34.8 (33.5–36.2)	2,900	19.3 (18.3–20.3)	5,200
≥16	27.7 (26.8–28.6)	3,600	36.4 (35.0–37.8)	2,800	19.3 (18.3–20.3)	5,200
12–18	16.0 (13.9–18.4)	6,300	11.1 (8.8–14.1)	9,000	21.0 (17.7–25.1)	4,800
18–30	35.7 (33.5–38.2)	2,800	30.3 (27.4–33.4)	3,300	41.4 (37.9–45.1)	2,400
30–50	30.5 (29.0–32.2)	3,300	40.1 (37.6–42.8)	2,500	21.0 (19.2–23.0)	4,800
≥50	23.0 (21.9–24.2)	4,300	37.6 (35.5–39.8)	2,700	9.7 (8.7–10.8)	10,300

*Data are presented as number (95% CI).

Table 4. Characteristics of people with regret

Case	Type	Year started HT	Age (y) at start of HT	Year of gonadectomy	Time after HT (mo)	Time after gonadectomy (mo)	Reversal surgery	Reason for regret
1	M-F-M	1978	31	1979	±153	±130	None	Social acceptance
2	M-F-M	1982	25	1984	±54	±27	Mastectomy	Social acceptance
3	M-F-M	1986	47	1988	±216	±197	Mastectomy	Social acceptance
4	M-F-M	1988	33	1990	±186	±167	None	True regret
5	M-F-M	1988	38	1990	±70	±44	Mastectomy	Social acceptance
6	M-F-M	1991	41	1993	±67	±49	Mastectomy, vaginectomy, phalloplasty	Social acceptance
7	M-F-M	1991	38	1995	±271	±225	Mastectomy	True regret
8	M-F-M	1993	30	1994	±79	±61	None	Feels non-binary
9	M-F-M	1996	33	1997	±90	±73	Mastectomy, phalloplasty	True regret
10	M-F-M	1997	43	1999	±46	±27	Mastectomy	True regret
11	M-F-M	2004	54	2007	±130	±92	Mastectomy, vaginectomy	True regret
12	F-M-F	1987	25	1990	±91	±50	Breast augmentation, remove testicular implants	True regret
13	F-M-F	1990	34	1993	±102	±74	Remove testicular implants	Feels non-binary
14	F-M-F	1993	31	1997	±258	±212	None	True regret

F-M-F = female to male to female; HT = hormonal treatment; M-F-M = male to female to male.

older for adult transwomen than for transmen. The percentage of adult people starting HT within 5 years after the 1st visit decreased over time, whereas the percentage of people who underwent gonadectomy within 5 years after starting HT remained stable. Of the total population treated with HT, 77.8% underwent a gonadectomy. Only a very small percentage of people who underwent gonadectomy regretted their decision, expressed as the start of HT in line with their sex assigned at birth.

An explanation for the increase in referrals could be the increased attention in society and media, which contributes not only to awareness of the existence of GD and possibilities for medical treatment but also to greater social acceptance. In addition, information about transgender identities has become much more accessible through the internet within the past decade, which could lead to an earlier recognition of gender identity issues. Also, transgender and gender non-binary individuals might be more willing to access care and more access to care has become available.

The increase in the prevalence of people with GD who sought medical treatment in the Netherlands (1:11,900 transwomen and 1:30,400 transmen in 1990[8] vs 1:2,800 transwomen and 1:5,200 transmen currently) suggests that the transgender population is dramatically increasing. The highest prevalence for transwomen was found for the 30- to 50-year age group (1:2,500), whereas that for transmen was found in the 18- to 30-year age group (1:2,400). Transgender people in the Netherlands seem to experience a reasonable degree of acceptance owing to a tolerant social climate in contrast to many other countries.[20] For example, medical costs are reimbursed by medical insurance companies, and it is possible to change the legal sex status (even without gonadectomy). These points can lead to a lower threshold to seek help, making this study population useful for an adequate estimation of the current prevalence of people with GD who seek medical treatment. More than 95% of transgender people are treated in our gender identity clinic. However, not all transgender people seek medical help. Some use self-medication or go abroad for treatment. Therefore, these numbers might still be an underestimation of the real prevalence. Our data represent a population that actively sought help in a medical setting. In 2012, a Dutch study of non-clinical people reported that 0.6% (1:167) of those with male sex assigned at birth and 0.2% (1:500) of those with female sex assigned at birth reported an incongruent gender identity with a wish for hormones or surgery.[21] However, that was a population-based study with a response rate of 20.9%, which could lead to non-response bias. In addition, the existence of incongruent gender identities was based on self-report and no detailed assessment of GD was performed, which could have led to higher prevalence rates.

An interesting finding is the percentage of children who were referred in childhood (before 12 years of age) and who started PS when the GD persisted and the eligibility criteria were fulfilled. This 40% of children who started PS is almost identical to the 39% of persistence of childhood GD reported in a previous

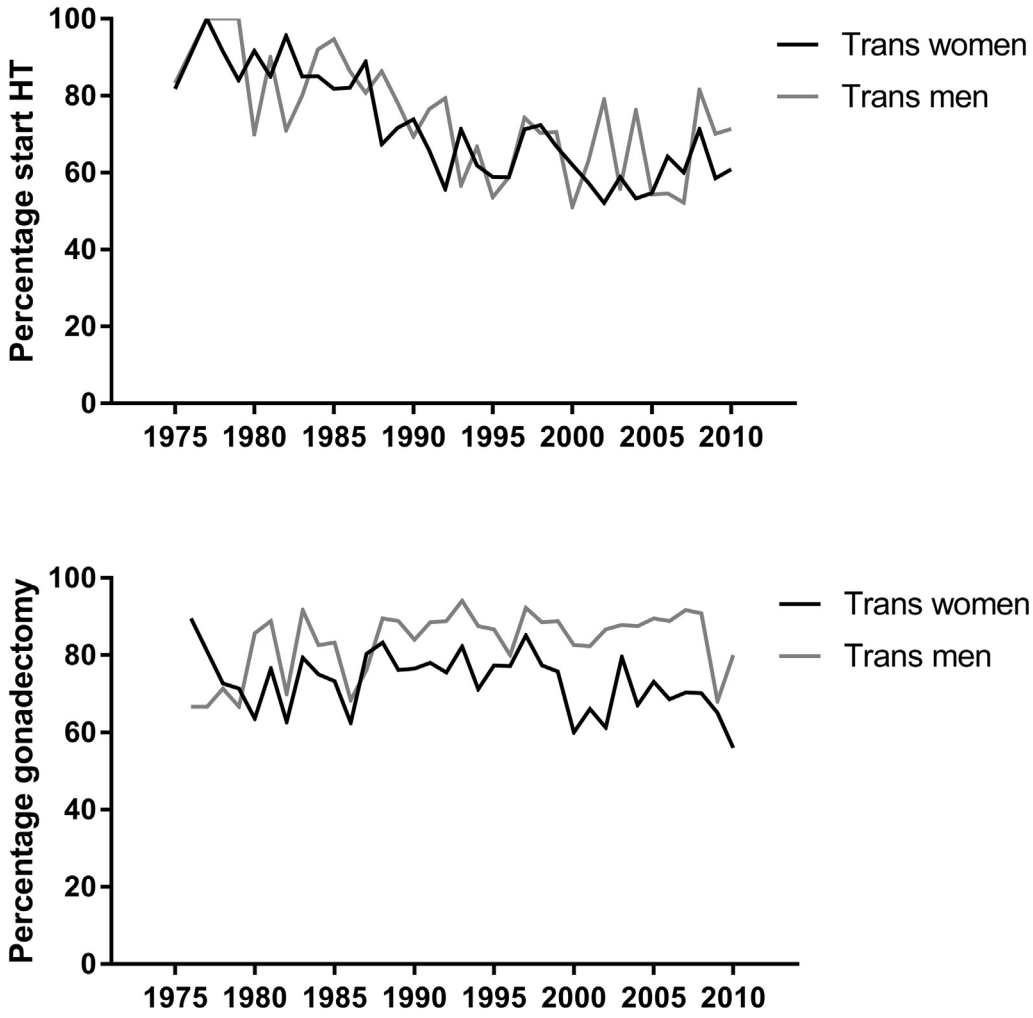

Figure 2. Top panel shows percentage of transgender adults beginning gender-affirming HT within 5 years after the 1st visit, stratified for transwomen and transmen. Bottom panel shows percentage of transgender adults with occurrence of gonadectomy within 5 years after starting HT for each year, stratified for transwomen and transmen. Year is defined as the year of the 1st visit. HT = gender-affirming hormonal treatment.

Dutch study (using a smaller cohort of children).[22] In addition, the finding that the persistence is higher in natal girls (49.1%) compared with natal boys (33.6%) is in line with observations in previous follow-up studies on the persistence of GD in children (for an overview, see Ristori and Steensma[23]).

Remarkably, we found a decrease over time in the percentage of referred adult people who actually started HT. This finding might be explained by the fact that in the past it was harder to find information about GD and its treatment, and only people with extreme types of GD managed to visit our gender identity clinic for treatment. Currently, owing to media attention and the internet, it is easier to access information about our gender identity clinic, making the threshold lower to search for help. This could have led to referrals of people with milder forms of GD and people who were not sure of their feelings and just wanted to explore these with a psychologist. Such people eventually might not pursue HT. Another explanation might be that not all transgender people want to undergo HT, such as transmen or people with a non-binary identity who only want a mastectomy.[24]

By contrast, we noticed that the percentage of people who underwent gonadectomy within 5 years after the start of HT remained stable over time. At the start of the clinic in 1972, knowledge about transgender care was limited and only people who wished for a classic treatment, consisting of a diagnostic phase, HT plus social transitioning, and surgery (in this order), were treated. There was no room for partial treatments. Since the publication of the Standards of Care Version 6 in 2001, other types of treatment are offered.[25] In addition, in 2014, a change in Dutch law allowed transgender people without a wish to undergo gonadectomy to alter the sex on their birth certificate with a statement of an expert who declared that the individual was diagnosed with GD (Dutch civil law, article 1:28). Although these changes in clinical guidelines and the law might have led to a decrease in the number of transgender people choosing gonadectomy, the current results do not show this. However, the follow-up time of this study might be too short to notice such changes.

In the HT group, 22% of people who were eligible for surgery had not undergone gonadectomy. These numbers are

comparable with a study from Sweden[26] but larger than in a study from Belgium,[27] in which approximately 15% of transwomen and transmen did not undergo gonadectomy. A possible wish to carry a child could change these numbers in the future, because fertility has become a more important issue.

Despite the large increase in treated transgender people, the percentage of people who underwent gonadectomy but regretted their decision was still very small (0.5%). In a review by Pfäfflin[28] in 1992, regret was reported by less than 1% of transmen and 1% to 1.5% by transwomen after gonadectomy. More recent studies have reported regret percentages of 0%[29,30] to 2%[7] and 6%[31] after gonadectomy. 13 of the 14 people who regretted gonadectomy had started HT from 1978 through 1997 and 1 started in 2004. At best, this indicates that the diagnostic and eligibility criteria for treatment have improved over the past decade. Another explanation might be the altered treatment protocol, which also allowed people to receive HT without gonadectomy. Our findings could be an underestimation of people with regret after gonadectomy, because some might choose to go elsewhere for reversal therapy or might experience regret without pursuing reversal surgery or HT. Regret might not always result in a desire for reversal therapy, as it may be hidden from others. In addition, in our population the average time to regret was 130 months, so it might be too early to examine regret rates in people who started with HT in the past 10 years.

The Center of Expertise on Gender Dysphoria of the VUmc Amsterdam is the largest gender identity clinic in the Netherlands, where people of all ages, including children and adolescents, are treated. Life-time follow-up is recommended, making it a useful study population for collection of epidemiologic data and future long-term studies of treatment effects. However, there are some limitations. Because this is a retrospective chart review study, some data could be lacking. (i) Some people who once visited our clinic might not be reported in our database. However, we used several search strategies to identify the total study population, thereby decreasing the possibility of missing people. (ii) A large number of transgender people who had initially received treatment in our center were lost to follow-up. Although transgender people receive lifelong care, a large group (36%) did not return to our clinic after several years of treatment. Therefore, we could have missed some information on, for example, gonadectomies performed at other centers or people with regret.

CONCLUSIONS

We found that the prevalence of treated transgender people increased exponentially. Because of this growing population, it is necessary that health care providers outside university clinics also have knowledge about GD and its treatment, because HT can influence the course of several diseases[32,33] and interact with several types of medication.[34] We also found that of all transgender people treated with HT, approximately 22% kept their gonads in situ. These people require special attention, because the long-term effects of HT on the testes, ovaries, and uterus are not established. These topics and other possible complications, such as cancer risks, are subjects for further research.

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Corresponding Author: M. den Heijer, MD, PhD, Department of Internal Medicine, Section Endocrinology, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, the Netherlands. Tel: +31-20-444-0530; Fax: +31-20-444-4313; E-mail: m.denheijer@vumc.nl

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STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
C.M. Wiepjes; N.M. Nota; C.J.M. de Blok; M. Klaver; R.T. de Jongh; P. Cohen-Kettenis; L.J.G. Gooren; B.P.C. Kreukels; M. den Heijer

(b) Acquisition of Data
C.M. Wiepjes; N.M. Nota; C.J.M. de Blok; M. Klaver; T.D. Steensma; B.P.C. Kreukels

(c) Analysis and Interpretation of Data
C.M. Wiepjes; N.M. Nota; C.J.M. de Blok; M. Klaver; A.L.C. de Vries; S.A. Wensing-Kruger; R.T. de Jongh; M. Bouman; T.D. Steensma; P. Cohen-Kettenis; L.J.G. Gooren; B.P.C. Kreukels; M. den Heijer

Category 2

(a) Drafting the Article
C.M. Wiepjes; N.M. Nota; P. Cohen-Kettenis; L.J.G. Gooren; B.P.C. Kreukels

(b) Revising It for Intellectual Content
N.M. Nota; C.J.M. de Blok; M. Klaver; A.L.C. de Vries; S.A. Wensing-Kruger; R.T. de Jongh; M. Bouman; T.D. Steensma; P. Cohen-Kettenis; L.J.G. Gooren; B.P.C. Kreukels; M. den Heijer

Category 3

(a) Final Approval of the Completed Article
C.M. Wiepjes; N.M. Nota; C.J.M. de Blok; M. Klaver; A.L.C. de Vries; S.A. Wensing-Kruger; R.T. de Jongh; M. Bouman; T.D. Steensma; P. Cohen-Kettenis; L.J.G. Gooren; B.P.C. Kreukels; M. den Heijer

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.

2. Wylie K, Knudson G, Khan SI, et al. Serving transgender people: clinical care considerations and service delivery models in transgender health. **Lancet 2016;388:401-411.**
3. Arcelus J, Bouman WP, Van Den Noortgate W, et al. Systematic review and meta-analysis of prevalence studies in transsexualism. **Eur Psychiatry 2015;30:807-815.**
4. De Cuypere G, Van Hemelrijck M, Michel A, et al. Prevalence and demography of transsexualism in Belgium. **Eur Psychiatry 2007;22:137-141.**
5. Esteva de Antonio I, Gomez-Gil E, Almaraz MC, et al. [Organization of healthcare for transsexual persons in the Spanish national health system]. **Gac Sanit 2012;26:203-209 [in Spanish].**
6. Caldarera A, Pfäfflin F. Transsexualism and sex reassignment surgery in Italy. **Int J Transgend 2011;13:26-36.**
7. Dhejne C, Oberg K, Arver S, et al. An analysis of all applications for sex reassignment surgery in Sweden, 1960–2010: prevalence, incidence, and regrets. **Arch Sex Behav 2014;43:1535-1545.**
8. Bakker A, van Kesteren P, Gooren L, et al. The prevalence of transsexualism in the Netherlands. **Acta Psychiatr Scand 1993;87:237-238.**
9. Van Kesteren P, Asscheman H, Megens J, et al. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. **Clin Endocrinol 1997;47:337-342.**
10. Cohen-Kettenis PT, Delemarre-van de Waal HA, Gooren LJ. The treatment of adolescent transsexuals: changing insights. **J Sex Med 2008;5:1892-1897.**
11. Kreukels BP, Cohen-Kettenis PT. Puberty suppression in gender identity disorder: the Amsterdam experience. **Nat Rev Endocrinol 2011;7:466-472.**
12. World Health Organization. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. Geneva: World Health Organization; 1993.
13. Asscheman H, Giltay EJ, Megens JA, et al. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. **Eur J Endocrinol 2011;164:635-642.**
14. Asscheman H, Gooren LJG, Eklund PLE. Mortality and morbidity in transsexual patients with cross-gender hormone treatment. **Metabolism 1989;38:869-873.**
15. Dekker MJ, Wierckx K, Van Caenegem E, et al. A European network for the investigation of gender incongruence: endocrine part. **J Sex Med 2016;13:994-999.**
16. Kreukels BP, Haraldsen IR, De Cuypere G, et al. A European network for the investigation of gender incongruence: the ENIGI initiative. **Eur Psychiatry 2012;27:445-450.**
17. Aitken M, Steensma TD, Blanchard R, et al. Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. **J Sex Med 2015;12:756-763.**
18. de Vries AL, Cohen-Kettenis PT. Clinical management of gender dysphoria in children and adolescents: the Dutch approach. **J Homosex 2012;59:301-320.**
19. Sullivan KM, Dean A, Soe MM. OpenEpi: a web-based epidemiologic and statistical calculator for public health. **Public Health Rep 2009;124:471-474.**
20. Kuyper L. Transgenders in Nederland: prevalentie en attitudes. **Tijdschr Seksuol 2012;36:129-135 [in Dutch].**
21. Kuyper L, Wijsen C. Gender identities and gender dysphoria in the Netherlands. **Arch Sex Behav 2014;43:377-385.**
22. Wallien MSC, Cohen-Kettenis PT. Psychosexual outcome of gender-dysphoric children. **J Am Acad Child Adolesc Psychiatry 2008;47:1413-1423.**
23. Ristori J, Steensma TD. Gender dysphoria in childhood. **Int Rev Psychiatry 2016;28:13-20.**
24. Beek TF, Kreukels BP, Cohen-Kettenis PT, et al. Partial treatment requests and underlying motives of applicants for gender affirming interventions. **J Sex Med 2015;12:2201-2205.**
25. De Cuypere G, Gijs L. Care for adults with gender dysphoria. In: Kreukels BPC, Steensma TD, de Vries ALC, eds. Gender dysphoria and disorders of sex development: progress in care and knowledge. New York: Springer Science + Business Media; 2014. p. 231-254.
26. Johansson A, Sundbom E, Hojerback T, et al. A five-year follow-up study of Swedish adults with gender identity disorder. **Arch Sex Behav 2010;39:1429-1437.**
27. Wierckx K, Elaut E, Declercq E, et al. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. **Eur J Endocrinol 2013;169:471-478.**
28. Pfäfflin F. Regrets after sex reassignment surgery. **J Psychol Hum Sex 1993;5:69-85.**
29. Vujovic S, Popovic S, Sbutega-Milosevic G, et al. Transsexualism in Serbia: a twenty-year follow-up study. **J Sex Med 2009;6:1018-1023.**
30. Lawrence AA. Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. **Arch Sex Behav 2003;32:299-315.**
31. Imbimbo C, Verze P, Palmieri A, et al. A report from a single institute's 14-year experience in treatment of male-to-female transsexuals. **J Sex Med 2009;6:2736-2745.**
32. Johnson EL, Kaplan PW. Caring for transgender patients with epilepsy. **Epilepsia 2017;58:1667-1672.**
33. Tauboll E, Sveberg L, Svalheim S. Interactions between hormones and epilepsy. **Seizure 2015;28:3-11.**
34. Polderman KH, Gooren LJG, Asscheman H, et al. Induction of insulin resistance by androgens and estrogens. **J Clin Endocrinol Metab 1994;79:265-271.**

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Original Research

Children and adolescents in the Amsterdam Cohort of Gender Dysphoria: trends in diagnostic- and treatment trajectories during the first 20 years of the Dutch Protocol

Maria ATC van der Loos, MD[1], Daniel T Klink, MD, PhD[2], Sabine E Hannema, MD, PhD[3], Sjoerdje Bruinsma, MSc[4], Thomas D Steensma, PhD[4], Baudewijntje PC Kreukels, PhD[4], Peggy T Cohen-Kettenis, PhD[4], Annelou LC de Vries, MD, PhD[5], Martin den Heijer, MD, PhD[1], Chantal M Wiepjes, MD, PhD[1,*]

[1]Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Endocrinology and Metabolism, 1081HV, Amsterdam, The Netherlands
[2]Ghent University Hospital, Division of Pediatric Endocrinology, 9000, Ghent, Belgium
[3]Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Pediatrics, 1081HV, Amsterdam, The Netherlands
[4]Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Medical Psychology, 1081HV, Amsterdam, The Netherlands
[5]Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Child and Adolescent Psychiatry, 1081HV, Amsterdam, The Netherlands

*Corresponding author: Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Endocrinology and Metabolism, de Boelelaan 1117, 1081HV, Amsterdam, The Netherlands. Email: c.wiepjes@amsterdamumc.nl

Abstract

Background: Twenty years ago, the Dutch Protocol—consisting of a gonadotropin-releasing hormone agonist (GnRHa) to halt puberty and subsequent gender-affirming hormones (GAHs)—was implemented to treat adolescents with gender dysphoria.
Aim: To study trends in trajectories in children and adolescents who were referred for evaluation of gender dysphoria and/or treated following the Dutch Protocol.
Methods: The current study is based on a retrospective cohort of 1766 children and adolescents in the Amsterdam Cohort of Gender Dysphoria.
Outcomes: Outcomes included trends in number of intakes, ratio of assigned sex at birth, age at intake, age at start of GnRHa and GAH, puberty stage at start of GnRHa, proportions of adolescents starting and stopping GnRHa, reasons for refraining from GnRHa, and proportions of people undergoing gender-affirming surgery.
Results: A steep increase in referrals was observed over the years. A change in the AMAB:AFAB ratio (assigned male at birth to assigned female at birth) was seen over time, tipping the balance toward AFAB. Age at intake and at start of GnRHa has increased over time. Of possibly eligible adolescents who had their first visit before age 10 years, nearly half started GnRHa vs around two-thirds who had their first visit at or after age 10 years. The proportion starting GnRHa rose only for those first visiting before age 10. Puberty stage at start of GnRHa fluctuated over time. Absence of gender dysphoria diagnosis was the main reason for not starting GnRHa. Very few stopped GnRHa (1.4%), mostly because of remission of gender dysphoria. Age at start of GAH has increased mainly in the most recent years. When a change in law was made in July 2014 no longer requiring gonadectomy to change legal sex, percentages of people undergoing gonadectomy decreased in AMAB and AFAB.
Clinical Implications: A substantial number of adolescents did not start medical treatment. In the ones who did, risk for retransitioning was very low, providing ongoing support for medical interventions in comprehensively assessed gender diverse adolescents.
Strengths and Limitations: Important topics on transgender health care for children and adolescents were studied in a large cohort over an unprecedented time span, limited by the retrospective design.
Conclusion: Trajectories in diagnostic evaluation and medical treatment in children and adolescents referred for gender dysphoria are diverse. Initiating medical treatment and need for surgical procedures depends on not only personal characteristics but societal and legal factors as well.

Keywords: adolescents; gonadotropin-releasing hormone agonist; gender dysphoria; transgender.

Introduction

Over 20 years ago, clinicians in the Netherlands had a pioneering role in the development of medical treatment for adolescents diagnosed with gender dysphoria (GD). These adolescents are troubled by an incongruence between their experienced gender and their gender assigned at birth.[1] This may lead to the desire to obtain the physical characteristics of the experienced gender. Therefore, development of endogenous secondary sex characteristics during puberty can be distressing.

In the Netherlands, gender-affirming medical treatment was already available for transgender adults aged >18 years since 1972. Nevertheless, children and adolescents experiencing GD were devoid of treatment options until 1987, when psychologist Peggy T. Cohen-Kettenis noticed an increasing number of transgender teenagers requesting medical intervention. After careful deliberation, gender-affirming hormone (GAH) treatment was made available for thoroughly screened well-functioning young people between 16 and 18 years of age—after first-stage treatment

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with antiandrogens for assigned males at birth (AMAB) and progesterone for assigned females at birth (AFAB).[2] Thenceforth, a modest number of adolescents were treated with GAH. Around the same time, pediatric endocrinologist Henriette A. Delemarre-van de Waal treated an adolescent diagnosed with GD with a gonadotropin-releasing hormone agonist (GnRHa) to halt puberty. After following the then-current diagnostic protocol, she added GAH treatment a few years later.[3,4] Internationally, this approach of diagnostic procedure and combined treatment of GnRHa and subsequent GAH came to be known as the Dutch Protocol.[5,6]

Few studies have assessed the prevalence of GD in children and adolescents. Based on the current literature, 1.3% to 2.7% of schoolchildren self-identify as transgender or gender-nonconforming people.[7] Nevertheless, ever since the implementation of the Dutch Protocol, a rise in the number of adolescents requesting this treatment has been seen.[8-10] The protocol has become common practice in gender identity clinics throughout the Western world and has been incorporated into the Endocrine Society's guideline for the medical treatment of GD from the earliest edition and into the standards of care by the World Professional Association for Transgender Health since 1998.[11,12] However, the approach is not endorsed worldwide. For example, in Sweden the eligibility for treatment with puberty suppression in adolescents has recently been restricted.[13]

Now, the time has come to review how practice has evolved since the start of the Dutch Protocol and to evaluate the treatment trajectories in people who were treated accordingly. We set out to answer the following questions:

- Is there a trend in the number of intakes and the ratio in assigned sex at birth, as well as the age at presentation, age at the start of GnRHa, and/or age at GAH treatment in referred children and adolescents?
- Do adolescents start GnRHa earlier in puberty over the years?
- Do the proportions of adolescents starting medical treatment vary over time?
- Does the proportion of adolescents starting GnRHa differ between those who are prepubertal and pubertal at first visit?
- How many adolescents using GnRHa subsequently start GAH?
- Are there distinct differences over time in reasons for refraining from treatment?
- Does puberty stage at start of GnRHa affect the number of individuals choosing to undergo surgical gender-affirming treatment?

Last, we wanted to study trends in gender-affirming surgery being performed over time. However, a possible trend in surgery cannot be regarded separately from a change in a Dutch law in July 2014. Due to this change, people were no longer obliged to have undergone gonadectomy to change their legal sex. Therefore, we adapted the research question and investigated whether this change in law made a difference in the number of people undergoing gonadal surgery.

Methods

Study design and population

This study is part of the Amsterdam Cohort of Gender Dysphoria.[8] This cohort is composed of all people who underwent diagnostic assessment and/or medical treatment for GD (per the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition–text revision and fifth edition)[14,15] at the Center of Expertise on Gender Dysphoria of the Amsterdam UMC, location Vrije Universiteit Amsterdam (VUmc), between 1972 and December 31, 2018. The dataset contains age at intake, age at start of GnRHa and/or GAH treatment, type of hormone treatment, pubertal stage at start of GnRHa, and date of gender-affirming surgery. Data were extracted from the medical charts.

The VUmc clinic has provided mental health and medical care to transgender adults since 1972. In some cases, people close to turning 18 years old could already attend the adult gender identity clinic. Mental health care for children and adolescents was located at the University Medical Center Utrecht since 1987. If treatment was indicated, medical care was provided at the VUmc. From 2002 onward, the mental health and medical care departments have been located at the VUmc. After establishment of the gender identity clinic for children and adolescents at the VUmc around 2002, adolescents diagnosed with GD elsewhere were able to start or continue medical treatment at this center. All referrals to the gender identity clinic were added to the study cohort if they visited the gender identity clinic at least once.

To select our study population, the following inclusion criteria were applied to the Amsterdam Cohort of Gender Dysphoria: either a visit to the gender identity clinic or the start of GnRHa before the age of 18 years. There was no lower limit for age. Hence, the study sample included pubertal adolescents who followed the Dutch Protocol, as used from 1997 onward, which could include GnRHa with or without subsequent GAH, as well as prepubertal children who adopted a "watchful waiting" approach. This approach meant that the child returned to the gender identity clinic only when puberty had begun. The child was not seen in the meanwhile because medical intervention is not provided to prepubertal children at out clinic.[16] People with disorders of sex development were excluded.

People with all kinds of gender identity were included. For clarity, the terms AMAB and AFAB are used.

The entire inclusion process is shown in Figure 1.

Medical treatment protocol

The medical treatment protocol has been described comprehensively.[17] In short, adolescents diagnosed with GD and fulfilling eligibility criteria according to Hembree et al[18] could start on intramuscular or subcutaneous triptorelin (GnRHa), 3.75 mg every 4 weeks or 11.25 mg every 12 weeks, to suppress pubertal development when at least 12 years old. In addition, Tanner genital or breast stage of at least 2 was required for AMAB and AFAB to start GnRHa, respectively.

If GD persisted, adolescents were eligible for puberty induction with GAH from age ≥16 years. Over the years, the protocol was adapted so that adolescents could start GnRHa before age 12 if puberty had started, and those who had already been treated with GnRHa for several years were eligible to start GAH from age 15 years.[19] Puberty was induced with estrogen in AMAB and testosterone in AFAB according to the Endocrine Society's clinical practice guideline.[18]

After at least 1 year of GAH and a minimum age of 18 years, people became eligible for gender-affirming surgery, including gonadectomy. After gonadectomy, GnRHa is no longer indicated, while estrogen or testosterone supplementation becomes indispensable.

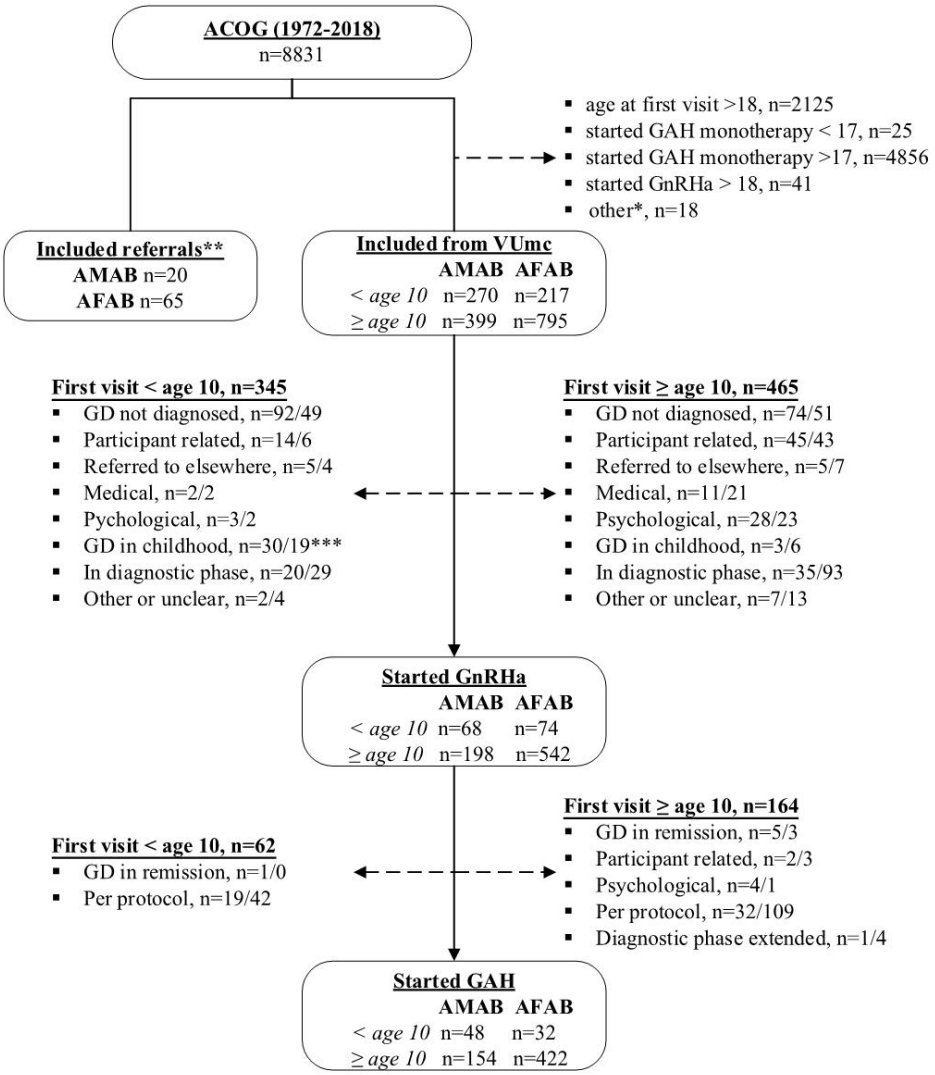

Figure 1. Flowchart of inclusion process and treatment trajectories. n = AMAB/AFAB. *Disorder of sex development, n = 6; wrongfully included, n = 1; did not follow Dutch Protocol, n = 11. **People referred from elsewhere had already started medical treatment or were referred specifically to start. ***Additionally, 34 AMAB and 28 AFAB first visiting before age 10 years were diagnosed with GD in childhood but were not yet potentially eligible for start of GnRHa at the end of data collection. ACOG, Amsterdam Cohort of Gender Dysphoria; AFAB, assigned female birth; AMAB, assigned male at birth; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone agonist.

Pubertal development

Pubertal development according to the Tanner staging scale was assessed by a pediatric endocrinologist prior to starting GnRHa. Hence, Tanner stages were available only for adolescents who started GnRHa. Testicular volume was measured with an orchidometer.

The study population was divided into early and late puberty groups. Early puberty was defined as testicular volume ≤9 mL or maximum Tanner breast stage 2 for AMAB and AFAB, respectively. Testicular volume ≥10 mL or Tanner breast stage ≥3 was considered late puberty.

Start of GnRHa and GAH treatment

The percentage of people starting GnRHa is calculated as the number of people who started GnRHa divided by the number of people who were potentially eligible for the start of GnRHa at the end of data collection, multiplied by 100. Potential eligibility for start of GnRHa was defined as a minimum age of 12 years and at least 1 year after the first visit. Addition of this last criterion allowed for a diagnostic evaluation of at least 1 year.

Reasons for not yet starting GnRHa by the end of 2018 were extracted from the hospital chart and divided into categories (Table 1). For the percentage of people starting GAH, the denominator was composed of the number of people eligible for start of GAH based on their age and duration of GnRHa treatment (see Medical treatment protocol).

Gender-affirming surgery

The overall proportion of people undergoing gender-affirming surgery is reported. In the Netherlands, people were obliged to have undergone gonadectomy to be able to change their legal sex until a new law came into effect in July 2014. To analyze if this affected the number of people opting for gonadectomy, the proportion of people who had undergone it was calculated before and after passing of the bill. To ensure eligibility for

Table 1. Reasons for not having started GnRHa.[a]

Category	Description
1. In diagnostic phase	Participants were still in the diagnostic phase at the end of data collection.
2. Referred elsewhere for diagnostic evaluation	Participants were initially seen at our gender identity clinic but referred to another mental health care provider for diagnostic evaluation and did not return to our clinic before the end of data collection.
3. GD in childhood	Participants diagnosed with GD in childhood but not yet eligible for start of GnRHa were advised to return to our gender identity clinic at the start of puberty if GD persisted. People who did not return before end of data collection but meanwhile became potentially eligible for GnRHa belong to this category.
4. GD not diagnosed	After diagnostic assessment, a diagnosis of GD was not established.
5. Medical/per protocol	Medical reasons for not starting GnRHa were severe obesity and childhood osteoporosis, as use of GnRHa may aggravate these conditions. Also in this category are participants who had previously had an intake at our gender identity clinic before turning 18 years old but turned 18 during diagnostic evaluation and were therefore not eligible for puberty suppression.
6. Psychological	Start of GnRHa was precluded by mental health issues that required treatment first, such as severe depressive or anxiety disorders. Mental incompetence to provide informed consent for treatment was also classified under this category.
7. Participant related	Diagnostic evaluation was discontinued at request of the participant or because of not attending appointments without notice.
8. Other/unclear	

Abbreviations: GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone agonist. [a]End of data collection: December 31, 2018.

surgery, only people meeting the criteria of age ≥18 years and at least 1 year of GAH were included in this analysis.

The majority of gender-affirming surgery in the Netherlands has been performed at the VUmc. If surgery was performed in another center, this was added to the participants' medical record and included in the Amsterdam Cohort of Gender Dysphoria database.

Statistical analyses

Characteristics are reported as mean ± SD for normally distributed data or median (IQR) for nonnormally distributed data. Dichotomous variables are presented as percentages. AMAB and AFAB were analyzed separately. To analyze trends over time, repeated analyses were done on cohorts defined by the year of first visit. Cohorts were created by 2-year intervals, except for the first 3 years, which were taken together. Reasons for not starting medical treatment were described over a 5-year time frame, except for the 2 most recent years.

Puberty stage was assessed in individuals starting GnRHa. To study whether there was a difference in the proportion of people starting GnRHa between those who were prepubertal and pubertal at their first visit, we compared those who had their first visit at age <10 and ≥10 years.

To avoid bias, participants who were diagnosed with GD elsewhere and referred to the VUmc to start treatment immediately were not included in the analyses of age at first visit and the proportion starting GnRHa and/or GAH. Similarly, people who started treatment prior to referral were left out of these analyses.

A ridgeline plot was created to visualize the distribution of years between intake and start of GnRHa and GAH.

Analyses were performed with Stata Statistical Software version 15.1 (StataCorp LLC).

Results

Overall

In total, 1766 children and adolescents visited our gender identity clinic between 1997 and 2018. The median duration of follow-up of people starting GnRHa and GAH at the VUmc was 4.6 years (IQR, 2.8-8.5; range, 0.7-18.9). Overall characteristics of this group are shown in Table 2. The number of applicants has increased over time (Figure 2). Since 2012 this increase is mainly generated by AFAB who were ≥10 years old at first visit. The overall ratio of AMAB to AFAB was 1:1.6. In earlier years the predominant proportion of referrals concerned AMAB. However, since 2009 the ratio has shifted, favoring AFAB 1:2.9 in 2018.

The overall median age at first visit was lower for AMAB than AFAB. For both groups, median age at first visit has increased from 2005 onward. Trends in the median age at first visit are shown in Figure 3.

Start of GnRHa treatment

Of all participants who went through the diagnostic evaluation process at the VUmc gender identity clinic (ie, without external referrals; n = 1681), 63% of all 1401 adolescents potentially eligible for GnRHa at the end of data collection had started GnRHa. Overall the percentage of individuals starting GnRHa was greater for AFAB (Table 2).

Out of all potentially eligible young people attending the clinic before turning 10 years old, 36% of AMAB and 53% of AFAB started GnRHa. Of all potentially eligible individuals first visiting when aged ≥10 years, 53% of AMAB and 77% of AFAB started GnRHa (Figure 4). After an initial decline, the percentage of AMAB and AFAB starting GnRHa who first visited before age 10 has increased over time. The percentage of AMAB and AFAB starting GnRHa who first visited at or over age 10 has mildly fluctuated.

Figure 5 shows that the time between first visit and start of GnRHa varies greatly due to diversity in duration of diagnostic evaluation, age, and puberty stage. For AMAB and AFAB, the median age at start of GnRHa has risen slightly over time (Figure 3), except for a temporary decrease in AFAB during 2011 to 2012. The proportion of AMAB starting GnRHa that was in early puberty has fluctuated over time. For AFAB, this proportion decreased until 2009. Except for an increase in 2011 to 2012, the percentage of AFAB who start GnRHa in early puberty has stayed relatively stable after 2009 (Figure 3).

Figure 6 shows reasons for not starting GnRHa in people who completed diagnostic evaluation. The proportion of

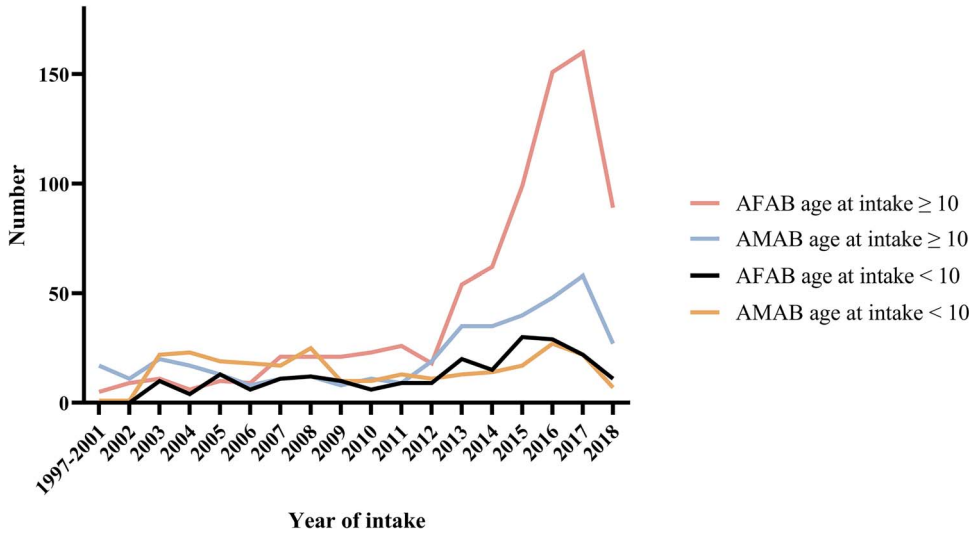

Figure 2. Number of all AMAB and AFAB seen at the VUmc gender identity clinic, stratified by age at intake. Due to a low number of visits to the gender identity clinic in the first years, 1997 to 2001 are taken together. From 2018 onward, the number of intakes was restricted because of overwhelming demand. AFAB, assigned female at birth; AMAB, assigned male at birth.

Table 2. Characteristics of pediatric population referred to VUmc gender identity clinic.[a]

	AMAB	AFAB
Total sample	689 (39)	1077 (61)
Total minus external referrals	669 (40)	1012 (60)
Age at first visit, y[b]	11.5 (8.0-15.2)	14.1 (10.5-16.0)
GnRHa		
Started GnRHa[b,c]	266 (47)	616 (73)
Age at first visit, y		
<10	68 (36)	74 (53)
≥10	198 (53)	542 (77)
Age at start of GnRHa, y	14.0 (12.8-16.1)	15.5 (12.9-16.8)
Starting GnRHa in early puberty, %[d]	34	4.6
Testicular volume at start of GnRHa, mL	12 (7-20)	NA
Menarche prior to start of GnRHa, %	NA	73[e]
Duration of GnRHa monotherapy, y	1.6 (0.7-2.6)	0.7 (0.5-1.9)
Discontinued GnRHa[b]	9 (3.4)	5 (0.8)
GAH		
Started GAH[b,f]	202 (93)	454 (93)
Age at first visit, y		
<10	48 (100)	32 (100)
≥10	154 (91)	422 (92)
Age at start of GAH, y	16.0 (15.5-17.1)	16.7 (16.0-17.5)

Abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; GAH, gender-affirming hormone; GnRHa, gonadotropin-releasing hormone agonist; NA, not applicable. [a] Unless stated otherwise, numbers are reported as median (IQR) or No. (%). [b] Referrals who had started hormone treatment elsewhere were excluded. [c] Percentages are based on those potentially eligible for indicated treatment. Eligible for start of GnRHa: age <10 years, AMAB (n = 191) and AFAB (n = 139); age ≥10 years, AMAB (n = 371) and AFAB (n = 700). [d] Early puberty was defined as testicular volume ≤9 mL or maximum Tanner breast stage 2 for AMAB and AFAB, respectively. [e] 21% missing. [f] Percentages are based on those potentially eligible for indicated treatment. Eligible for start of GAH: age <10 years, AMAB (n = 48) and AFAB (n = 32); age ≥10 years, AMAB (n = 91) and AFAB (n = 458).

individuals not fulfilling diagnostic criteria for GD was larger for AMAB than AFAB during all time frames. The percentage of AMAB first visiting at age <10 years who were not diagnosed with GD was stable over time. In AFAB this increased in only the most recent years. The relative number of AMAB first visiting at age ≥10 who were not diagnosed with GD showed a decreasing trend. For AFAB this fluctuated over time. A GD diagnosis was more often not present in children first visiting before age 10 than those first visiting when age ≥10 years.

The percentage of AMAB diagnosed with GD in childhood (ie, before the onset of puberty) who had not returned to the gender identity clinic despite being potentially eligible to start GnRHa was more or less stable, regardless of the age at first visit. This number showed a decreasing trend in AFAB first visiting at age <10 and ≥10 years.

The relative number of people not starting GnRHa due to medical/protocol reasons increased in both groups during the last time frame (2017-2018). A more detailed review of this subgroup showed that the majority had not started puberty suppression because they had already turned 18 years old during diagnostic evaluation and thus could start GAH directly.

No trend was found in the number of adolescents who had not started GnRHa on psychological or participant-related grounds as defined in Table 1.

Discontinuation of GnRHa treatment

Of all 266 AMAB who started GnRHa at our center, 9 (3.4%) discontinued treatment. Six (2.3%) ceased treatment because of abating GD. In 2 AMAB (0.8%), GnRHa treatment ended due to psychological or social issues hindering transition. In 1 individual (0.4%), GnRHa was discontinued due to compliance issues. Of all 616 AFAB, 5 (0.8%) broke off GnRHa. In 3 (0.5%), remission of GD led to discontinuation. In 2 (0.3%), GnRHa was suspended due to compliance issues. A temporal trend in people stopping GnRHa was not observed.

Start of GAH treatment

Of 707 eligible VUmc participants using GnRHa, 93% subsequently started GAH (Table 2). Additionally, 3 persons could

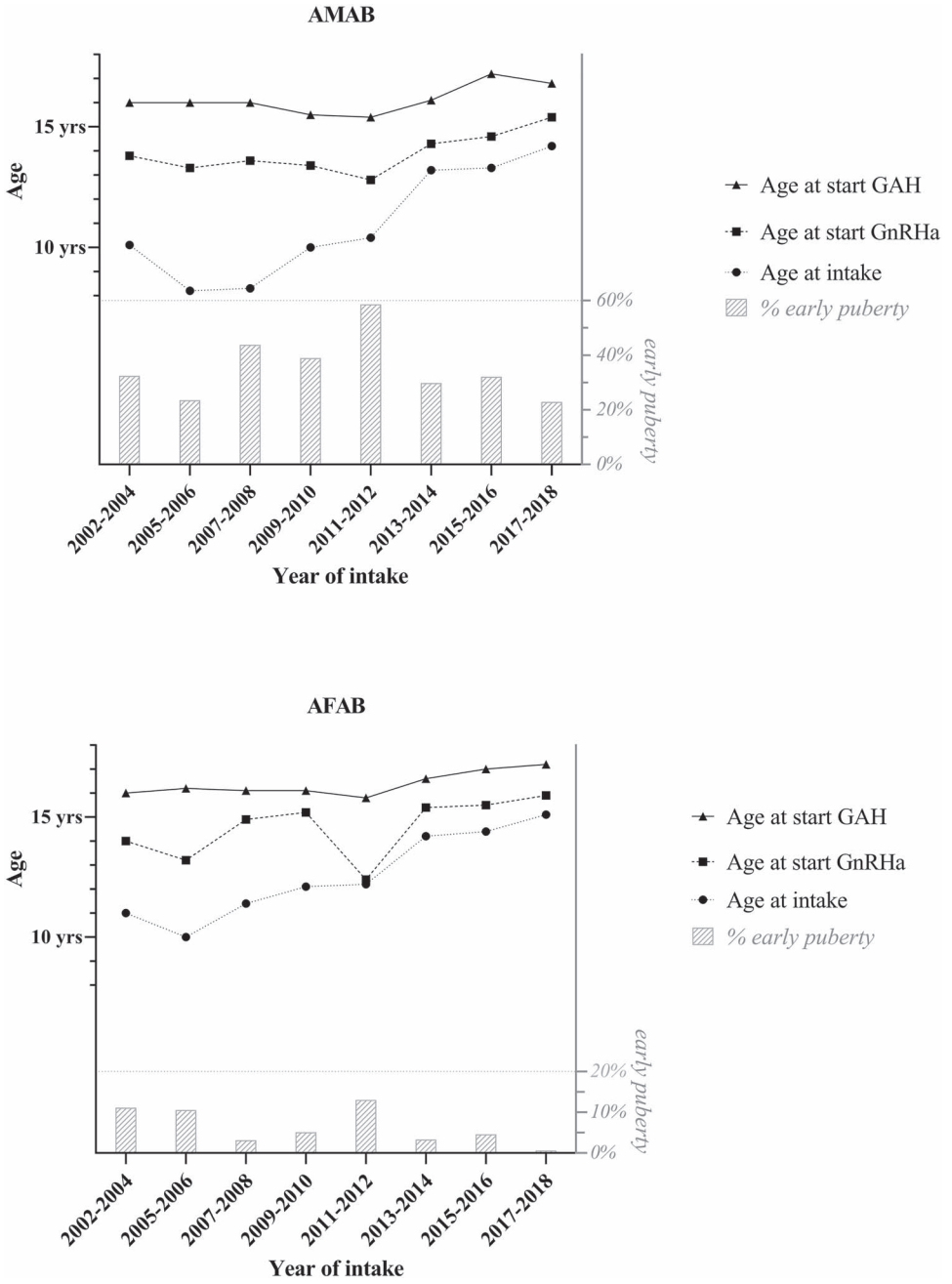

Figure 3. Trends in median age at intake, start of GnRHa and GAH treatment, and proportion of adolescents starting GnRHa in early puberty, for all people attending the gender identity clinic before age 18 years based on year of intake. Left y-axis: median age at start of GnRHa and GAH treatment. Right y-axis: percentage starting GnRHa in early puberty. The scale on the right y-axis is different for AMAB (top) and AFAB (bottom). AFAB, assigned female birth; AMAB, assigned male at birth; GAH, gender-affirming hormone; GnRHa, gonadotropin-releasing hormone agonist.

have started GnRHa but needed to start GAH directly for medical reasons.

The majority of people who had not yet started GAH did so for protocol reasons respectively. They were either too young or had not used GnRHa for the required amount of time. Otherwise, of all 266 AMAB starting GnRHa treatment, 1 (0.4%) moved abroad before a decision on starting GAH could be made. Of all 616 AFAB starting GnRHa treatment, 1 (0.2%) chose to continue GnRHa at another gender identity clinic before deciding on GAH. Of all 266 AMAB and 616 AFAB starting GnRHa treatment, psychological reasons precluded start of GAH for 2 (0.8%) and 1 (0.2%), respectively. Of all 266 AMAB and all 616 AFAB who had started GnRHa and were eligible for GAH, GAH was postponed for 1 (0.4%) and 4 (0.6%), respectively, because the diagnosis of GD had become uncertain. GnRHa was continued while the diagnostic phase was extended.

A clear trend in reasons for not starting GAH could not be found. With the exception of 2007 to 2008, the relative number of AFAB starting GAH was equal to or larger than AMAB, resulting in an overall larger proportion of AFAB who started GAH. The percentage of people starting GAH was stable for AMAB and AFAB first visiting before age 10 years. A downtrend was noted for both groups first visiting at or

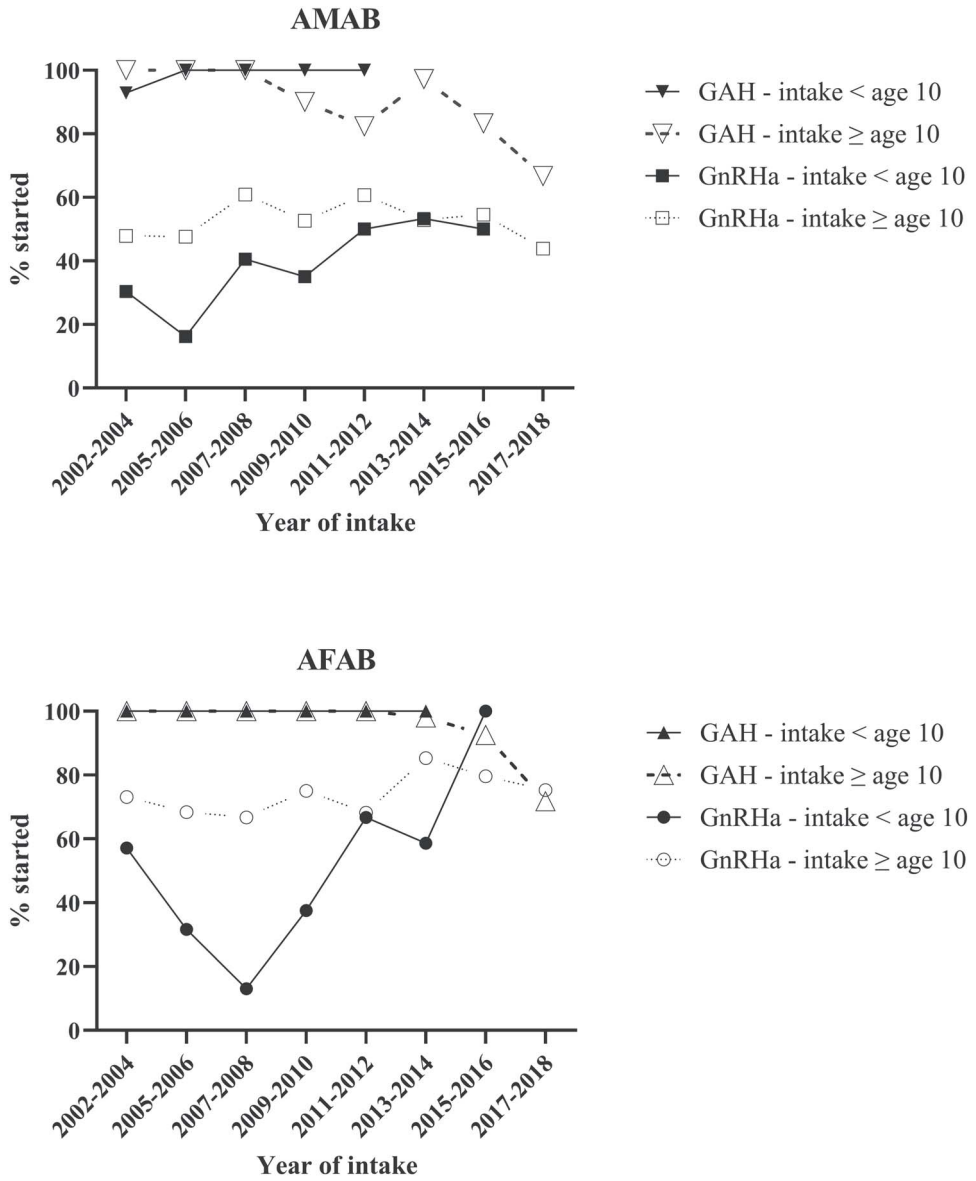

Figure 4. Percentages of people starting GnRHa and GAH treatment, stratified by age at first visit <10 or ≥10 years. In people who first visited before age 10 years, no one was eligible yet for start of GnRHa from 2017 onward. Similarly, in AMAB and AFAB, no one was eligible yet for start of GAH from 2013 and 2015 onward, respectively. AFAB, assigned female birth; AMAB, assigned male at birth; GAH, gender-affirming hormone; GnRHa, gonadotropin-releasing hormone agonist.

after age 10 (Figure 4). In parallel to a varying time between intake and start of GnRHa, time between intake and start of GAH was diverse as well (Figure 5). Until 2011, age at start of GAH in both groups was reasonably stable, but an increase was observed over the most recent years (Figure 3).

Gender-affirming surgery

In total 115 AMAB underwent gonadectomy. Until July 2014, 69 were eligible for gonadectomy based on age and duration of treatment, of whom 58 (84%) proceeded with surgery. Three did not opt for gonadectomy at all, and 8 underwent gonadectomy after July 2014. From July 2014 until the end of data inclusion, 93 AMAB became eligible for gonadectomy, of whom 49 (53%) had this operation.

Gonadectomy was performed in 189 AFAB. Before July 2014, 104 were eligible for gonadectomy. Of these, 78 (75%) underwent surgery before July 2014. Nine did not opt for gonadectomy at all. The remaining 17 underwent gonadectomy after July 2014. Of the 249 AFAB who became eligible for gonadectomy after July 2014, 94 (38%) had this operation. The remaining 155 have not (yet) had a gonadectomy.

Table 3 provides an overview of all gender-affirming surgery performed and the proportion of people undergoing it. Additionally, the percentage of people undergoing surgery stratified by puberty stage at start of GnRHa is shown.

Discussion

This article describes trends in trajectories of children and adolescents who were referred for GD in the oldest and largest European gender identity clinic. We provide answers to questions regarding the number and ratio of assigned sex at birth of people first visiting, the age at first visit and at

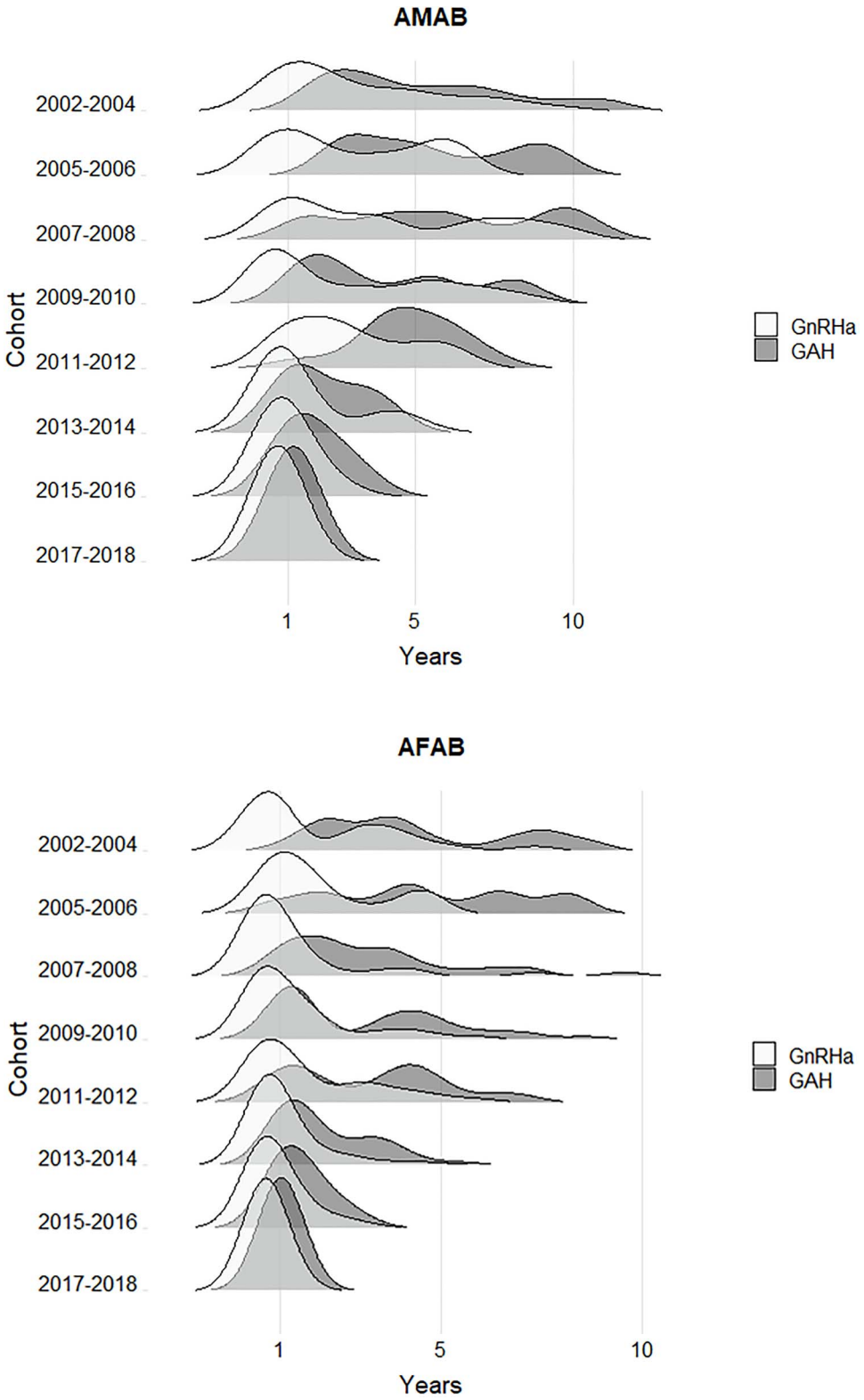

Figure 5. Time between intake and start of GnRHa and GAH treatment per cohort based on year of intake for AMAB (top) and AFAB (bottom). Follow-up is limited by the end of data collection (December 31, 2018). AFAB, assigned female birth; AMAB, assigned male at birth; GAH, gender-affirming hormone; GnRHa, gonadotropin-releasing hormone agonist.

start of medical treatment, trends in proportions of people starting and stopping medical treatment, differences over time in the puberty stage of people starting GnRHa, reasons for not starting treatment, and proportions of people undergoing gender-affirming surgery.

In a recent study, Arnoldussen et al reported on a subset of our participants but included only adolescents who were already potentially eligible for GnRHa and/or GAH, instead of all data from the start of the Dutch Protocol, including prepubertal children, thus making it difficult to compare

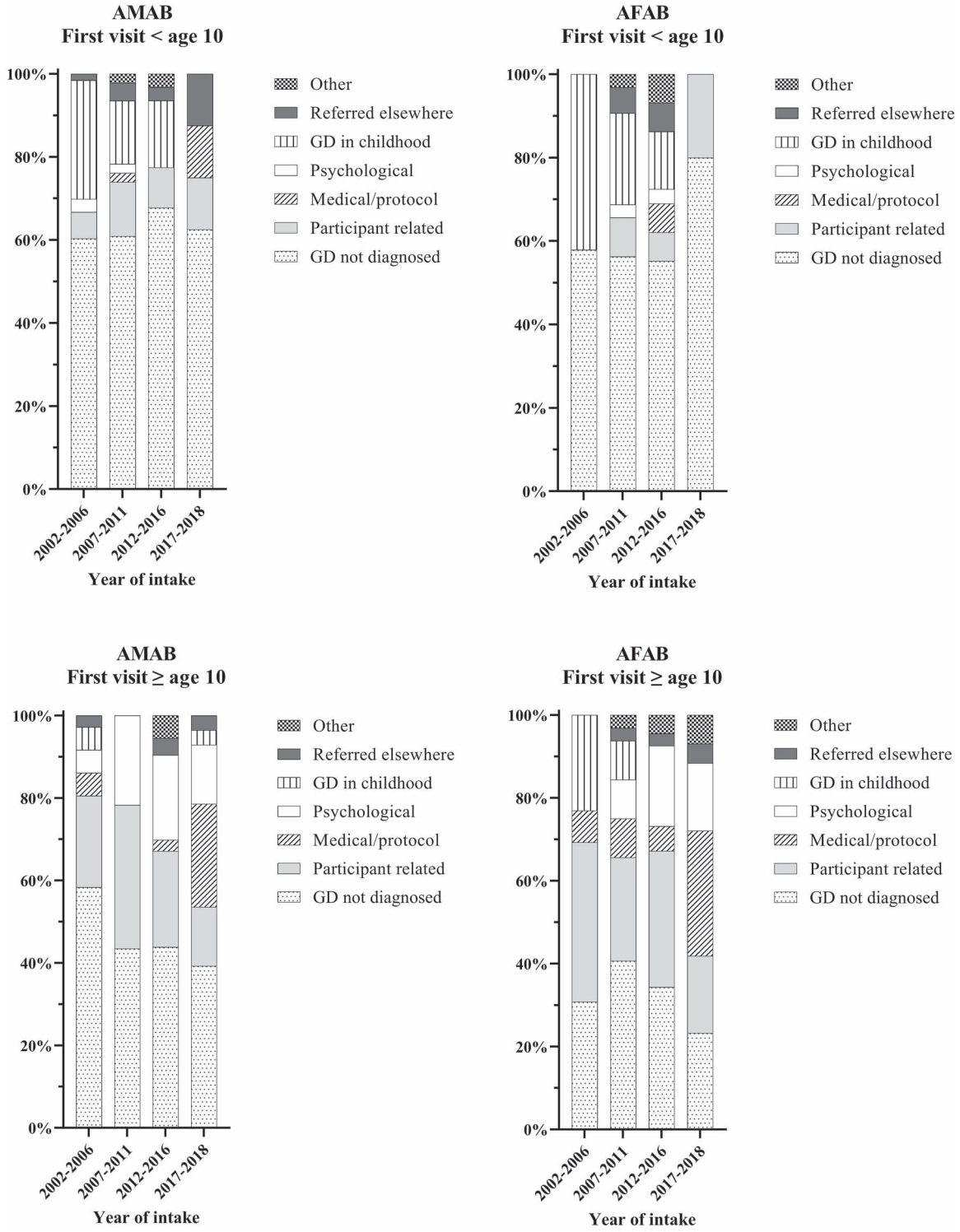

Figure 6. Reasons for not having started GnRHa for people who completed diagnostic evaluation, stratified by age at first visit <10 or ≥10 years during 4 time frames. People still in diagnostic phase: 2012-2016—age <10 years, AMAB (n = 14) and AFAB (n = 19); age ≥10 years, AMAB (n = 4) and AFAB (n = 6); 2017-2018—age <10 years, AMAB (n = 6) and AFAB (n = 10); age ≥10 years, AMAB (n = 31) and AFAB (n = 87). AFAB, assigned female birth; AMAB, assigned male at birth; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone agonist. Categories are explained in Table 1.

outcomes.[10] Additionally, the previous study put more focus on the adolescents' psychological functioning, while we provided data on reasons for refraining for medical intervention and puberty stage at start of GnRHa.

The number of people seen at our clinic has rapidly increased over the last years, a phenomenon that has become familiar not only in our center.[20-23] Until 2007 the ratio of AMAB to AFAB referred to our center tipped toward AMAB. Yet, this ratio clearly shifted after 2009, tipping toward AFAB from then on. This shift seems to have occurred because the increase in referrals is steeper for AFAB than AMAB and has been observed before.[9,21,24-26] An explanation that has been

Table 3. People undergoing gender-affirming surgery overall and stratified by puberty stage at start of GnRHa.

		Started GnRHain, No. (%)	
	No. (%)	Early puberty	Late puberty
AMAB			
Sample	162[a]	35	120
Orchiectomy	115 (71)	26 (74)	82 (68)
Vaginoplasty	112 (69)	26 (74)	79 (66)
Breast augmentation	21 (13)	4 (11)	12 (10)
Adam's apple reduction	3 (1.9)	0	3 (2.5)
Voice feminization surgery	3 (1.9)	0	3 (2.5)
Facial feminization surgery	6 (3.7)	0	6 (5.0)
AFAB			
Sample	353[a]	9	336
Mastectomy	280 (79)	3 (33)	265 (79)
Hysterectomy	193 (55)	9 (100)	177 (53)
Salpingo-oophorectomy	190 (54)	9 (100)	175 (52)
Colpectomy	58 (16)	3 (33)	54 (16)
Metoidioplasty/phalloplasty	37 (10)	1 (11)	35 (10)

Abbreviations: AFAB, assigned female at birth; AMAB, assigned male at birth; GnRHa, gonadotropin-releasing hormone agonist. [a]Percentages are based on the number of people potentially eligible for gender-affirming surgery. Puberty stage missing in 7 AMAB and 8 AFAB.

mentioned is that in most Western cultures, it is more widely accepted for AFAB to come out as trans men, as opposed to AMAB longing for a more feminine appearance.[24] However, a conclusive explanation has yet to be found.

Unfortunately, the increase in applicants has resulted in a considerable waiting time to access transgender care. This might explain why the age at which people had their first appointment has been rising over the recent periods for AMAB and AFAB. From 2002 onward, AMAB presented at a younger age as compared with AFAB. This finding was not in line with the previously mentioned study[10] on a subset of this cohort, most likely due to different inclusion criteria as indicated, but it has been noted by others.[27] It might be that AMAB experience gender dysphoric feelings at an earlier age, but this thought is not supported by a study that found no statistically significant difference in age of first experiencing feelings of GD between AMAB and AFAB.[28] Otherwise, it is likely that AMAB with gender-variant behavior are more rapidly considered deviant from the societally accepted standard and that professional care is sought at younger ages than for their AFAB counterparts.

A slight increase in median age at start of GnRHa was found for AMAB and AFAB. In general, AFAB started GnRHa at a later age and more often than AMAB. This is in line with an earlier study on the trajectories of people starting GnRHa.[29] The difference in age at start of treatment is most likely a reflection of older age at presentation in AFAB. A not-yet-elucidated drop in age at start of GnRHa was seen during 2011 to 2012, most outspoken in AFAB.

The proportion of AMAB starting GnRHa in early puberty was larger than in AFAB. This may be related to the sex difference in age of onset of puberty, as AMAB are known to enter puberty at a later age than AFAB. Adding to this, AMAB already presented at an earlier age, thereby enabling this group to start GnRHa at an earlier age and thus amplifying the difference in puberty stage at start of GnRHa.

The difference between AMAB and AFAB in the relative number of people starting GnRHa is remarkable. It seems to be partly due to the fact that GD is absent in a larger percentage of AMAB than AFAB, which is line with previous findings.[30] It may be that GD is more severe in AFAB, as indeed found in studies by Olson et al.[31] Alternatively, this might be related to sociocultural acceptance of gender-variant behavior as well. Altogether, the primary explanation underlying this finding is complex, and more compelling arguments need to be identified.

The majority of adolescents (93%) using GnRHa go on to start with GAH. This finding may imply that GnRHa treatment is used as a start of transition rather than an extension of the diagnostic phase. Only a few individuals (1.6%) discontinued GnRHa. The main reason for discontinuing GnRHa was remission of GD. Previous research suggests that the period between the ages of 10 to 13 years is pivotal for continuation or resolution of GD.[32] Since nearly all participants started GnRHa after turning 13 and underwent a thorough diagnostic assessment before treatment was started, it is likely that most people starting GnRHa experienced sustained GD. Still, one cannot exclude the possibility that starting GnRHa in itself makes adolescents more likely to continue medical transition.[33,34] This percentage of 1.6% is lower than that found at a Scottish pediatric endocrinology service, where among the 79 young people who had started GnRHa, 6 (8%) discontinued treatment.[35] Yet, the sample size of 79 is markedly smaller than that in our study. A Dutch study that assessed trajectories in 143 young people diagnosed with GD found that 3.5% of all young people discontinued GnRHa treatment because the desire for gender-affirming treatment had abated.[29] A recent study at the Gender Identity Development Service in England showed that of 431 young people consenting to the start of GnRHa, 30 (7%) did not start or eventually stopped GnRHa.[36] However, some of these might have received further care at private clinics. Therefore, as put forward by the authors themselves, it is difficult to compare these data with outcomes from our gender identity clinic. A complementary study reporting on the reasons for discharge from the Gender Identity Development Service demonstrated that between 2008 and 2021, 49 (4%) out of 1089 young people stopped GnRHa because they identified with their gender assigned at birth.[37]

Age at start of GAH increased over time in parallel with age at start of GnRHa, probably as an unfortunate result of waiting lists. The indicated difference in age at presentation

and start of GnRHa between AMAB and AFAB did not affect age at start of GAH, as this was largely similar in both groups. Overall AFAB were more likely to start GAH. Although the difference was small, it was observed particularly from 2011 onward. This was also noticed in previous research.[30]

In the recent years, the proportion of participants visiting after age 10 years who started GAH has decreased. These numbers may have increased when reexamined at a later time, as Figure 5 shows that GAH may still be pursued many years after starting GnRHa. However, it might be that treatment trajectories have changed over time, with more adolescents not desiring GAH in the recent years or possibly taking more time to consider GAH while using GnRHa.

Overall, more AMAB opted for gender-affirming genital surgery than AFAB. Masculinizing gender-affirming genital surgery is a challenging, high-risk procedure,[38,39] which may explain why only a modest number of AFAB chose to undergo it. Otherwise, the AFAB group might consist of a greater number of people with a nonbinary gender identity not seeking masculinizing genital surgery. However, considerations for choosing genital surgery were beyond the scope of this study.

A very clear distinction was found in the relative number of participants undergoing gonadectomy before and after July 2014. This is likely a result of the "transgender law" that took effect at that time. It emphasizes that this kind of legislation can lead to people undergoing irreversible procedures, with far-reaching consequences and for nonintrinsic motives, and should be abolished. Yet, due to the long waiting lists for gender-affirming surgery, it is possible that the number of people undergoing gonadectomy after July 2014 will still increase. Considering the finding that an increasing number of trans people want to keep their reproductive organs in situ while on GAH, it is important that nationwide screening programs (eg, for cervix carcinoma) be brought to their attention during medical check-ups. Furthermore, future research should focus on the long-term effects of this approach.

The size of our study population, originating from the oldest and largest pediatric gender identity clinic in the Netherlands, is a valuable asset to this study. This population can serve as a representative of young people diagnosed with GD receiving health care in the Netherlands according to the Dutch Protocol. The long time span in this study is unprecedented.

We are aware of some limitations to our study. As these results originate from 1 center that followed 1 diagnostic and treatment protocol, the results may be different for centers following a different treatment approach. Due to the retrospective design, data might be lacking. Caution needs to be taken when interpreting results from the most recent years. Although the percentages of people starting GnRHa and GAH are calculated per the number of people who met the criteria for initiation of treatment, the calculated proportions in the most recent years are likely an underestimation. Many might have started treatment after data collection ended. The proportion of participants from the 2017-2018 cohort who start GnRHa in early puberty may well increase when reviewed in the future. Many prepubescent participants have not yet had time to enter puberty and start treatment as the age at intake was relatively low for AMAB and AFAB. Although great care was taken to complete participants' medical history, some might have undergone gender-affirming surgery elsewhere and beyond our knowledge, thereby underestimating numbers on this operation.

Conclusion

This study confirmed a steep increase of referrals to our gender identity clinic and a change in sex ratio predominantly propelled by an influx of older AFAB, which are still only partly understood. A substantial proportion of children first visiting before age 10 years did not meet criteria for a GD diagnosis, underlining the need for an individualized diagnostic approach. Novel findings are that detransition was very rare and that the majority of people starting GnRHa continued with subsequent GAH. This provides ongoing support for medical interventions in gender-diverse adolescents. Last, as such a striking difference was found in the number of people undergoing gonadectomy before and after July 2014—coinciding with the "transgender law" coming into effect—it seems reasonable to suggest that certain legislation affected the choices made regarding gonadectomy and might have motivated people to undergo medical procedures for nonintrinsic reasons.

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Conceptualization: M.A.T.C.v.d.L., D.T.K., S.E.H., T.D.S., A.L.C.d.V., M.d.H., C.M.W. Methodology: M.A.T.C.v.d.L., M.d.H., C.M.W. Validation: M.A.T.C.v.d.L., C.M.W. Formal analysis: M.A.T.C.v.d.L., C.M.W. Investigation: M.A.T.C.v.d.L., D.T.K., S.E.H., S.B., C.M.W. Data curation: M.A.T.C.v.d.L., S.B. Writing–original draft: M.A.T.C.v.d.L. Writing–review and editing, all authors. Visualization: M.A.T.C.v.d.L., C.M.W. Supervision: D.T.K., S.E.H., T.D.S., B.P.C.K., P.T.C.-K., A.L.C.d.V., M.d.H., C.M.W.

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References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.
2. Cohen-Kettenis PT, van Goozen SH. Sex reassignment of adolescent transsexuals: a follow-up study. *J Am Acad Child Adolesc Psychiatry*. 1997;**36**:263–271.
3. Cohen-Kettenis PT, van Goozen SH. Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent. *Eur Child Adolesc Psychiatry*. 1998;**7**:246-248.
4. Cohen-Kettenis PT, Schagen SE, Steensma TD, de Vries AL, Delemarre-van de Waal HA. Puberty suppression in a gender-dysphoric adolescent: a 22-year follow-up. *Arch Sex Behav*. 2011;**40**:843–847.
5. Delemarre-van de Waal HA, Cohen Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *Eur J Endocrinol*. 2006;**155**:S131–S137.
6. Shumer DE, Spack NP. Paediatrics: transgender medicine—long-term outcomes from "the Dutch model." *Nat Rev Urol*. 2015;**12**:12-13.
7. Goodman M, Adams N, Corneil T, Kreukels B, Motmans J, Coleman E. Size and distribution of transgender and gender nonconforming populations: a narrative review. *Endocrinol Metab Clin North Am*. 2019;**48**:303–321.
8. Wiepjes CM, Nota NM, de Blok CJM, *et al*. The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): trends in prevalence, treatment, and regrets. *J Sex Med*. 2018;**15**:582–590.

9. de Graaf NM, Giovanardi G, Zitz C, Carmichael P. Sex ratio in children and adolescents referred to the gender identity development service in the UK (2009-2016). *Arch Sex Behav*. 2018;**47**:1301–1304.
10. Arnoldussen M, Steensma TD, Popma A, van der Miesen AIR, Twisk JWR, de Vries ALC. Re-evaluation of the Dutch approach: are recently referred transgender youth different compared to earlier referrals? *Eur Child Adolesc Psychiatry*. 2020;**29**:803–811.
11. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, *et al*. Endocrine Society. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2009;**94**:3132-3154.
12. World Professional Association for Transgender Health. Standards of care for the health of transsexual, transgender, and gender nonconforming people, 5th version. 1998. https://www.wpath.org/publications/soc.
13. Socialstyrelsen. Care of children and adolescents with gender dysphoria. 2022. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-3-7799.pdf.
14. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth edition, text revision. ed. American Psychiatric Association; 2000.
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth edition. American Psychiatric Association; 2013.
16. de Vries AL, Cohen-Kettenis PT. Clinical management of gender dysphoria in children and adolescents: the Dutch approach. *J Homosex*. 2012;**59**:301–320.
17. Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. *J Clin Endocrinol Metab*. 2015;**100**:E270–E275.
18. Hembree WC, Cohen-Kettenis PT, Gooren L, *et al*. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2017;**102**:3869-3903.
19. de Vries AL, Klink D, Cohen-Kettenis PT. What the primary care pediatrician needs to know about gender incongruence and gender dysphoria in children and adolescents. *Pediatr Clin North Am*. 2016;**63**:1121–1135.
20. Handler T, Hojilla JC, Varghese R, Wellenstein W, Satre DD, Zaritsky E. Trends in referrals to a pediatric transgender clinic. *Pediatrics*. 2019;**144(5):e20191368**.
21. Kaltiala R, Bergman H, Carmichael P, *et al*. Time trends in referrals to child and adolescent gender identity services: a study in four Nordic countries and in the UK. *Nord J Psychiatry*. 2020;**74**:40-44.
22. Butler G, De Graaf N, Wren B, Carmichael P. Assessment and support of children and adolescents with gender dysphoria. *Arch Dis Child*. 2018;**103**:631–636.
23. Segev-Becker A, Israeli G, Elkon-Tamir E, *et al*. Children and adolescents with gender dysphoria in Israel: increasing referral and fertility preservation rates. *Endocr Pract*. 2020;**26**:423–428.
24. Aitken M, Steensma TD, Blanchard R, *et al*. Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. *J Sex Med*. 2015;**12**:756-763..
25. Chiniara LN, Bonifacio HJ, Palmert MR. Characteristics of adolescents referred to a gender clinic: are youth seen now different from those in initial reports? *Horm Res Paediatr*. 2018;**89**:434–441.
26. Steensma TD, Cohen-Kettenis PT, Zucker KJ. Evidence for a change in the sex ratio of children referred for gender dysphoria: data from the Center of Expertise on Gender Dysphoria in Amsterdam (1988-2016). *J Sex Marital Ther*. 2018;**44**:713–715.
27. Spack NP, Edwards-Leeper L, Feldman HA, *et al*. Children and adolescents with gender identity disorder referred to a pediatric medical center. *Pediatrics*. 2012;**129**:418–425.
28. Holt V, Skagerberg E, Dunsford M. Young people with features of gender dysphoria: demographics and associated difficulties. *Clin Child Psychol Psychiatry*. 2016;**21**:108-118.
29. Brik T, Vrouenraets L, de Vries MC, Hannema SE. Trajectories of adolescents treated with gonadotropin-releasing hormone analogues for gender dysphoria. *Arch Sex Behav*. 2020;**49**:2611–2618.
30. Wagner S, Panagiotakopoulos L, Nash R, *et al*. Progression of gender dysphoria in children and adolescents: a longitudinal study. *Pediatrics*. 2021;**148(1):e2020027722**.
31. Olson J, Schrager SM, Belzer M, Simons LK, Clark LF. Baseline physiologic and psychosocial characteristics of transgender youth seeking care for gender dysphoria. *J Adolesc Health*. 2015;**57**:374–380.
32. Steensma TD, Biemond R, de Boer F, Cohen-Kettenis PT. Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. *Clin Child Psychol Psychiatry*. 2011;**16**:499–516.
33. Richards C, Maxwell J, McCune N. Use of puberty blockers for gender dysphoria: a momentous step in the dark. *Arch Dis Child*. 2019;**104**:611–612.
34. Vrouenraets LJ, Fredriks AM, Hannema SE, Cohen-Kettenis PT, de Vries MC. Early medical treatment of children and adolescents with gender dysphoria: an empirical ethical study. *J Adolesc Health*. 2015;**57**:367–673.
35. McCallion S, Smith S, Kyle H, Shaikh MG, Wilkinson G, Kyriakou A. An appraisal of current service delivery and future models of care for young people with gender dysphoria. *Eur J Pediatr*. 2021;**180**:2969–2976.
36. Masic U, Butler G, Carruthers P, Carmichael P. Trajectories of transgender adolescents referred for endocrine intervention in England. *Arch Dis Child*. Published online July 28, 2022. https://doi:10.1136/archdischild-2022-324283.
37. Butler G, Adu-Gyamfi K, Clarkson K, *et al*. Discharge outcome analysis of 1089 transgender young people referred to paediatric endocrine clinics in England 2008-2021. *Arch Dis Child*. Published online July 28, 2022. https://doi:10.1136/archdischild-2022-324302.
38. Frey JD, Poudrier G, Chiodo MV, Hazen A. A systematic review of metoidioplasty and radial forearm flap phalloplasty in female-to-male transgender genital reconstruction: is the "ideal" neophallus an achievable goal? *Plast Reconstr Surg Glob Open*. 2016;**4**:e1131.
39. Veerman H, de Rooij FPW, Al-Tamimi M, *et al*. Functional outcomes and urological complications after genital gender affirming surgery with urethral lengthening in transgender men. *J Urol*. 2020;**204**:104–109.

Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment

WHAT'S KNOWN ON THIS SUBJECT: Puberty suppression has rapidly become part of the standard clinical management protocols for transgender adolescents. To date, there is only limited evidence for the long-term effectiveness of this approach after gender reassignment (cross-sex hormones and surgery).

WHAT THIS STUDY ADDS: In young adulthood, gender dysphoria had resolved, psychological functioning had steadily improved, and well-being was comparable to same-age peers. The clinical protocol including puberty suppression had provided these formerly gender-dysphoric youth the opportunity to develop into well-functioning young adults.

abstract

BACKGROUND: In recent years, puberty suppression by means of gonadotropin-releasing hormone analogs has become accepted in clinical management of adolescents who have gender dysphoria (GD). The current study is the first longer-term longitudinal evaluation of the effectiveness of this approach.

METHODS: A total of 55 young transgender adults (22 transwomen and 33 transmen) who had received puberty suppression during adolescence were assessed 3 times: before the start of puberty suppression (mean age, 13.6 years), when cross-sex hormones were introduced (mean age, 16.7 years), and at least 1 year after gender reassignment surgery (mean age, 20.7 years). Psychological functioning (GD, body image, global functioning, depression, anxiety, emotional and behavioral problems) and objective (social and educational/professional functioning) and subjective (quality of life, satisfaction with life and happiness) well-being were investigated.

RESULTS: After gender reassignment, in young adulthood, the GD was alleviated and psychological functioning had steadily improved. Well-being was similar to or better than same-age young adults from the general population. Improvements in psychological functioning were positively correlated with postsurgical subjective well-being.

CONCLUSIONS: A clinical protocol of a multidisciplinary team with mental health professionals, physicians, and surgeons, including puberty suppression, followed by cross-sex hormones and gender reassignment surgery, provides gender dysphoric youth who seek gender reassignment from early puberty on, the opportunity to develop into well-functioning young adults. *Pediatrics* 2014;134:696–704

AUTHORS: Annelou L.C. de Vries, MD, PhD,[a] Jenifer K. McGuire, PhD, MPH,[b] Thomas D. Steensma, PhD,[a] Eva C.F. Wagenaar, MD,[a] Theo A.H. Doreleijers, MD, PhD,[a] and Peggy T. Cohen-Kettenis, PhD[a]

[a]Center of Expertise on Gender Dysphoria, VU University Medical Center, Amsterdam, Netherlands; and [b]Department of Human Development, Washington State University, Pullman, Washington

KEY WORDS

gender dysphoria, transgenderism, adolescents, psychological functioning, puberty suppression, longitudinal outcomes

ABBREVIATIONS

ABCL—Adult Behavior Checklist
ASR—Adult Self-Report
BDI—Beck Depression Inventory
BIS—Body Image Scale
CBCL—Child Behavior Checklist
CGAS—Children's Global Assessment Scale
CSH—cross-sex hormones
GD—gender dysphoria
GnRHa—gonadotropin-releasing hormone analogs
GRS—gender reassignment surgery
SHS—Subjective Happiness Scale
STAI—Spielberger's Trait Anxiety Scale
SWLS—Satisfaction With Life Scale
TPI—Spielberger's Trait Anger Scale
UGDS—Utrecht Gender Dysphoria Scale
YSR—Youth Self-Report

Dr de Vries conceptualized the study, clinically assessed the participants, drafted the initial manuscript, and reviewed and revised the manuscript; Dr McGuire conceptualized the study, planned and carried out the analyses, assisted in drafting the initial manuscript, and reviewed and revised the manuscript; Dr Steensma conceptualized the study, coordinated and supervised data collection, and reviewed and revised the manuscript; Dr Wagenaar coordinated and invited participants for assessments and reviewed and revised the manuscript; Drs Doreleijers and Cohen-Kettenis conceptualized the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

Dr McGuire's current affiliation is Department of Family Social Science, College of Education and Human Development, St Paul, Minnesota.

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Address correspondence to Annelou L.C. de Vries, MD, PhD, Child and Adolescent Psychiatrist, Center of Expertise on Gender Dysphoria, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, Netherlands. E-mail: alc.devries@vumc.nl

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Puberty Suppression Treatment for Patients with Gender Dysphoria

Patient Information and Informed Parental Consent and Assent for Minors

Your child has been diagnosed with gender dysphoria. Gender dysphoria is a term used to describe people who have significant feelings of discomfort or distress that may accompany a difference between experienced/expressed gender (gender with which they identify) and their physically assigned gender (biological sex). Gender dysphoria affects people in different ways.

This document provides information regarding treatment to suppress puberty (put puberty "on hold"). Before consenting to treatment to suppress your child's puberty with "puberty blockers", you need to be aware of the possible benefits and risks of such treatment.

After all your questions or concerns are addressed to your satisfaction, if you decide to proceed with puberty suppression for your child, you will need to initial the statements below on this form as well as sign acknowledging consent to such treatment. If there is more than one parent/legal guardian, both will have to sign. Your child will also need to sign expressing assent (approval) to treatment.

What are the benefits of suppressing puberty in adolescents with gender dysphoria?

The Endocrine Society recommends suppression of puberty for children that have the diagnosis of gender dysphoria and meet other criteria listed below. Experts in treating youth with gender dysphoria have made this recommendation on the premise that suppression of puberty may:

a) Allow for a smooth social transition to the gender role that is congruent (in harmony) with the child's gender identity, by testing persistence of the gender identity after living a "real-life experience" with the expressed gender, but before receiving irreversible hormonal or surgical treatment;
b) Possibly diminish the psychological trauma and risk of suicide often observed during the physical changes of puberty; and,
c) Avoid the need for surgery and other treatments that are required to reverse the physical effects of puberty (i.e. removal of breasts, tracheal and facial shaving, and electrolysis).

What are my other options if I do not wish to have my child undergo treatment for suppression of puberty?

Due to the high risk of anxiety, depression, self-harm and even suicide associated with gender dysphoria, psychological therapy with a mental health provider that has experience in treating youth with gender dysphoria is highly recommended regardless of whether your child undergoes suppression of puberty. No studies have been done comparing psychological therapy only (i.e., without puberty suppression treatment) versus puberty suppression treatment.

What medications are used to suppress puberty?

The main mechanism by which physical changes of puberty can be put on hold is by blocking the signal from the brain to the organs that make the hormones of puberty. These hormones are estrogen and testosterone. Estrogen is made by the ovaries. Testosterone is made by the testicles.

Medications, also called "pubertal blockers", are effective for both males and females and can be started just after the early physical changes of puberty. None of the medications have been approved by the Food and Drug Administration ("FDA") for use in adolescents with gender dysphoria, which is considered an "off label" use. However, pediatric endocrinologists (children's doctors who specialize in hormones and puberty), use these medications frequently to suppress puberty in children with precocious (early) puberty.

a. Lupron® and Histrelin are called GnRH analogs and are the most effective forms of treatment.

   - Lupron® (an "Injectable GnRH Analog") is given as a monthly or every 3-month intramuscular injection and is approved for children with precocious (early) puberty. ***With your consent, we will treat your child with an Injectable GnRH Analog.***

   - Histrelin (a "Surgical GNRH Analog") is an implant that is placed under the skin surgically, and needs to be replaced yearly to every 2 years. Histrelin is approved for children with precocious puberty with the brand name of Supprelin®, and on a slightly smaller dose, it is approved in adults with prostate cancer under the name of Vantas. However, it only comes in one dose for children which cannot be adjusted and it also requires a surgical procedure to be placed and removed, so therefore Histrelin will not be used to treat your child without additional consent.

b. Provera is a pill that needs to be taken twice a day and is approved to be used

in female adolescents with irregular menstrual bleeding. Provera was used for early puberty before Lupron® and Histrelin were available, and is less effective in suppressing puberty. Since Provera is not very effective and has a high risk of side effects, including blood clots, we will not be using any form of Provera to treat your child.

What are the anticipated effects of using an Injectable GnRH Analog to suppress puberty?

The administration of an Injectable GnRH Analog will completely or nearly completely suppress all of your child's sex hormone production and reproductive capacity. Hence, secondary sexual characteristics may recede in size (i.e., breasts will shrink in size as well as testicles) or may not further increase in size, maintaining a sexually infantile appearance. The capacity to ovulate in girls and produce sperm in boys will also be halted. Sex hormones are important for the development of muscle mass in males and for the normal thickness of bones in both males and females.

What are the requirements to receive suppression of puberty for gender dysphoria at Nemours Children's Specialty Care ("Nemours")?

In order to receive therapy to put puberty on hold at Nemours, there are specific requirements that need to be met before and during the treatment. These requirements will allow us to monitor your child's medical wellbeing as well as mental health during hormone therapy. If these requirements are not, met treatment with puberty blockers may be discontinued in the best interest and safety of your child.

Before beginning treatment with an Injectable GnRH Analog your child will need a thorough psychological and social evaluation performed by our Psychology Department. Your child also must have participated in at least 6 months of psychological therapy as confirmed in writing by your child's therapist. Additionally, your child will need to have started puberty, which varies from person to person but usually occurs at age 10.8 years in girls with breast buds, and age 11 ½ years in boys with testicular enlargement.

After proper evaluations have taken place, treatment to suppress puberty can be initiated if your child meets specific criteria recommended by the Endocrine Society, which includes ALL of the following:

1. Fulfills the current DSM or ICD criteria for gender dysphoria.
2. Has (early) pubertal changes that have resulted in an increase in gender

dysphoria.

3. Does not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment.
4. Has adequate psychological and social support during treatment.
5. Has experienced puberty to at least Tanner stage 2, which is the first stage of puberty and refers to breast or testicle growth. This must be confirmed by a trained physician.
6. Demonstrates knowledge and understanding of the expected outcomes of suppression of puberty, future cross-sex (gender-affirming) hormone treatment, and gender affirming surgery, as well as the medical and social risks and benefits of gender reassignment.

After initiation of treatment for suppression of puberty, the following will be required:

1. Visits with the endocrinologist or adolescent medicine physician in our program every 3 months.
2. Suicide risk assessment performed by our social worker during each clinic visit every 3 months.
3. Laboratory testing every 3-4 months.
4. X-ray of the hand (bone age) once a year.
5. Bone density scan (DXA): this will allow us to monitor your child's bone density (bone strength) during treatment, since puberty blockers may decrease bone density if given for long periods of time.
6. Quarterly mental health assessment and completion of questionnaires with a member of our mental health care team. This will allow us to monitor your child's psychological wellbeing and adjustment while on puberty blockers.
7. Continued counseling with a therapist during the treatment period, with the frequency recommended by the therapist.

Both parents please initial each statement below to show that you understand the benefits, risks, and changes that may occur from giving treatment to your child to suppress his/her puberty.

<u>Effects of Treatment of Suppression of Puberty</u>

_____ _____ I understand that an Injectable GnRH Analog will be used to help temporarily

suspend or block the physical changes of puberty for my child.

_____ _____ I understand that this treatment will not change my child's genetic sex (chromosomes), and it will not change the external genitals other than secondary sexual characteristics which may recede in size (i.e., breasts will shrink in size as well as testicles) or may not further increase in size,.

_____ _____ I understand that the effect of this medication is not permanent. If my child stops treatment, in a few months my child's body will likely restart the changes of puberty at the developmental stage they were at when they started the treatment.

_____ _____ I understand that it can take several months for the medication to be effective. I understand that no one can predict how quickly or slowly my child's body will respond.

_____ _____ I understand that by taking these medications, my child's body will not be making the hormones of puberty, testosterone or estrogen. At this time, I support my child in putting on hold the hormones and the changes induced by puberty.

_____ _____ I understand that an Injectable GnRH Analog works fairly rapidly to reduce the testosterone to a very low level. This will halt the physical changes of male puberty, such as enlargement of the testicles and penis; development of muscles; development of pubic, armpit and facial hair; lowering of the voice; broadening of the shoulders and widening of the jaw; development of a male Adam's apple; sex drive, erections and ejaculations (wet dreams). An Injectable GnRH Analog will not reverse some of the changes of male development that have already happened (Adam's apple, voice changes, shoulder and jaw bone changes, and penis size). It will cause a decrease in testicular size, body hair and muscle development. It will reduce the sex drive and ability to have erections and ejaculations. While an Injectable GnRH Analog interferes with fertility, it does not affect the ability to get a sexually transmitted infection. Precautions against getting an STI must still be taken.

_____ _____I understand that an Injectable GnRH Analog works fairly rapidly to reduce the estrogen to a very low level. This will halt the physical changes of female puberty, such as enlargement of the breasts, widening of the hips; and the onset of menstrual periods. An Injectable GnRH Analog will not reverse some of the changes of female development that have already happened (breast size, width of hips). It will stop menstrual periods and cause vaginal dryness. It will reduce the sex drive. While an

Injectable GnRH Analog interferes with fertility, it does not affect the ability to get a sexually transmitted infection ("STI"). Precautions against getting an STI must still be taken.

_____ _____ I understand that the use of an Injectable GnRH Analog in adolescents with gender dysphoria is off- label use. I know this means the medication is not approved by the FDA for this specific diagnosis.

Risks of Treatment of Suppression of Puberty

_____ _____ I understand that information on adverse effects and safety of an Injectable GnRH Analog used in transgender youth is not well known.

_____ _____ I realize that this treatment may not necessarily prevent serious psychiatric events such as a suicidal attempt.

_____ _____ I understand that the treatments may cause weight gain.

_____ _____ I understand that the treatments to suppress puberty may decrease bone density and increase fracture risk.

_____ _____ I understand that my child may grow less than his/her peers while on these medications.

_____ _____ I understand there is a chance that a person taking an Injectable GnRH Analog can develop an allergy to the medication, which presents as a red, painful sterile abscess (boil) at the injection site. This may start out gradually and get worse with each injection. Rarely, the abscess will have to be drained by incision. If a person develops this problem, the Injectable GnRH Analog must be stopped, and there may not be an alternate medication.

_____ _____ I understand that physical examinations and blood tests are needed on a regular basis to check for the effects of an Injectable GnRH Analog.

_____ _____ I understand that an Injectable GnRH Analog can interact with other medications, dietary supplements, herbs, alcohol, and street drugs. I understand that being honest with my care provider about what else I am taking will help prevent medical complications that could be serious.

_____ _____ I understand there could be a stalling of typical adolescent cognitive or brain development while on these medications.

_____ _____ I understand that stopping the development of puberty for my child may

have social consequences.

_____ _____ I understand that my doctor may suggest I stop taking an Injectable GnRH Analog if there are severe side effects or health risks that can't be controlled.

Requirements of Treatment of Suppression of Puberty

_____ _____ I understand and agree with all the requirements explained above, in order to receive suppression of puberty therapy in our program.

_____ _____ I understand that if my child's mental health team and/or treating physician recommends treatment be stopped because the benefits of treatment no longer outweighs the risks, my child has insufficient social or psychological support, or Nemours' program requirements to treat are not met, that Nemours retains the prerogative to discontinue drug therapy.

_____ _____ I understand that I am responsible for the cost of the medical management, including medical appointments, psychological evaluations, laboratory and imaging tests, as well as drug therapy.

_____ _____ I understand that I can change my mind and withdraw consent for further treatment at any time.

_____ _____ I agree to tell a member of my child's treatment team if I think my child has any problems or is unhappy with the treatment.

_____ _____ I understand that after my child turns age18, medical care must be transitioned to an adult endocrinologist.

Prevention of Complications while under Treatment of Suppression of Puberty

_____ _____ I agree to tell my health care provider if my child has any problems or side effects or is unhappy with the medication, and in particular, if I have concerns that my child has worsening signs of depression or anxiety, or wants to harm him/herself or attempt suicide.

_____ _____ I understand my child needs periodic medical evaluations clinic to make sure that my child is responding appropriately. This includes clinic visits with the pediatric endocrinologist every 3 months, laboratory and imaging tests.

_____ _____ I agree to have my child on continued psychological therapy or counseling with the frequency recommended by his therapist

PARENTAL CONSENT:

My signature below confirms that I have read the above, or had it read to me, and that I understand the information and was given the opportunity to ask questions and that all of my questions were answered to my satisfaction. Furthermore, my child's health care provider has discussed:

- The benefits and risks of puberty blockers for my child.
- The possible or likely consequences of using puberty blockers.
- Potential alternative treatments.
- I understand the risks that may be involved.
- I know that the information in this form includes the known effects and risks. I also know that there may be unknown long-term effects or risks.
- I agree with the requirements that must be met before and during treatment to receive puberty blockers in this program.
- I have had sufficient opportunity to discuss treatment options with my child's health care provider.
- I believe I know enough to give informed consent for my child to take, refuse, or postpone using puberty blocking medications.
- My child is in agreement with this treatment and the signature of my child on the assent form attests to this agreement.
- My signature attests to my consent for my child to begin treatment for suppression of puberty.

Based on all this information:I want my child to receive puberty suppression treatment using an Injectable GnRH Analog as Prescribed.

_____	_____	_____
Name of Parent/Legal Representative (Print)	Signature of Parent/Legal Representative	Date / Time
_____	_____	_____
Name of Parent/Legal Representative (Print)	Signature of Parent/Legal Representative	Date / Time

ASSENT OF A MINOR:

I have discussed the benefits and risks of treatment to suppress puberty with my parent(s) or legal guardian(s), and I wish to receive it.

_____	_____	
Minor's Name (printed)	Minor's Signature	Date / Time
_____	_____	_____
Name of Physician or Designee Obtaining Permission (Print)	Signature of Person Obtaining Permission	Date / Time
_____	_____	_____
Name of Witness (Print)	Signature of Witness	Date / Time

For patients whose primary language is not English:

I certify that I am fluid in English and in the native language of the person(s) indicating consent and/or assent on the above form. I certify that I have accurately and completely interpreted the contents of this form, and that the patient and/or adult(s) legally responsible for the minor child has indicated understanding of the contents of this form.

_____	_____	_____
Interpreter's Signature	Interpreter's Name (Print)	Date