Regret after Gender-affirmation Surgery: A Systematic Review and Meta-analysis of Prevalence

Article *in* Plastic and Reconstructive Surgery (1946) · March 2021

DOI: 10.1097/GOX.0000000000003477

CITATIONS
37

READS
1,114

9 authors, including:

Valeria P. Bustos
Beth Israel Deaconess Medical Center
46 PUBLICATIONS **99** CITATIONS
SEE PROFILE

Samyd Said Bustos
Mayo Clinic - Rochester
58 PUBLICATIONS **336** CITATIONS
SEE PROFILE

Pedro Ciudad
China Medical University Hospital
210 PUBLICATIONS **1,851** CITATIONS
SEE PROFILE

Oscar Javier Manrique
University of Rochester Medical Center
216 PUBLICATIONS **1,536** CITATIONS
SEE PROFILE

Pl. Trial Ex. 161

OPEN

PRS GLOBAL OPEN

ORIGINAL ARTICLE

Reconstructive

Regret after Gender-affirmation Surgery: A Systematic Review and Meta-analysis of Prevalence

Valeria P. Bustos, MD*
Samyd S. Bustos, MD†
Andres Mascaro, MD‡
Gabriel Del Corral, MD, FACS§
Antonio J. Forte MD, PhD, MS¶
Pedro Ciudad, MD, PhD‖
Esther A. Kim, MD**
Howard N. Langstein, MD††
Oscar J. Manrique MD, FACS††

Background: There is an unknown percentage of transgender and gender nonconfirming individuals who undergo gender-affirmation surgeries (GAS) that experiences regret. Regret could lead to physical and mental morbidity and questions the appropriateness of these procedures in selected patients. The aim of this study was to evaluate the prevalence of regret in transgender individuals who underwent GAS and evaluate associated factors.

Methods: A systematic review of several databases was conducted. Random-effects meta-analysis, meta-regression, and subgroup and sensitivity analyses were performed.

Results: A total of 27 studies, pooling 7928 transgender patients who underwent any type of GAS, were included. The pooled prevalence of regret after GAS was 1% (95% CI <1%–2%). Overall, 33% underwent transmasculine procedures and 67% transfemenine procedures. The prevalence of regret among patients undergoing transmasculine and transfemenine surgeries was <1% (IC <1%–<1%) and 1% (CI <1%–2%), respectively. A total of 77 patients regretted having had GAS. Twenty-eight had minor and 34 had major regret based on Pfäfflin's regret classification. The majority had *clear regret* based on Kuiper and Cohen-Kettenis classification.

Conclusions: Based on this review, there is an extremely low prevalence of regret in transgender patients after GAS. We believe this study corroborates the improvements made in regard to selection criteria for GAS. However, there is high subjectivity in the assessment of regret and lack of standardized questionnaires, which highlight the importance of developing validated questionnaires in this population.

(Plast Reconstr Surg Glob Open 2021;9:e3477; doi: 10.1097/GOX.0000000000003477; Published online 19 March 2021.)

INTRODUCTION

Discordance or misalignment between gender identity and sex assigned at birth can translate into disproportionate discomfort, configuring the definition of gender dysphoria.[1–3] This population has increased risk of psychiatric conditions, including depression, substance abuse disorders, self-injury, and suicide, compared with cis-gender individuals.[4,5] Approximately 0.6% of adults in the United States identify themselves as transgenders.[6] Despite advocacy to promote and increase awareness of the human rights of transgender and gender non-binary (TGNB) individuals, discrimination continue to afflict the daily life of these individuals.[4,7]

Gender-affirmation care plays an important role in tackling gender dysphoria.[5,8–10] Gender-affirmation surgeries (GAS) aim to align the patients' appearance with their gender identity and help achieve personal comfort with one-self, which will help decrease psychological distress.[5,10] These interventions should be addressed by a multidisciplinary team, including psychiatrists, psychologists, endocrinologists, physical therapists, and surgeons.[1,9] The number of GAS has consistently increased during the last

*From the *Division of Plastic and Reconstructive Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Mass.; †Department of Plastic Surgery, University of Pittsburgh, Pittsburgh, Pa.; ‡Department of Plastic and Reconstructive Surgery, Cleveland Clinic, Weston, Fla.; §Department of Plastic and Reconstructive Surgery, MedStar Georgetown University Hospital, Washington, D.C.; ¶Division of Plastic and Reconstructive Surgery, Mayo Clinic, Jacksonville, Fla.; ‖Department of Plastic, Reconstructive and Burn Surgery, Arzobispo Loayza National Hospital, Lima, Peru; **Division of Plastic and Reconstructive Surgery, University of California, San Francisco, Calif.; ††Division of Plastic and Reconstructive Surgery, University of Rochester Medical Center, Strong Memorial Hospital, Rochester, N.Y.*

Received for publication July 27, 2020; accepted January 25, 2021.

DOI: 10.1097/GOX.0000000000003477

Disclosure: *The authors have no financial interest to declare in relation to the content of this article.*

Related Digital Media are available in the full-text version of the article on www.PRSGlobalOpen.com.

years. In the United States, from 2017 to 2018, the number of GAS increased to 15.3%.[8,11,12]

Significant improvement in the quality of life, body image/satisfaction, and overall psychiatric functioning in patients who underwent GAS has been well documented.[5,13–19] However, despite this, there is a minor population that experiences regret, occasionally leading to de-transition surgeries.[20] Both regret and de-transition may add an important burden of physical, social, and mental distress, which raises concerns about the appropriateness and effectiveness of these procedures in selected patients. Special attention should be paid in identifying and recognizing the prevalence and factors associated with regret. In the present study, we hypothesized that the prevalence of regret is less than the last estimation by Pfafflin in 1993, due to improvements in standard of care, patient selection, surgical techniques, and gender confirmation care. Therefore, the aim of this study was to evaluate the prevalence of regret and assess associated factors in TGNB patients 13-years-old or older who underwent GAS.[20]

METHODS

Search Methodology

Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, a comprehensive research of several databases from each database's inception to May 11, 2020, for studies in both English and Spanish languages, was conducted.[21] The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian, with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for studies of de-transition and regret in adult patients who underwent gender confirmation surgery. The actual strategy listing all search terms used and how they are combined is available in Supplemental Digital Content 1. (**See Supplemental Digital Content 1,** which displays the search strategy. http://links.lww.com/PRSGO/B598.)

Study Selection

Search results were exported from the database into XML format and then uploaded to Covidence.[22] The study selection was performed in a 2-stage screening process. The first step was conducted by 2 screeners (V.P.B. and S.S.B.), who reviewed titles and abstracts and selected those of relevance to the research question. Then, the same 2 screeners reviewed full text of the remaining articles and selected those eligible according to the inclusion and exclusion criteria (Fig. 1). If disagreements were encountered, a third reviewer (O.J.M.) moderated a discussion, and a joint decision between the 3 reviewers was made for a final determination. Inclusion criteria were all the articles that included patients aged 13 years or more who underwent GAS and report regret or de-transition rates, and observational or interventional studies in English or Spanish language. Exclusion criteria were letter to the editors, case series with <10 patients, case reports correspondences, and animal studies.

Data Extraction/Synthesis

After selecting the articles, we assessed study characteristics. We identified year of publication, country in which the study was conducted, population size, and number of transmasculine and transfemenine patients with their respective mean age (expressed with SD, range, or interquartile range if included in the study). In addition, we extracted information of the method of data collection (interviews versus questionnaires), number of regrets following GAS, as well as the type of surgery, time of follow-up, and de-transition procedures. We classified the type of regret based on the patient's reasons for regret if they were mentioned in the studies. We used the Pfäfflin and Kuiper and Cohen-Kettenis classifications of regret (Table 1).[20,23]

Quality Assessment

To assess the risk of bias within each study, the National Institute of Health (NIH) quality assessment tool was used.[24] This tool ranks each article as "good," "fair," or "poor," and with this, we categorized each article into "low risk," "moderate risk," or "high risk" of bias, respectively.

Outcomes

Our primary outcome of interest was the prevalence of regret of transgender patients who underwent any type of GAS. Secondary outcomes of interest were discriminating the prevalence of regrets by type gender transition (transfemenine and transmasculine), and type of surgery.

Data Analysis and Synthesis

The binominal data were analyzed, and the pooled prevalence of regret was estimated using proportion meta-analysis with Stata Software/IC (version 16.1).[25] Given the heterogeneity between studies, we conducted a logistic-normal-random-effect model. The study-specific proportions with 95% exact CIs and overall pooled estimates with 95% Wald CIs with Freeman-Turkey double arcsine transformation were used. The effect size and percentage of weight were presented for each individual study.[25,26]

To evaluate heterogeneity, I^2 statistics was used. If $P < 0.05$ or $I^2 > 50\%$, significant heterogeneity was considered. A univariate meta-regression analysis was performed to assess the significance in country of origin, tools of measurement, and quality of the studies.

To assess publication bias, we used funnel plot graphic and the Egger test. If this test showed us no statistical significance ($P > 0.05$), we assumed that the publication bias had a low impact on the results of our metanalysis. To assess the impact of the publication bias on our missing studies, we used the trim-and-fill method.

A sensitivity analysis was conducted to assess the influence of certain characteristics in the magnitude and precision of the overall prevalence of regret. The following characteristics were excluded: <10 participants included, and the presence of a high risk of bias.

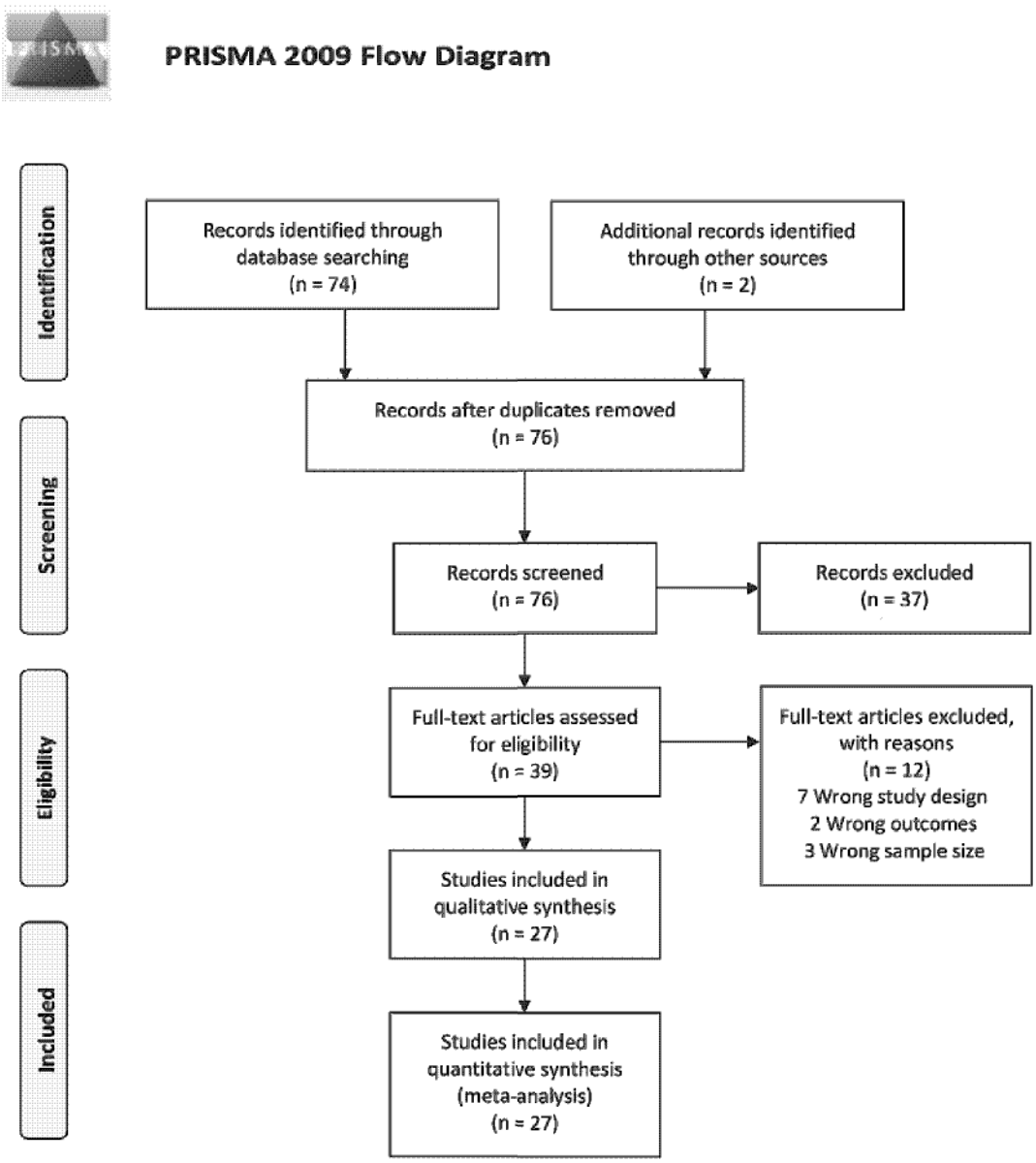


Fig. 1. PRISMA flow diagram for systematic reviews.

Table 1. Pfäfflin and Kuiper and Cohen-Kettenis Categories of Regret

Pfäfflin, 1993	Minor	Feeling of regret secondary to surgical complications or social problems.
	Major	"True" regret. Feeling of dysphoria secondary to the new appearance, or desires of pursuing a de-transition surgery.
Kuiper and Cohen-Kettenis, 1998	Clear regret	Patients openly express their regret and have role reversal either by undergoing de-transition surgery or returning to their former gender role.
	Regret uncertain	Patients don't have role reversal, but freely express their regret by never considering doing GAS or pass through the same preoperative scenario again. They are truly disappointed with the results of GAS. Also, they don't consider the new gender role so difficult and might consider a second GAS.
	Regret	Patients have role reversal but don't express their feelings of regret. Some might state that they are happy about their decision and consider themselves as transgender. However, they live as their former gender role for practical and social reasons.
	Regret assumed by others	Don't have role reversal and don't express feelings of regret but have unfavorable social circumstances or psychological disturbances that raise concerns to relatives, clinicians, and others that patient might be regretful (eg, feeling loneliness, suicide attempts).

Table 2. Study Characteristics

Authors and Year of Publication	Country	Sample Size	Transmasculine	Mean Age (y)	Transfemenine	Mean Age (y)	Mean Follow-up (y)	Assessment Tool	Risk of Bias
Blanchard et al, 1989	Canada	111	61	28.5	50	41.4 (Hc), 29.0 (Ho)	4.4	Q	H
Bouman, 1988	Netherlands	55	NA	NA	55	NS	2.3	NS	M
Cohen-Kettenis et al, 1997	Netherlands	19	14	22*	5	22*	2.6	I	H
De Cuypere et al, 2006	Belgium	62	27	33.3	35	41.4	Transmasculine = 7.6 Transfemenine = 4.1	I	M
Garcia et al, 2014	London	25	25	34 –RAP without 39.2 – RAP 35.1 – SP	NA	NA	RAP without = 6.8 RAP = 2.2 SP = 2.2	I	H
Imbimbo et al, 2009	Italia	139	NA	NA	139	31.4	1–1.6	Q	H
Jiang et al, 2018	USA	80	NA	NA	79 (+1 NB)	57.9 – Vulvoplasty 39.2 – Vaginoplasty†	0.7	NS	H
Johansson et al, 2010	Sweden	32	14	38.9	18	46	9	Q/I	L
Krege et al, 2001	Germany	31	NA	NA	31	Me 36.9	0.5	Q	H
Kuiper et al, 1998	Netherlands	1100	300	46.4*	800	46.4*	NS	Q	H
Lawrence, 2003	USA	232	NA	NA	232	44	3	Q	M
Lobato et al, 2006	Brazil	19	1	31.2*	18	31.2*	2.1	Q/I	M
Nelson et al, 2009	UK	17	17	31	NA	NA	0.8	Q	M
Olson-Kennedy et al, 2018	USA	68	68	18.9	NA	NA	<1–5	Q	M
Papadopulos et al, 2017	Germany	47	NA	NA	47	38.3	1.6	Q	L
Pfafflin, 1993	Germany	295	99	NS	196	NS	Range: 1–29	NS	M
Rehman et al, 1999	USA	28	NA	NA	28	38.0	NS	Q	L
Smith et al, 2001	Netherlands	20	13	21*	7	21*	1.3	I	M
Song et al, 2011	Singapore	19	19	NS	NA	NA	Range: 1–10	Q	H
Van de Grift et al, 2018	Netherlands, Belgium, Germany, Norway	132	51	36.3*	81	36.3*	NS	Q	M
Wierjes et al, 2018	Netherlands	4863	1733	Adults: Me 23 Adolescents: Me 26	3130	Adults: Me 33 Adolescents: Me 16	8.5	Q	M
Zavlin et al, 2018	Germany	40	NA	NA	40	38.6	0.9	Q	M
Judge et al, 2014	Ireland	55	19	32.2‡	36	36.2‡	NS	I	M
Vujovic et al, 2009	Serbia	118	59	25.7	59	25.4	NS	NS	H
Weyers et al, 2009	Belgium	50	NA	NA	50	43.1	6.3	Q	L
Poudrier et al, 2019	USA	58	58	33	NA	NA	NS	Q	M
Ladcn et al, 1998	Sweden	213	NS	NS	NS	NS	NS	Medical records and verdicts	M

*Reflects the mean of both transmasculine and transfemenine.
†Includes both scheduled and completed surgery.
‡Includes both surgery and no surgery patients.
H, High; Hc, Heterosexual; Ho, Homosexual; I, Interview; IQR, Interquartile Range; L, Low; M, Moderate; Mc, Median; NA, Not applicable; NS: Not specified, Q: Questionnaire; RAP: Radial Arterial Forearm-Flap Phalloplasty without or with cutaneous nerve to clitoral nerve anastomosis; SP: Supraputbic Pedicle-Flap Phalloplasty.

Table 3. Studies Differentiating Type of Surgery among Transfemenine Patients

Type of Surgery	No. Procedures
Breast Augmentation	
Smith et al, 2001	7
Van de Grift et al, 2018	33
Judge et al, 2014	19
Weyers et al, 2009	48
Total	107
Vaginoplasty	
Blanchard et al, 1989	50
Bouman, 1988	7
Cohen-Kettenis et al, 1997	5
Imbimbo et al, 2009	139
Jiang et al, 2018	64
Krege et al, 2001	31
Kuiper et al, 1998	8
Lawrence, 2003	232
Papadopulos et al, 2017	47
Rehman et al, 1999	28
Van de Grift et al, 2018	71
Zavlin et al, 2018	40
Weyers et al, 2009	50
Total	772
Vulvoplasty	
Rehman et al, 1999	28
Jiang et al, 2018	16
Total	44
Others	
Lawrence, 2003	Clitoroplasty 232
Rehman et al, 1999	Clitoroplasty + labioplasty 28 + Orchiectomy 5
Van de Grift et al, 2018	Thyroid cartilage reduction 9, facial surgeries 7, and vocal cord 3
Wiepjes et al, 2018	Gonadectomy 2868 (adults), 262 (adolescents)
Judge et al, 2014	Facial surgeries 6, laryngeal surgeries 2, GAS not specified 15
Weyers et al, 2009	Vocal cord surgeries 20, cricoid reduction 15

Table 4. Studies Differentiating the Type of Surgery among Transmasculine Patients

Type of Surgery	No. Procedures
Mastectomy	
Blanchard et al, 1989	61
Cohen-Kettenis et al, 1997	14
Kuiper et al, 1998	1
Nelson et al, 2009	17
Olson-Kennedy et al, 2018	68
Smith et al, 2001	13
Van de Grift et al, 2018	49
Judge et al, 2014	16
Poudrier et al, 2019	58
Total	297
Phalloplasty	
Cohen-Kettenis et al, 1997	1
Garcia et al, 2014	25
Smith et al, 2001	1
Song et al, 2011	19
Van de Grift et al, 2018	15
Total	61
Hysterectomy	
Kuiper et al, 1998	1
Smith et al, 2001	2
Van de Grift et al, 2018	48
Total	51
Others	
Cohen-Kettenis et al, 1997	Neoscrotum 2
Kuiper et al, 1998	Oophorectomy 1
Van de Grift et al, 2018	Metoidioplasty 3
Wiepjes et al, 2018	Gonadectomy 1361 (adults), 372 (adolescents)
Judge et al, 2014	GAS not specified 9

RESULTS

Study Selection

A total of 74 articles were identified in the search, and 2 additional records were identified through other sources. After the first-step screening process, 39 articles were relevant based on the information provided in their titles and abstracts. After the second-step process, a total of 27 articles were included in the systematic review and metanalysis (Fig. 1).

Quality Assessment

Based on the NIH quality assessment tool, the majority of article ranged between "poor" and "fair" categories.[24] (**See Supplemental Digital Content 2,** which displays the score of each reviewed study. http://links.lww.com/PRSGO/B599.)

Study Characteristics

In total, the included studies pooled 7928 cases of transgender individuals who underwent any type of GAS. A total of 2578 (33%) underwent transmasculine procedures, 5136 (67%) underwent transfemenine surgeries, and 1 non-binary patient underwent surgery. In Table 2 characteristics of studies are listed. Without discriminating type of surgical technique, from all transfemenine surgeries included, 772 (39.3%) were vaginoplasty, 260 (13.3%) were clitoroplasty, 107 (5.5%) were breast augmentation, 72 (3.7%) were labioplasty and vulvoplasty, and a small minority were facial feminization surgery, vocal cord surgery, thyroid cartilage reduction, and oophorectomy surgery. The rest did not specify type of surgery. In regard to transmasculine surgeries, 297 (12.4%) were mastectomies, 61 (2.6%) were phalloplasties, and 51 (2.1%) hysterectomies (Table 3 and 4). Overall, follow-up time from surgery to the time of regret assessment ranged from 0.8 to 9 years (Table 2).

Regrets and De-transition

Almost all studies conducted non-validated questionnaires to assess regret due to the lack of standardized questionnaires available in this topic.[15, 19–33] Most of the questions evaluating regret used options such as, "*yes,*" "*sometimes,*" "*no*" or "*all the time,*" "*sometimes,*" "*never,*" or "*most certainly,*" "*very likely,*" "*maybe,*" "*rather not,*" or "*definitely not.*"[14, 18, 19, 23, 27–38] Other studies used semi-structured interviews.[34,37,39–43] However, in both circumstances, some studies provided further specific information on reasons for regret.[14,20,23,29,32,36,41,44–46] Of the 7928 patients, 77 expressed regret (12 transmen, 57 transwomen, 8 not specified), understood by those who had "sometimes" or "always" felt it.

Reasons for Regret

The most prevalent reason for regret was the difficulty/dissatisfaction/acceptance in life with the new gender role.[23,29,32,36,44] Other less prevalent reasons were "failure" of surgery to achieve their surgical goals in an aesthetic level and psychological level.[29,32,36,47] Based on the reasons presented, we classified the types of regrets according to Pfäfflin's types of regret and Kuiper and

Table 5. Type of Regret

Studies	No. Regrets	Transmasculine	Transfeminine	Type of Regrets based on Pfafflin, 1993		Type of Regrets based on Kuiper and Cohen-Kettenis, 1998				Surgery	De-transition (Y/N)
				Minor	Major	1	2	3	4		
Blanchard et al, 1989	4	—	4	4	—	2	2	—	—	Vaginoplasty	N
Bouman, 1988	1	—	1	—	1	1	—	—	—	Vaginoplasty	NS
De Cuypere et al, 2006	2	1	1	2	—	—	2	—	—	NS	NS
Imbimbo et al, 2009	8	—	8	NS	NS	NS	NS	NS	NS	Vaginoplasty	NS
Jiang et al, 2018	1	—	1	1	—	—	1	—	—	Vulvoplasty	NS
Kuiper et al, 1998	10	1	9	4	6	6	3	1	—	NS	1 testicles implant removal and underwent breast augmentation
Lawrence, 2003	15	—	15	13	2	2	13	—	—	Vaginoplasty	NS
Olson-Kennedy et al, 2018	1	1	—	NS	NS	NS	NS	NS	NS	Mastectomy	NS
Pfafflin, 1993	3	3	—	—	3	3	—	—	—	NS (complication urethral-vaginal fistula)	NS
Van de Grift et al, 2018	2	1	1	2	—	—	2	—	—	Transfemenine = Vaginoplasty Transmasculine = mastectomy and uterus extirpation (hematoma)	NS
Wiepjes et al, 2018	14	3	11	0	14	13	1	0	0	Gonadectomy	Y (10)*
Zavlin et al, 2018	1	—	1	NS	NS	NS	NS	NS	NS	Vaginoplasty	NS
Judge et al, 2014	3	—	3	NS	NS	NS	NS	NS	NS	NS	NS
Weyers et al, 2009	2	—	2	NS	NS	NS	NS	NS	NS	Vaginoplasty	NS
Poudrier et al, 2019	2	2	—	2	—	—	2	—	—	Mastectomy	NS
Laden et al, 1998	8	NS	NS	—	8	8	—	—	—	NS	Y

*8 mastectomies, 2 vaginectomies, 2 phalloplasties, 2 testicular implants removal, and 1 breast augmentation.
N, no; NS, not specified; Y, Yes.

Cohen-Kettenis classification. According to Pfäfflin's types, 28 patients had minor regret, and 34 patients had major regret.[14,20,23,29,32,36,41,44,45] Based on the Kuiper and Cohen-Kettenis regret classification, 35 patients had clear regret, 26 uncertain regret, 1 regret, and none presented with regret assumed by others.[23] In Table 5 and 6, the reasons and classifications are shown.

Prevalence of Regret

The pooled prevalence of regret among the TGNB population after GAS was 1% (95% Confidence interval [CI] <1%–2%; I^2 = 75.1%) (Fig. 2). The prevalence for transmasculine surgeries was <1% (CI <1%–<1%, I^2 = 28.8%), and for transfemenine surgeries, it was 1% (CI <1%–2%, I^2 = 75.5%) (Fig. 3). The prevalence of regret after vaginoplasty was of 2% (CI <1%–4%, I^2 = 41.5%) and that after mastectomy was <1% (CI <1–<1%, I^2 = 21.8%) (Fig. 4).

Meta-regression and Publication Bias

No covariates analyzed affected the pooled endpoint in this metanalysis. The Funnel Plot shows asymmetry between studies (Fig. 5). The Egger test resulted in a *P* value of 0.0271, which suggests statistical significance for publication bias. The Trim & Fill method imputed 14 approximated studies, with limited impact of the adjusted results. The change in effect size was from 0.010 to 0.005 with no statistical significance (Fig. 6).

Sensitivity Analysis

When excluding studies with sample sizes less than 10 and high-risk biased studies, the pooled prevalence was similar 1% (CI <1%–3%) compared with the pooled prevalence when those studies were included 1% (CI <1%–2%).

DISCUSSION

The prevalence of regret in the TGNB population after GAS was of 1% (CI <1%–2%). The prevalence of regret for transfemenine surgeries was 1% (CI <1%–2%), and the prevalence for transmasculine surgeries was <1% (CI <1%–<1%). Traditionally, the landmark reference of regret prevalence after GAS has been based on the study by Pfäfflin in 1993, who reported a regret rate of 1%–1.5%. In this study, the author estimated the regret prevalence by analyzing two sources: studies from the previous 30 years in the medical literature and the author's own clinical practice.[20] In the former, the author compiled a total of approximately 1000–1600 transfemenine, and 400–550 transmasculine. In the latter, the author included a total of 196 transfemenine, and 99 transmasculine patients.[20] In 1998, Kuiper et al followed 1100 transgender subjects that underwent GAS using social media and snowball sampling.[23] Ten experienced regret (9 transmasculine and 1 transfemenine). The overall prevalence of regret after GAS in this study was of 0.9%, and 3% for transmasculine and <0.12% for transfemenine.[23] Because these studies were conducted several years ago and were limited to specific countries, these estimations may not be generalizable to the entire TGNB population. However, a clear trend towards low prevalences of regret can be appreciated.

The causes and types of regrets reported in the studies are specified and shown in Table 5 and 6. Overall, the most common reason for regret was psychosocial circumstances, particularly due to difficulties generated by

Table 6. Causes of Regret

Studies	Reasons of Regrets
Blanchard et al, 1989	• 1 patient was dissatisfied with life as a woman and considered returning to the masculine role • 1 patient reported that surgery failed to produce the coherence of mind and the body he wanted • 1 patient would not opt for a new surgery as it had not accomplished what she wanted • 1 patient dressed as a man but didn't felt as feminine nor masculine
Bouman, 1988	Work and social acceptance
De Cuypere et al, 2006	• Transmasculine = Physiologic period before GAS (delusional disorder-erotomaniac type), scored very low in credibility • Transfemenine = Emotionally troubled by a break-up with his girlfriend
Imbimbo et al, 2009	NS
Jiang et al, 2018	Didn't want to wait genital electrolysis prior vaginoplasty
Kuiper et al, 1998	• 4 patients mentioned they were not transsexual • 1 patient after surgery she realized she did not want to live as a woman. 1 never wished for the surgery (forced by the partner) • 2 patients lost the partner and had social problems • 1 patient had no doubts (double role requested by the partner)
Lawrence, 2003	• 8 patients felt disappointed with physical or functional outcomes of surgery (lost clitoris sensation) • 2 participants reported reversion to living as a man after GAS. There were family and social problems
Olson-Kennedy et al, 2018	NS
Pfafflin, 1993	NS
Van de Grift et al, 2018	• Transmasculine = Body does not meet the feminine ideal • Transfemenine = Recurrent abdominal pains, dependence on exogenous hormones
Wiepjes et al, 2018	• 5 patients had social regret (still as their former role/"ignored by surroundings" or "the loss of relatives is a large sacrifice") • 7 patients had true regret (though that the surgery was the solution) • 2 patients felt non-binary
Zavlin et al, 2018	NS
Judge et al, 2014	NS
Weyers et al, 2009	NS
Poudrier et al, 2019	Aesthetic outcomes
Laden et al, 1998	NS

NS, not specified.

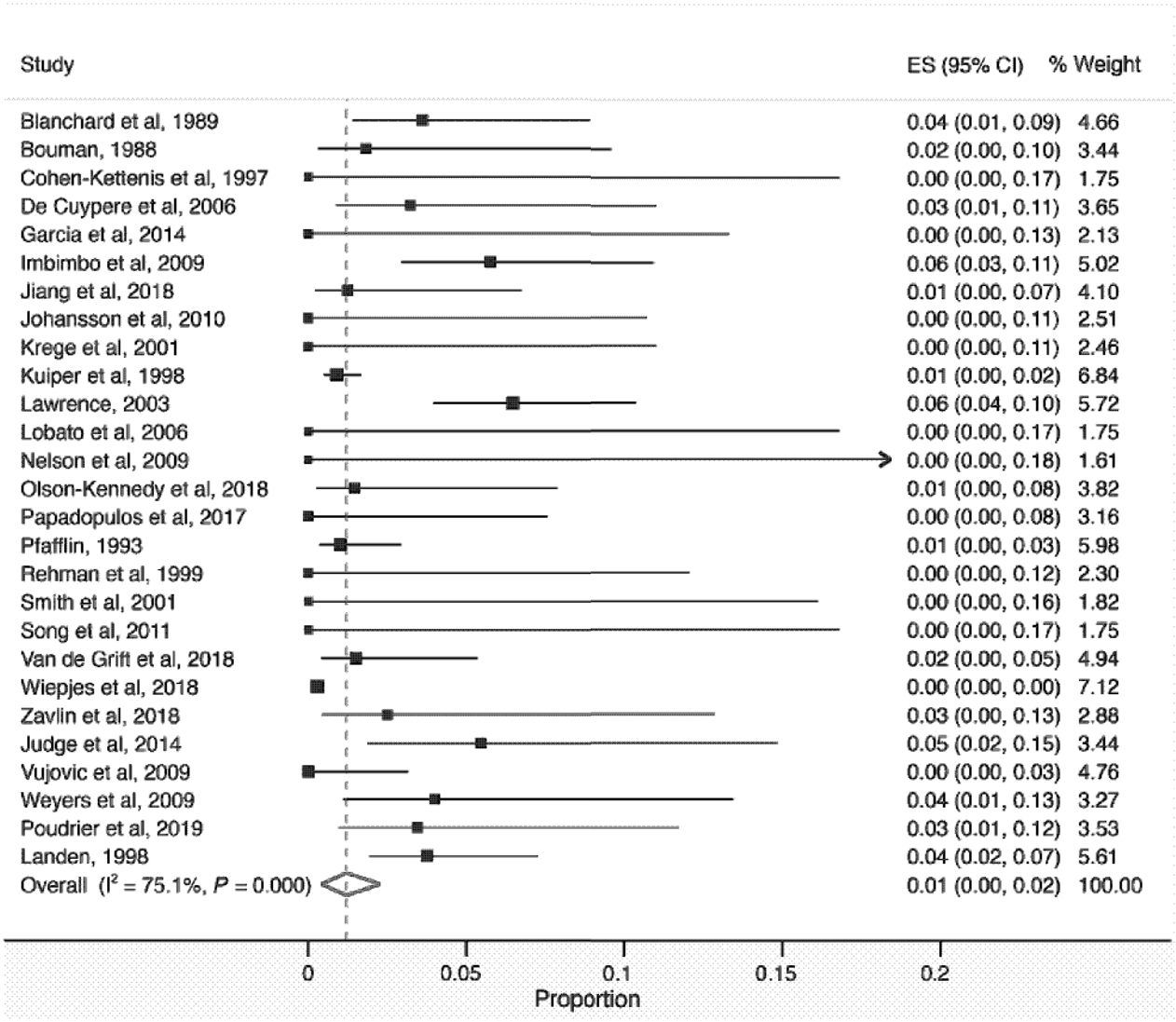


Fig. 2. Pooled prevalence of regret among TGNB individuals after gender confirmation surgery. Heterogeneity $\chi 2$ = 104.31 (d.f. = 26), P = 0.00, I^2 [variation in effect size (ES) attributable to heterogeneity] = 75.08%, Estimate of between-study variance T^2 = 0.02, Test of ES = 0, z = 4.22, P = 0.00.

return to society with the new gender in both social and family enviroments.[23,29,32,33,36,44] In fact, some patients opted to reverse their gender role to achieve social acceptance, receive better salaries, and preserve relatives and friends relationships. These findings are in line with other studies. Laden et al performed a logistic regression analysis to assess potential risk factors for regret in this population.[46] They found that the two most important risk factors predicting regret were "poor support from the family" and "belonging to the non-core group of transsexuals."[46] In addition, a study in Italy hypothesized that the high percentage of regret was attributed to social experience when they return after the surgery.[33]

Another factor associated with regret (although less prevalent) was poor surgical outcomes.[20,23],[36] Loss of clitoral sensation and postoperative chronic abdominal pain were the most common reported factors associated with surgical outcomes.[14,36] In addition, aesthetic outcomes played an important role in regret. Two studies mentioned concerns with aesthetic outcomes.[14,47] Only one of them quoted a patient inconformity: "body doesn't meet the feminine ideal."[14] Interestingly, Lawrence et al demonstrated in their study that physical results of surgery are by far the most influential in determining satisfaction or regret after GAS than any preoperative factor.[36] Concordantly, previous studies have shown absence of regret if sensation in clitoris and vaginal is achieved and if satisfaction with vaginal width is present.[36]

Other factors associated to regret were identified. Blanchard et al in 1989 noted a strong positive correlation between heterosexual preference and postoperative regret.[32] All patients in this study who experienced regret were heterosexual transmen.[32] On the contrary, Lawrence et al in 2003 did not find such correlation and attributed

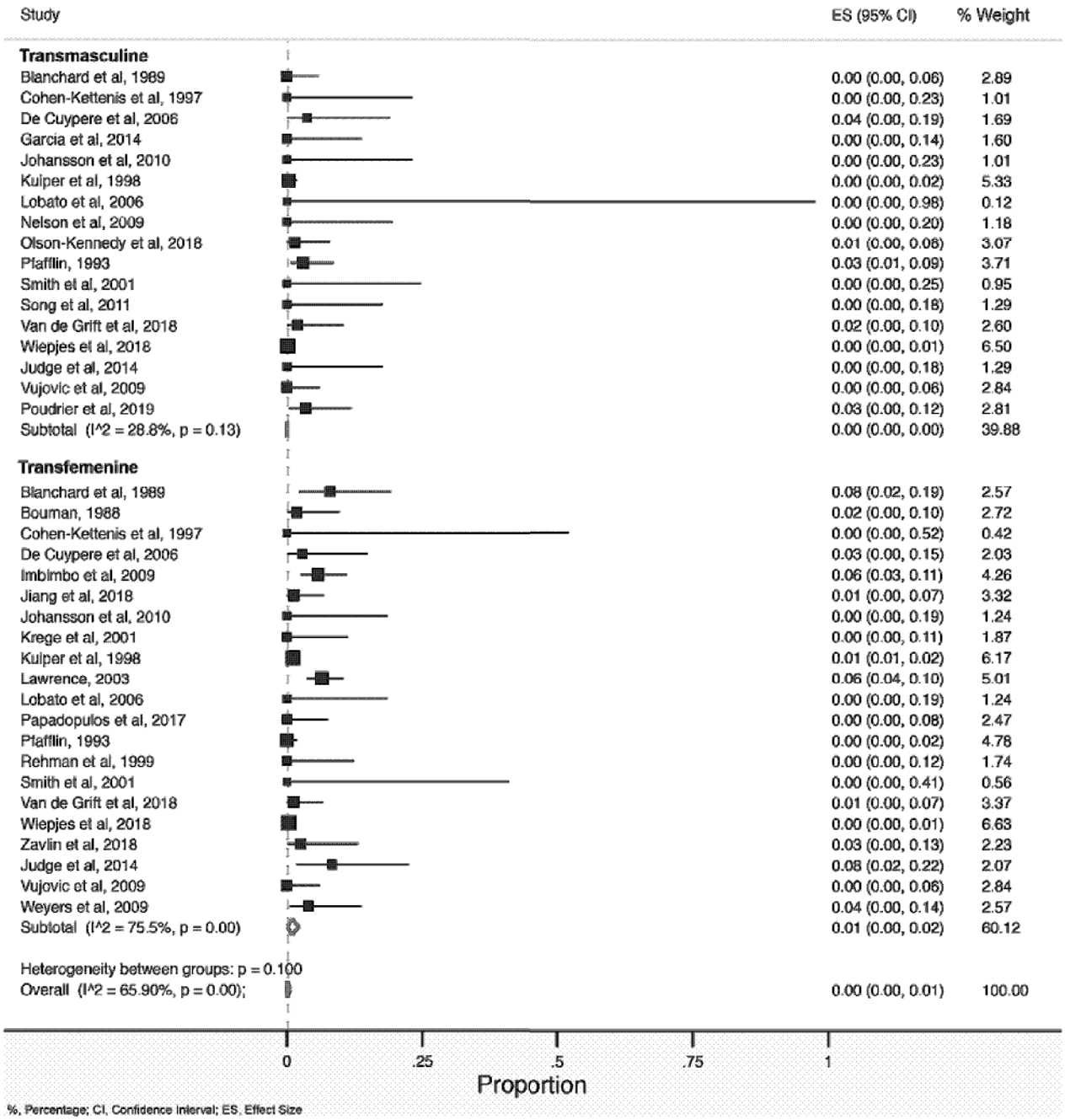


Fig. 3. Subgroup analysis of the prevalence of regret among TGNB individuals after gender confirmation surgery based on gender. ES, effect size.

their findings to the increase in social tolerance in North American and Western European societies.[36] Bodlund et al found that clinically evident personality disorder was a negative prognostic factor for regret in patients undergoing GAS.[18] On the other hand, Blanchard et al did not find a correlation among patient's education, age at surgery, and gender assigned at birth.[32]

In the present review, nearly half of the patients experienced *major regret* (based on Pfäfflin classification), meaning that they underwent or desire de-transition surgery, that will never pass through the same process again, and/or experience increase of gender dysphoria from the new gender. One study found that 10 of 14 patients with regret underwent de-transition surgeries (8 mastectomies, 2 vaginectomies, 2 phalloplasties, 2 testicular implants removal, and 1 breast augmentation) for reasons of social regret, true regret or feeling non-binary.[23] On the other hand, based on the Kuiper and Cohen Kettenis'

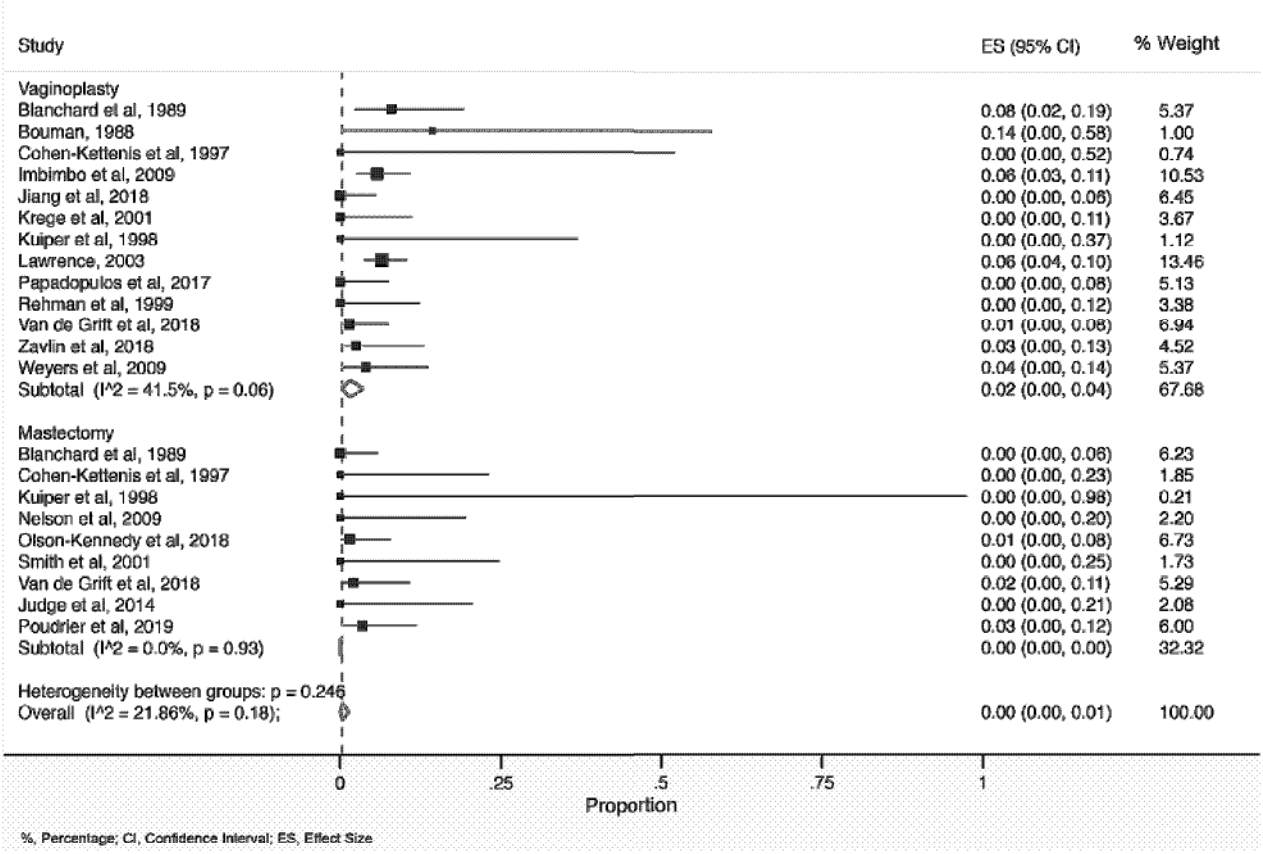


Fig. 4. Subgroup analysis of the prevalence of regret among TGNB individuals after gender confirmation surgery based on the type of surgery. ES, effect size.

classification, half of the patients in this review had *clear regret* and *uncertain regret*. This means that they freely expressed their regret toward the procedure, but some had role reversal to the former gender and others did not. Interestingly, Pfäfflin concluded that from a clinical standpoint, trangender patients suffered from many forms of *minor regrets* after GAS, all of which have a temporary course.[20] This is an important consideration meaning that the actual true regret rate will always remain uncertain, as temporarity and types of regret can bring a huge challenge for assessment.

Regret after GAS may result from the ongoing discrimination that afflicts the TGNB population, affecting their freely expression of gender identity and, consequently feeling regretful from having had surgery.[15] Poor social and group support, late-onset gender transition, poor sexual functioning, and mental health problems are factors associated with regret.[15] Hence, assessing all these

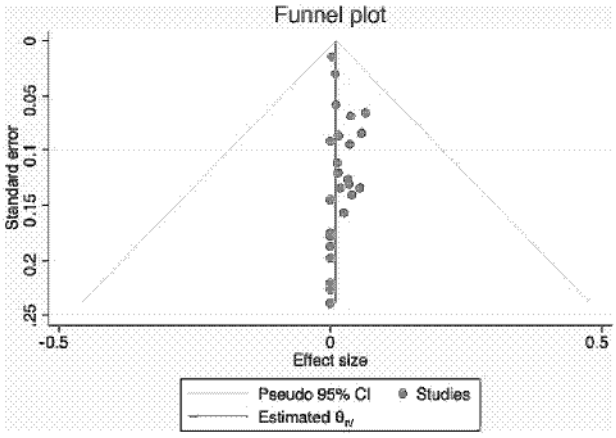


Fig. 5. Funnel plot.

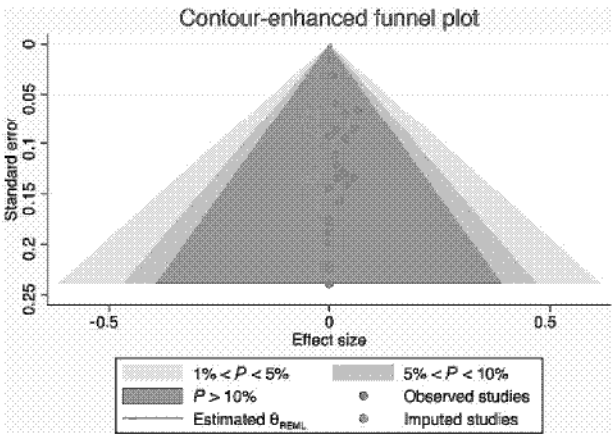


Fig. 6. Funnel plot of the Trim & Fill method.

potential factors preoperatively and controlling them if possible could reduce regret rates even more and increase postoperative patient satisfaction.

Regarding transfemenine surgery, vaginoplasty was the most prevalent.[14, 19, 23, 30–33, 35, 36, 44, 45]Interesintgly, regret rates were higher in vaginoplasties.[14,36,44] In this study, we estimated that the overall prevalence of regret after vaginoplasty was 2% (from 11 studies reviewed). This result is slightly higher than a metanalysis of 9 studies from 2017 that reported a prevalence of 1%.[13] Moreover, vaginoplasty has shown to increase the quality of life in these patients.[13] Mastectomy was the most prevalent transmasculine surgery. Also, it showed a very low prevalence of regret after mastectomy (<1%). Olson-Kennedy et al demonstrated that chest surgery decreases chest dysphoria in both minors and young adults, which might be the major reason behind our findings.[38]

In the current study, we identified a total of 7928 cases from 14 different countries. To the best of our knowledge, this is the largest attempt to compile the information on regret rates in this population. However, limitations such as significant heterogeneity among studies and among instruments used to assess regret rates, and moderate-to-high risk of bias in some studies represent a big barrier for generalization of the results of this study. The lack of validated questionnaires to evaluate regret in this population is a significant limiting factor. In addition, bias can occur because patients might restrain from expressing regrets due to fear of being judged by the interviewer. Moreover, the temporarity of the feeling of regret in some patients and the variable definition of regret may underestimate the real prevalence of "true" regret.

Based on this meta-analysis, the prevalence of regret is 1%. We believe this reflects and corroborates the increased in accuracy of patient selection criteria for GAS. Efforts should be directed toward the individualization of the patient based on their goals and identification of risk factors for regrets. Surgeons should continue to rigorously follow the current Standard of Care guidelines of the World Professional Association for Transgender Health (WATH).[49]

CONCLUSIONS

Our study has shown a very low percentage of regret in TGNB population after GAS. We consider that this is a reflection on the improvements in the selection criteria for surgery. However, further studies should be conducted to assess types of regret as well as association with different types of surgical procedure.

Oscar J. Manrique, MD, FACS
Division of Plastic and Reconstructive Surgery
University of Rochester Medical Center
Strong Memorial Hospital
160 Sawgrass Drive, Suite 120
Rochester, NY 14620
E-mail: oscarj.manrique@gmail.com

ACKNOWLEDGMENTS

All the authors have completed the ICMJE uniform disclosure form. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Safer JD, Tangpricha V. Care of transgender persons. *N Engl J Med.* 2019;381:2451–2460.
2. Schechter LS. Gender confirmation surgery: an update for the primary care provider. *Transgend Health.* 2016;1:32–40.
3. Schechter LS. Background. In LS Schechter (Ed.): *Surgical Management of the Transgender Patient.* Philadelphia, Pa.: Elsevier; 2016:3–7.
4. Carmel TC, Erickson-Schroth L. Mental health and the transgender population. *Psychiatr Ann.* 2016;46:346–349.
5. Wernick JA, Busa S, Matouk K, et al. A systematic review of the psychological benefits of gender-affirming surgery. *Urol Clin North Am.* 2019;46:475–486.
6. Flores A R, Brown, et al. How many adults identify as transgender in the United States. *The Williams Institute.* 2016;(June):15. Available at https://williamsinstitute.law.ucla.edu/publications/trans-adults-united-states/ Accessed June 15, 2020.
7. Downing JM, Przedworski JM. Health of transgender adults in the U.S., 2014–2016. *Am J Prev Med.* 2018;55:336–344.
8. Lane M, Ives GC, Sluiter EC, et al. Trends in gender-affirming surgery in insured patients in the United States. *Plast Reconstr Surg Glob Open.* 2018;6:e1738.
9. Nolan IT, Dy GW, Levitt N. Considerations in gender-affirming surgery: demographic trends. *Urol Clin North Am.* 2019;46:459–465.
10. Rider GN, Mcmorris BJ, Gower AL, et al. Health and care utilization of transgender and gender nonconforming youth: a population-based study. www.aappublications.org/news. Accessed May 12, 2020.
11. American Society of Plastic Surgeons. *Plastic Surgery Statistics Report 2018.* 2018.
12. American Society of Plastic Surgeons. *Plastic Surgery Statistics Report 2017.* www.plasticsurgery.org. Accessed May 28, 2020.
13. Manrique OJ, Adabi K, Martinez-Jorge J, et al. Complications and patient-reported outcomes in male-to-female vaginoplasty-where we are today: a systematic review and meta-analysis. *Ann Plast Surg.* 2018;80:684–691.
14. van de Grift TC, Elaut E, Cerwenka SC, et al. Surgical satisfaction, quality of life, and their association after gender-affirming surgery: a follow-up study. *J Sex Marital Ther.* 2018;44:138–148.
15. Hadj-Moussa M, Ohl DA, Kuzon WM. Feminizing genital gender-confirmation surgery. *Sex Med Rev.* 2018;6:457–468.e2.
16. Barone M, Cogliandro A, Di Stefano N, et al. A systematic review of patient-reported outcome measures following transsexual surgery. *Aesthetic Plast Surg.* 2017;41:700–713.
17. Agarwal CA, Scheefer MF, Wright LN, et al. Quality of life improvement after chest wall masculinization in female-to-male transgender patients: a prospective study using the BREAST-Q and body uneasiness test. *J Plast Reconstr Aesthet Surg.* 2018;71:651–657.
18. Nelson L, Whallett EJ, McGregor JC. Transgender patient satisfaction following reduction mammaplasty. *J Plast Reconstr Aesthet Surg.* 2009;62:331–334.
19. Papadopulos NA, Lellé JD, Zavlin D, et al. Quality of life and patient satisfaction following male-to-female sex reassignment surgery. *J Sex Med.* 2017;14:721–730.
20. Pfäfflin F. Regrets after sex reassignment surgery. *J Psychol Hum Sex.* 1993;5:69–85.
21. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* 2009;6.

22. Covidence. Better systematic review management. https://www.covidence.org/home. Accessed May 28, 2020.
23. Kuiper AJ, Cohen-Kettenis PT. Gender role reversal among postoperative transsexuals. *Int J Transgenderism.* 1998;2.
24. NIH. *Study Quality Assessment Tools.* Bethesda, Md.: National Heart, Lung, and Blood Institute (NHLBI). https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed May 25, 2020.
25. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health.* 2014;72:39.
26. Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann Math Stat.* 1950;21:607–611.
27. Rehman J, Lazer S, Benet AE, et al. The reported sex and surgery satisfactions of 28 postoperative male-to-female transsexual patients. *Arch Sex Behav.* 1999;28:71–89.
28. Song C, Wong M, Wong CH, et al. Modifications of the radial forearm flap phalloplasty for female-to-male gender reassignment. *J Reconstr Microsurg.* 2011;27:115–120.
29. 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.
30. Zavlin D, Schaff J, Lellé JD, et al. Male-to-female sex reassignment surgery using the combined vaginoplasty technique: satisfaction of transgender patients with aesthetic, functional, and sexual outcomes. *Aesthetic Plast Surg.* 2018;42:178–187.
31. Weyers S, Elaut E, De Sutter P, et al. Long-term assessment of the physical, mental, and sexual health among transsexual women. *J Sex Med.* 2009;6:752–760.
32. Blanchard R, Steiner BW, Clemmensen LH, et al. Prediction of regrets in postoperative transsexuals. *Can J Psychiatry.* 1989;34:43–45.
33. Imbimbo C, Verze P, Palmieri A, et al. ORIGINAL RESEARCH-INTERSEX AND GENDER IDENTITY DISORDERS. A report from a single institute's 14-year experience in treatment of male-to-female transsexuals. *J Sex Med.* 2009;6:2736–2745.
34. Johansson A, Sundbom E, Höjerback T, et al. A five-year follow-up study of Swedish adults with gender identity disorder. *Arch Sex Behav.* 2010;39:1429–1437.
35. Krege S, Bex A, Lümmen G, et al. Male-to-female transsexualism: a technique, results and long-term follow-up in 66 patients. *BJU Int.* 2001;88:396–402.
36. Lawrence AA. Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. *Arch Sex Behav.* 2003;32:299–315.
37. Lobato MI, Koff WJ, Manenti C, et al. Follow-up of sex reassignment surgery in transsexuals: a Brazilian cohort. *Arch Sex Behav.* 2006;35:711–715.
38. Olson-Kennedy J, Warus J, Okonta V, et al. Chest reconstruction and chest dysphoria in transmasculine minors and young adults: comparisons of nonsurgical and postsurgical cohorts. *JAMA Pediatr.* 2018;172:431–436.
39. 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.
40. De Cuypere G, Elaut E, Heylens G, et al. Long-term follow-up: psychosocial outcome of Belgian transsexuals after sex reassignment surgery. *Sexologies.* 2006;15:126–133.
41. Garcia MM, Christopher NA, De Luca F, et al. Overall satisfaction, sexual function, and the durability of neophallus dimensions following staged female to male genital gender confirming surgery: the Institute of Urology, London U.K. experience. *Transl Androl Urol.* 2014;3:156–162.
42. Smith YLS, Van Goozen SHM, 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;40:472–481.
43. Judge C, O'Donovan C, Callaghan G, et al. Gender dysphoria – prevalence and co-morbidities in an Irish adult population. *Front Endocrinol (Lausanne).* 2014;5:87.
44. Bouman FG. Sex reassignment surgery in male to female transsexuals. *Ann Plast Surg.* 1988;21:526–531.
45. Jiang D, Witten J, Berli J, et al. Does depth matter? Factors affecting choice of vulvoplasty over vaginoplasty as gender-affirming genital surgery for transgender women. *J Sex Med.* 2018;15:902–906.
46. Landén M, Wålinder J, Hambert G, et al. Factors predictive of regret in sex reassignment. *Acta Psychiatr Scand.* 1998;97:284–289.
47. Poudrier G, Nolan IT, Cook TE, et al. Assessing quality of life and patient-reported satisfaction with masculinizing top surgery: a mixed-methods descriptive survey study. *Plast Reconstr Surg.* 2019;143:272–279.
48. Bodlund O, Kullgren G. Transsexualism–general outcome and prognostic factors: a five-year follow-up study of nineteen transsexuals in the process of changing sex. *Arch Sex Behav.* 1996;25:303–316.
49. Coleman E, Bockting W, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people. www.wpath.org. Accessed May 13, 2020.

Human Reproduction, Vol.32, No.7 pp. 1457–1464, 2017
Advanced Access publication on May 13, 2017 doi:10.1093/humrep/dex098

human reproduction ORIGINAL ARTICLE **Reproductive endocrinology**

Effects of long-term exogenous testosterone administration on ovarian morphology, determined by transvaginal (3D) ultrasound in female-to-male transsexuals

Mirte R. Caanen[1,*], Nienke E. Schouten[1], Esther A.M. Kuijper[1], Joukje van Rijswijk[1], Marleen H. van den Berg[2], Eline van Dulmen-den Broeder[2], Annelies Overbeek[1,2], Flora E. van Leeuwen[3], Mick van Trotsenburg[1], and Cornelis B. Lambalk[1]

[1]Division of Reproductive Medicine, Department of Obstetrics and Gynaecology, VU University Medical Center, 1081 HV Amsterdam, The Netherlands [2]Department of Paediatric Oncology–Haematology, VU University Medical Center, 1007 MB Amsterdam, The Netherlands [3]Department of Epidemiology, Netherlands Cancer Institute, 1006 BE Amsterdam, The Netherlands

*Correspondence address. E-mail: m.caanen@vumc.nl

Submitted on August 9, 2016; resubmitted on April 10, 2017; accepted on May 4, 2017

STUDY QUESTION: Does long-term exogenous testosterone administration result in polycystic ovarian morphology (PCOM), determined by (3D) transvaginal ultrasound (TVU) in female-to-male transsexuals (FtMs).

SUMMARY ANSWER: Long-term exogenous testosterone administration in FtMs does not result in PCOM determined by (3D) TVU.

WHAT IS KNOWN ALREADY: The role of androgens in the pathophysiology of polycystic ovary syndrome (PCOS) is still unclear. From animal studies, intra-ovarian androgens have been suggested to disturb folliculogenesis, through a pro-atretic effect on growing follicles. It remains debatable whether exogenous androgens induce PCOM in humans. In the past histomorphologic studies indicated that androgen administration in FtMs could cause PCO-like changes. However, ultrasound morphology is an established criterion for PCOS, TVU data of ovaries after prolonged androgen exposure are lacking.

STUDY DESIGN, SIZE, DURATION: Prospective, observational, case-control study, in an academic setting, performed in 2014–2015, including 56 FtMs and 80 controls.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The study population consisted of adult FtMs treated with long-term testosterone, as part of their cross-sex hormone treatment, and scheduled for sex-reassignment surgery (bilateral salpingo-oophorectomy). Prior to the operation, under anaesthetics TVU measurements (3D transvaginal probe 3–9 MHz; HD11, Philips Ultrasound, Inc.) of the ovaries were performed. The control group consisted of females from a general population who underwent the same TVU and analysis. Antral follicle count (AFC) (3D) and ovarian volume (3D) were calculated using specialized software. PCOM was defined as AFC of 12 or more follicles (2–10 mm) in at least one ovary.

MAIN RESULTS AND THE ROLE OF CHANCE: Prevalence rates of PCOM were not significantly different in the FtMs compared to controls, determined by (3D) TVU: 32.1% (17/53) versus 30.7% (23/75), $P = 0.87$.

LIMITATIONS, REASONS FOR CAUTION: Testosterone levels in FtMs are supraphysiological, and may not be comparable to the testosterone levels in women with PCOS. However, we applied a unique and ethically acceptable opportunity of exploring the effects of androgens on human ovaries.

WIDER IMPLICATIONS OF THE FINDINGS: This first explorative study shows that long-term exogenous testosterone administration in adult women does not seem to induce PCOM determined by TVU.

STUDY FUNDING/COMPETING INTEREST(S): None.

TRIAL REGISTRATION NUMBER: The trial was registered at the Dutch Trial Register (www.trialregister.nl), registration number NTR4784.

Key words: polycystic ovarian morphology / polycystic ovaries / androgens / polycystic ovary syndrome / female-to-male transsexuals

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder affecting 5–15% of women in their reproductive lifespan (Azziz *et al.*, 2004; Norman *et al.*, 2007; Lauritsen *et al.*, 2014). The syndrome is characterized by at least two of the following three features: oligo- or amenorrhoea, clinical and/or biochemical signs of hyperandrogenemia and polycystic ovarian morphology (PCOM) determined by ultrasound (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004). PCOS is associated with subfertility, abnormal glucose metabolism, dyslipidaemia and increased risk of cardiovascular disease (Franks, 1995; Legro *et al.*, 1999; Wild *et al.*, 2010).

The pathophysiology of PCOS remains to be unravelled; in particular the role of androgens in follicle development has been controversial for some time (Dewailly *et al.*, 2016). However, hyperandrogenism is considered the cornerstone of the syndrome (Azziz, 2003; Dewailly *et al.*, 2014). From animal studies intra-ovarian androgens have been suggested to disturb folliculogenesis through a pro-atretric effect on growing follicles. In mice, androgens stimulate growth of cultured preantral follicles (Murray *et al.*, 1998). In primates, administration of androgens causes ovarian morphologic changes (Vendola *et al.*, 1998) and an increase of granulosa androgen receptor gene expression (Weil *et al.*, 1998). Androgen effects may be significant in the developmental pathophysiology of PCOS, since prenatally androgenized female monkeys exhibit ovarian and endocrinological features similar to those found in women with PCOS. Therefore, prenatal androgen excess may provide an aetiology for hyperandrogenism and anovulation in adulthood (Abbott *et al.*, 1998, 2009; Abbott and Bird, 2009).

Since the administration of testosterone to women induces virilisation, such experiments are not ordinarily feasible, but an exception is female-to-male transsexuals (FtMs) using testosterone. In the nineties small scale studies concluded that the histomorphological finding in androgen-treated ovaries met the histological criteria for the diagnosis of polycystic ovaries, and hypothesized was that androgens may induce polycystic changes in ovaries (Futterweit and Deligdisch, 1986; Spinder *et al.*, 1989). However, a recent study did not confirm these results (Ikeda *et al.*, 2013).

Historically, detection of PCOM required histological confirmation (Stein and Leventhal, 1935) but in recent years ultrasound morphology has become one of the established criteria for PCOS (Balen *et al.*, 2003; Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004). Still, systematic transvaginal ultrasound (TVU) data on ovarian morphology after prolonged androgen exposure are lacking (Mueller *et al.*, 2007, 2010; Ikeda *et al.*, 2013). FtMs can serve as a model to help clarify the role of androgens in the development of ultrasound morphology and pathophysiology of PCOS. TVU was, performed preoperatively after a prolonged period of androgen treatment.

This prospective observational study aimed to identify the effect of long-term exogenous supraphysiological testosterone administration on ovarian morphology, determined by (3D) TVU in adult FtMs.

Materials and Methods

Study design

This single centre prospective, observational case–control study was performed by the Center of Expertise on Gender Dysphoria in collaboration with the Division Reproductive Medicine of the VU University Medical Center, Amsterdam, the Netherlands during 2014–2015. The study was approved by the local Ethical Committee, written informed consent was obtained from the participants. The trial was registered in the Dutch National Trial Registry (trial registration number NTR4784).

FtM subjects

Participants were FtMs diagnosed for Gender Dysphoria, age 18 and older, that underwent ≥1 year cross-sex hormonal treatment (i.e. testosterone administration) and were eligible for sex-reassignment surgery. The following exclusion criteria were applied: disorders of sexual development, endocrine pathology other than possibly related to PCOS, excessive smoking, alcohol and/or drug abuse. Data on baseline characteristics were retrieved from the medical records of the FtMs including information about their menstrual cycle and signs of hyperandrogenism.

Hormonal treatment

Following the European protocol (Dekker *et al.*, 2016), testosterone administration was based and adapted on trough serum testosterone levels in the normal reference range of biological males. Testosterone esters used were: intramuscular injections [Nebido®, Bayer, Germany] (1 g, per 10–14 weeks) or [Sustanon®, Aspen Pharma Trading Limited, Ireland] (250 mg per 2–4 weeks), transdermal gel: [Androgel®, Besins International, Belgium] (25 or 50 mg, daily) or [Tostran®, Prostakan, United Kingdom] (40 mg, daily). Adolescents are allowed to start puberty suppression treatment with gonadotropin-releasing hormone agonist (GnRHa), triptoline [Decapeptyl®, Ferring, Denmark] (3.75 mg per 4 weeks) (Dekker *et al.*, 2016), as it prevents development of secondary sex characteristics.

Control group

Control data were derived from the database of the so-called DCOG LATER-VEVO study (trial registration number NTR2922) (Overbeek *et al.*, 2012), a large Dutch nationwide study on reproductive function, ovarian reserve and premature menopause in female childhood cancer survivors. The controls consisted of females from the general population,

recruited via general practitioners. The following exclusion criteria were applied: disorders of sexual development, endocrine pathology other than possibly related to PCOS, or excessive smoking, alcohol and/or drug abuse, and furthermore use of hormonal contraceptives. Data on baseline characteristics were retrieved from a large self-reported questionnaire (adapted from a well-tested questionnaire used by the Department of Epidemiology of the Netherlands Cancer Institute) (de Boer *et al.*, 2005; van Leeuwen *et al.*, 2011).

Transvaginal ultrasound

In the FtMs, the TVU was performed by two research physicians (MC and JR), just prior to surgery (hysterectomy and bilateral salpingo-oophorectomy). TVU was performed under general anaesthesia because most FtMs are virgin and consider internal examination unbearable (van Trotsenburg, 2009). Controls underwent the same TVU measurements in an outpatient clinical setting (cycle days 2–5). In both study groups, identical equipment (ultrasound machines), ultrasound protocol and software analysis were used.

Ultrasound/equipment/software analysis

A HD11 XE ultrasound system with a 3D transvaginal probe (3–9 MHz; EnVisor HD, Philips Medical Systems, Eindhoven, the Netherlands) was used. An automatic mechanical sweep with an angle of 90° of both ovaries was made and data were stored. Afterwards analysis of the 3D data was performed by two trained researchers (MC and NS) using specialized software (QLAB 8.1, Image Analysis Software, Philips, Eindhoven, the Netherlands). The ovary was centred on the multiplanar view using the pan and zoom tools. Subsequently, in the GI 3D quantification mode, individual follicles were identified and coloured with the semi-automated stacked contour utility. In the Slice Plane View all identified follicles throughout the entire ovary could then be counted and coloured (Fig. 1).

Objectives and outcomes

Ovaries

The primary outcome of this study was *PCOM*, defined as 12 or more 2–10 mm antral follicle count (AFC) in at least one ovary, according to the Rotterdam criteria (Balen *et al.*, 2003; Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004). AFC was calculated using described 3D technique. *Ovarian volume* was estimated using 3D technique using the appropriate software (formula: $\pi/6$ transverse diameter x anteroposterior diameter x longitudinal diameter). In case of the presence of a corpus luteum or cyst ≥10 mm diameter, the ovarian volume was excluded from the analysis (Balen *et al.*, 2003; Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004).

Hormonal measurements

Blood samples from the FtMs were obtained pre testosterone treatment and closest to (median 10 months before) TVU; from the controls on the day of TVU. Serum levels of estradiol, FSH and LH were measured in both groups but testosterone was only measured in the FtMs. *Hormonal assays* were described in detail elsewhere (van den Berg *et al.*, 2010; Caanen *et al.*, 2015).

Statistical analysis

Statistical procedures were performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA). Baseline characteristics, hormonal measurements and

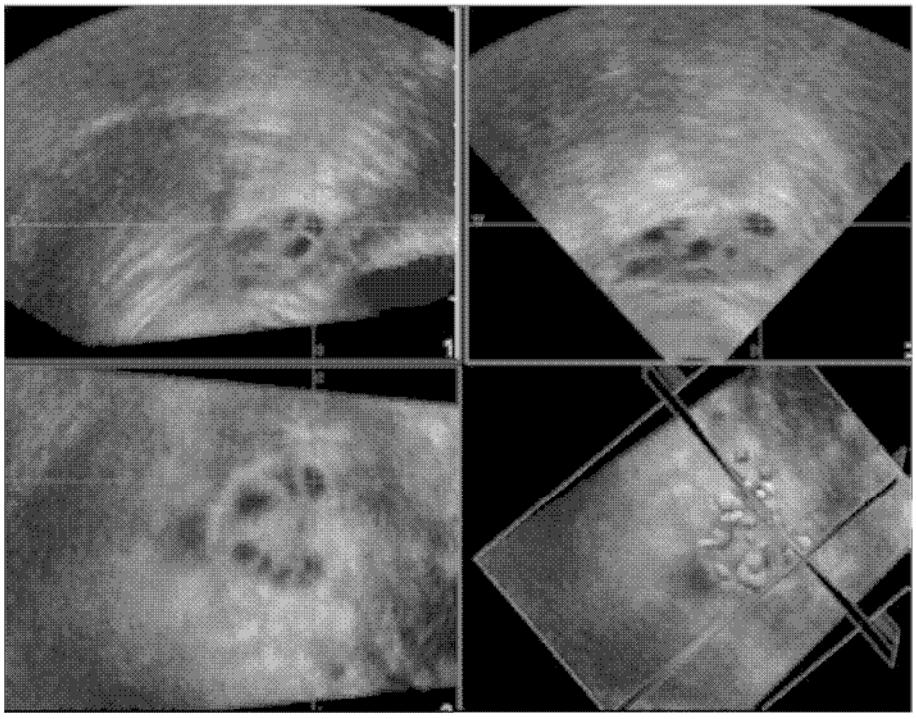


Figure 1 The ovary was centred on the multiplanar view using the pan and zoom tools. In the GI 3D quantification mode, individual follicles were identified and coloured with the semi-automated stacked contour utility. In the Slice Plane View, all identified follicles throughout the entire ovary could then be counted and coloured, shown in the different panels.

outcomes are reported as median (interquartile range) or number (percentages). Non-parametric Mann–Whitney *U*, Chi-squared, Fisher's exact or Wilcoxon signed rank tests were performed where appropriate. Logistic and linear regression analyses were conducted to correct for the confounders age and current use of GnRHa. A *P* value of <0.05 was considered significant.

Sample size calculation

Sample size of this study was based on the prevalence of PCOM in the average population as described in literature. Based on a prevalence of 32% of PCOM in a Caucasian population aged 25–45 years (Johnstone *et al.*, 2010), we presumed an increase of PCOM to a prevalence of (at least) 60% after testosterone administration to be clinically relevant. A sample size of 50 patients is calculated assuming the prevalence of PCOM is 32% in the normal population and will increase to 60% in the group treated with testosterone, $\alpha = 0{,}05$; $\beta = 0{,}15$.

Results

The baseline characteristics of the study population are presented in Table I, 56 FtMs and 80 controls matched the in- and exclusion criteria. The FtMs differ significantly from the controls with respect to age, height, BMI, ethnical background, age at menarche and signs of hyperandrogenism. Attributed to the specific study group, they also differ with respect to pregnancy and delivery dates. There are no differences observed for weight, menstrual cycle, smoking, alcohol use and diagnosis of PCOS.

Table II reports the characteristics specific of the FtMs. The median duration of testosterone use was 29.5 months, the median age at the start of testosterone administration was 20.5 years. Most FtMs used intramuscular testosterone injections (67.9%), the other 32.1% received transdermal testosterone gel. A number of the FtMs received GnRHa.

Table III presents the hormone levels measured prior to androgenic therapy (median 16.7 months), and closest to the ultrasound/surgery day (median 10.0 months). As expected hormonal measurements before and after testosterone therapy differed. Testosterone was significantly lower, and E2, FSH and LH were significantly higher prior to the start compared to afterwards. Serum hormone levels of the controls are also presented in Table III.

There were no reported adverse effects concerning lipid profiles, liver enzymes, glucose metabolism and haematology.

The main outcomes of the study are summarized in Table IV.

The prevalence of PCOM was not significantly different in the FtMs compared to the controls, 32.1% (17/53) versus controls 30.7% (23/75), $P = 0.87$.

Logistic regression analyses showed an OR 1.07 (95% CI 0.50–2.28, $P = 0.87$), and after correcting for age and current use of GnRHa: OR 0.63 (95% CI 0.20–1.95), $P = 0.42$.

No differences in PCOM in relation to GnRHa treatment were observed. Of 14 FtMs with current GnRHa use, 2 had PCOM, compared to 15 of 39 FtMs without current GnRHa use (14.3% versus 38.5%) $P = 0.18$. Of 25 FtMs with 'any use of GnRHa in the past', six had PCOM, compared to 11 of 28 FtMs that never used GnRHa (24.0% versus 39.3%) $P = 0.23$. Comparing the PCOM number in the FtMs that never used GnRHa to the controls, there is no difference (11 of 28; 23 of 75, 39.3% versus 30.7%) $P = 0.41$. Comparing the PCOM number in FtMs that did not currently use GnRHa to the controls, there is no difference (15 of 39; 23 of 75, 38.5% versus 30.7%) $P = 0.40$.

Table I Baseline characteristics of FtMs and controls.

Characteristic	FtMs	Controls	
	n = 56	*n* = 80	*P* value*
Age (years)	22.8 (19.6–26.3)	34.0 (31.0–35.9)	<0.01
Height (cm)	167.0 (162.0–174.0)	172.5 (168.0–178.0)	<0.01
Weight (kg)	67.5 (58.0–79.3)	65.0 (60.0–71.0)	0.51
BMI (kg/m^2)	23.4 (21.2–27.9)	22.0 (20.9–23.5)	<0.01
Ethnical background			
Caucasian	45 (81.8%)	79 (98.8%)	<0.01
Other	10 (18.2%)	1 (1.2%)	
Smoking			
No	44 (78.6%)	70 (88.6%)	0.11
Yes	12 (21.4%)	9 (11.4%)	
Alcohol			
No	16 (28.6%)	30 (38.0%)	0.26
Yes	40 (71.4%)	49 (62.0%)	
Age at menarche	12.0 (11.5–13.0)	13.0 (12.0–14.0)	<0.01
Menstrual cycle[a]			
Regular	39 (69.6%)	68 (85.0%)	0.06
Irregular	9 (16.1%)	9 (11.2%)	
Never	3 (5.4%)	0	
Unknown	5 (8.9%)	3 (3.8%)	
Signs of clinical hyperandrogenism[b]			
No	31 (55.4%)	65 (81.3%)	<0.01
Yes	8 (14.3%)	15 (18.8%)	
Acne	4 (7.1%)	9 (11.3%)	
Hirsutism	2 (3.6%)	5 (6.3%)	
Acne & hirsutism	2 (3.6%)	2 (2.5%)	
Alopecia androgenica	0	1 (1.3%)	
Unkown	17 (30.4%)	0	
Diagnosis PCOS			
No	55 (98.2%)	76 (97.4%)	1.00
Yes	1 (1.8%)	2 (2.6%)	
Pregnancy			
No	55 (98.2%)	39 (48.8%)	<0.01
Yes	1 (1.8%)	41 (51.2%)	
Delivery			
No	56 (100%)	50 (62.5%)	<0.01
Yes	0	30 (37.5%)	

FtMs, female-to-male transsexuals. Data are expressed as median (interquartile range) and numbers (%).
*P values for continuous variables non-parametric Mann–Whitney *U* test, categorical variables using Chi square tests or Fisher's Exact test were appropriate.
[a]Regular cycle < 35 days, irregular cycle > 35 days.
[b]Before start of androgen treatment.

The mean AFC per ovary did not differ between the groups: median FtMs 6.8 versus controls 7.0, $P = 0.90$, ß adjusted for age and current use of GnRHa: 0.97 (95% CI −1.87 to 3.81), $P = 0.50$.

The mean ovarian volume was higher in the control group: median controls 6.9 versus FtMs 5.4 ml, $P = 0.02$, ß adjusted for age and current use of GnRHa: −1.14 (95% CI −2.78 to 0.49), $P = 0.17$.

Discussion

Hyperandrogenism is a paramount characteristic of PCOS both clinically and biochemically. However, the extent to which it causes development of PCOM is uncertain and unclear.

Several histological studies on human ovaries from FtMs assume that hyperandrogenism can cause PCOM changes (Amirikia *et al.*, 1986; Futterweit and Deligdisch, 1986; Spinder *et al.*, 1989; Pache *et al.*, 1991). However recently this could not be confirmed (Ikeda *et al.*, 2013). A number of animal models that have been developed to model PCOS are based on hyper exposure to androgens (Abbott *et al.*, 1998; Murray *et al.*, 1998; Vendola *et al.*, 1998; Weil *et al.*, 1999). However, scarce data on postnatally administered androgens show conflicting results (Treloar *et al.*, 1972; McGee *et al.*, 2012).

Our prospective study is the first systematical and adequately powered study reporting on the possible effects of supraphysiological testosterone administration on human ovarian morphology determined by TVU. The results indicate that high androgen exposure in adulthood does not seem to induce PCOM.

Our findings raise at least two issues. First: how strong is the evidence that ultrasound appearance of PCOS agrees with histomorphological characterized PCOS? Only a few studies (Takahashi *et al.*, 1994; Hansen *et al.*, 2011) compared ultrasound appearance of ovaries and histomorphology in subsequently obtained surgical wedge resections or fractions. These show a strong correlation between numbers of cysts on histology and TVU. Other features of the classical histological criteria of Hughesdon (Hughesdon, 1982), such as ovarian volume and stromal hyperplasia, also seem to agree with these two types of observations (Parisi *et al.*, 1984; Cheung and Chang, 1990; Saxton *et al.*, 1990; Brown *et al.*, 2009). Therefore, it is reasonable to assume that ultrasound PCOM can be considered a reliable indicator for histomorphological PCOS. Second: what is the validity of previous studies suggesting that prolonged hyperandrogenism has caused PCO-like histomorphological changes? A few studies have reported that ovaries from FtMs exposed to exogenous androgens show PCOS like features such as ovarian cortex thickening, collagenization, larger numbers of cystic and atretic follicles. But most of these studies have done so without objective quantification, application of stringent statistics and with arbitrary modifications of the classical Hughesdon criteria (Hughesdon, 1982; Amirikia *et al.*, 1986; Futterweit and Deligdisch, 1986; Spinder *et al.*, 1989; Pache *et al.*, 1991; Grynberg *et al.*, 2010). Indeed, a recent quantitative morphological study (Ikeda *et al.*, 2013) detected hyperplasia of the ovarian cortex and stroma, but no PCO morphology.

Our finding is that androgen treatment does not seem to induce PCO ultrasound appearance. According to the literature, PCO ultrasound appearance correlates with PCO histomorphology (Takahashi *et al.*, 1994), which in turn does not seem consistent with androgen treatment. This brings us to the conclusion that prolonged overexposure to

Table II Characteristics of the FtMs.

Characteristic	$n = 56$
Testosterone use (months)	29.5 (23.0–35.0)
Age start testosterone (years)	20.5 (17.1–23.8)
Type of testosterone used	
Intramuscular	38 (67.9%)
Transdermal	18 (32.1%)
Current use of GnRHa	
No	40 (71.4%)
Yes	16 (28.6%)
Any use of GnRHa in the past	
No	29 (51.8%)
Yes	27 (48.2%)

Data are expressed as median (interquartile range) and numbers (%).

Table III Hormonal measurements.

	Before testosterone	Prior to TVU
Hormones FtMs,* $n = 56$		
Testosterone (nmol/l)	1.0 (1.0–1.3), $n = 55$	16.0 (10.0–27.0), $n = 55$
Estradiol (pmol/l)	112.0 (52.0–263.0), $n = 55$	102.0 (70.0–124.0), $n = 43$
FSH (U/l)	4.4 (3.3–5.4), $n = 22$	0.7 (0.4–1.0), $n = 19$
LH (U/l)	3.5 (1.1–5.0), $n = 55$	0.4 (0.1–2.4), $n = 47$
Months before TVU when blood was taken		10.0 (7.0–15.4)
Duration of testosterone therapy priorv to pre-TVU blood sample (months)		16.7 (13.1–25.3)
Hormones controls, $n = 80$		
Estradiol (pmol/l)	117.5 (96.9–159.9)	
FSH (U/l)	5.7 (4.9–6.8)	
LH (U/l)	4.5 (3.6–5.9)	

TVU, transvaginal ultrasound. Data are expressed as median (interquartile range).
* Hormonal measurements the 56 FtMs before testosterone treatment began and in the most recent sample prior to TVU.

Table IV Outcomes—results of 3D TVU of the ovaries.

	FtMs	Controls	Regression analysis				
			Crude			Adjusted**	
	$n = 56$	$n = 80$	*P* value*	Odds ratio	*P* value	Odds ratio	*P* value
PCOM (≥12 antral follicles (2–10 mm) in at least one ovary)	32.1% (17/53)	30.7% (23/75)	0.87	1.07	0.87	0.63	0.42
AFC per ovary	6.8 (4.4–15.8)	7.0 (5.0–11.0)	0.90	1.72	0.10	0.97	0.50
Ovarian volume (ml)	5.4 (3.9–8.0)	6.9 (5.5–8.6)	0.02	−1.12	0.049	−1.14	0.17

AFC, antral follicle count. Data are expressed as median (interquartile range) and % (numbers).
*P values for continuous variables non-parametric Mann–Whitney *U* test, categorical variables using Chi square tests.
**Adjusted for age and current GnRHa use.

exogenous androgen in adult human females may not be as straightforward a model for PCOS as previously assumed. It cannot be ruled out that in PCOS the only slightly higher androgen levels may cause PCOM. In any case, the extremely supraphysiological levels of testosterone we created, having been much higher than in PCOS, do not do so.

Of concern is to what extent animal models developed for PCOS, based on induction of hyperandrogenism, can be assumed valid for humans. It should be noted that nearly all assumptions are based on PCOS models that result from prenatal androgen exposure. Some studies in non-primate sheep and cattle models relate prenatal androgen exposure to postnatal androgen ultrasound appearance (Manikkam *et al.*, 2006; Steckler *et al.*, 2007; Bishop *et al.*, 2009). In only one primate study androgens were given postnatally (during neonatal life) (McGee *et al.*, 2012). These testosterone-treated primates did show changes in pulsatile LH secretion and responsiveness similar to PCOS, however there were no differences in ovarian morphology (the number of small antral follicles and ovarian size) determined by ultrasound, compared to control primates (McGee *et al.*, 2012). Moreover, except for this study there is hardly any data on ultrasound appearance of these non-human ovaries that could parallel this typical clinical human characteristic. In none of the studied species natural occurring PCOS is present to validate the induced model.

On the other hand, animal models did teach us that during the early stages of folliculogenesis, androgens act as an enhancer of follicle recruitment and differentiation, particularly through the synergism of androgens and FSH. Furthermore, in later stages androgens inhibit follicular development and serve as a substrate for oestrogen (McGee and Hsueh, 2000; Gleicher *et al.*, 2011; Gervásio *et al.*, 2014). *In vitro*, androgens promote growth and survival of multiple types of follicles and enhances FSH receptor expression in mice, bovines and primates (Murray *et al.*, 1998; Vendola *et al.*, 1998; Weil *et al.*, 1999; Yang and Fortune, 2006). However, these animal models have not been clearly confirmed in human (Walters, 2015).

Strengths and weaknesses

A strength of the study is that subjects and controls underwent exactly the same ultrasound procedure (device, software, analysis etc.). The follicle (3D) counting method has high reliability compared with 2D measure methods (Scheffer *et al.*, 2002; Lam and Raine-Fenning, 2006; Jayaprakasan *et al.*, 2007).

We recognize several limitations of the study. Unfortunately, there is the lack of an ultrasound prior to androgen treatment of the FtMs. One could question the current validity of the chosen threshold follicles per ovary of 12 for the definition of PCOM (Dewailly *et al.*, 2014). However, in absence of novel consensus on this topic we used the definition according to the Rotterdam criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004). Furthermore, a number of patients received GnRHa, which is nowadays part of the most ideal sex-reassignment treatment, preventing secondary sex characteristics when starting from adolescence. It was considered unethical to withhold FtMs treatment with GnRHa. Possibly its LH and FSH suppressive effects may have influenced the dynamics of folliculogenesis and suppressed PCOM. Older studies in small groups show conflicting evidence of a reduction on ultrasound appearance of polycystic ovaries, particularly volume (Dale *et al.*, 1989; Williams *et al.*, 1989; Macleod *et al.*, 1990; Goni *et al.*, 1994). Gonadotropin suppression via hormonal contraceptive use, does not suppress PCOM (Mes-Krowinkel *et al.*, 2014). Also, the reducing effect on AFC of GnRHa and hormonal contraceptives has shown to be reversible in a few months (Orsini *et al.*, 1985; Macleod *et al.*, 1990; ESHRE, 2001; Kriplani *et al.*, 2010).

In addition, we did not observe differences between FtMs who had not been treated with GnRHa compared to those who had, either currently or somewhere in the past.

Unfortunately, our sample size did not allow detection of the presence of small differences, especially in the subgroup analysis for GnRHa treatment. Concerning the subjects, the two groups were not an ideal match with regard to age and BMI. The FtMs were significantly younger and had a lower BMI. However, statistical correction did not change the results.

In conclusion, this first explorative study shows that long-term exogenous androgen administration in adult women does not seem to induce PCOM, determined by TVU. We applied a unique and ethically acceptable opportunity of exploring the effects of androgens on human ovaries in women with transsexualism.

Acknowledgements

The authors especially want to thank the patients for their participation, as well as Dr. H. Trum and the surgery teams for their help during surgery.

Authors' roles

M.R.C., N.E.S., E.M.A.K., M.v.T. and C.B.L. designed the study, recruited patients, collected data, analysed the data, interpreted the data

and wrote the first draft of the manuscript. J.v.R., M.H.v.B., E.v.D.B., A.O., and F.E.v. collected and analysed data and contributed with interpretation and the writing of the final version of the manuscript.

Funding

None.

Conflict of interest

None declared.

References

Abbott DH, Bird IM. Nonhuman primates as models for human adrenal androgen production: function and dysfunction. *Rev Endocr Metab Disord* 2009;**10**:33–42.

Abbott DH, Dumesic DA, Eisner JR, Colman RJ, Kemnitz JW. Insights into the development of polycystic ovary syndrome (PCOS) from studies of prenatally androgenized female rhesus monkeys. *Trends Endocrinol Metab* 1998;**9**:62–67.

Abbott DH, Tarantal AF, Dumesic DA. Fetal, infant, adolescent and adult phenotypes of polycystic ovary syndrome in prenatally androgenized female rhesus monkeys. *Am J Primatol* 2009;**71**:776–784.

Amirikia H, Savoy-Moore RT, Sundareson AS, Moghissi KS. The effects of long-term androgen treatment on the ovary. *Fertil Steril* 1986;**45**:202–208.

Azziz R. Androgen excess is the key element in polycystic ovary syndrome. *Fertil Steril* 2003;**80**:252–254.

Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metabol* 2004;**89**:2745–2749.

Balen AH, Laven JS, Tan SL, Dewailly D. Ultrasound assessment of the polycystic ovary: international consensus definitions. *Hum Reprod Update* 2003;**9**:505–514.

Bishop CV, Sparman ML, Stanley JE, Bahar A, Zelinski MB, Stouffer RL. Evaluation of antral follicle growth in the macaque ovary during the menstrual cycle and controlled ovarian stimulation by high-resolution ultrasonography. *Am J Primatol* 2009;**71**:384–392.

Brown DL, Henrichsen TL, Clayton AC, Hudson SB, Coddington CCIII, Vella A. Ovarian stromal hyperthecosis: sonographic features and histologic associations. *J Ultrasound Med* 2009;**28**:587–593.

Caanen MR, Soleman RS, Kuijper EA, Kreukels BP, De Roo C, Tilleman K, De Sutter P, van Trotsenburg MA, Broekmans FJ, Lambalk CB. Antimüllerian hormone levels decrease in female-to-male transsexuals using testosterone as cross-sex therapy. *Fertil Steril* 2015;**103**:1340–1345.

Cheung AP, Chang RJ. Polycystic ovary syndrome. *Clin Obstet Gynecol* 1990;**33**:655–657.

Dale PO, Tanbo T, Haug E, Abyholm T. GnRH-agonist therapy in women with the polycystic ovarian syndrome: effects on ovarian volume and on gonadotropin and sex steroid levels. *Gynecol Endocrinol* 1989;**4**:309–315.

de Boer EJ, den Tonkelaar I, Burger CW, van Leeuwen FE, and OMEGA Project Group. Validity of self-reported causes of subfertility. *Am J Epidemiol* 2005;**161**:978–986.

Dekker M, Wierckx K, Van Caenegem E, Klaver M, Kreukels B, Elaut E, Fisher A, van Trotsenburg M, Schreiner T, den Heijer M. A European network for the investigation of gender incongruence: endocrine part. *J Sex Med* 2016;**13**:994–999.

Dewailly D, Lujan ME, Carmina E, Cedars MI, Laven J, Norman RJ, Escobar-Morreale HF. Definition and significance of polycystic ovarian morphology: a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society. *Hum Reprod Update* 2014;**20**:334–352.

Dewailly D, Robin G, Peigne M, Decanter C, Pigny P, Catteau-Jonard S. Interactions between androgens, FSH, anti-Müllerian hormone and estradiol during folliculogenesis in the human normal and polycystic ovary. *Hum Reprod Update* 2016;**22**:709–724.

ESHRE Capri Workshop Group. Ovarian and endometrial function during hormonal contraception. *Hum Reprod* 2001;**16**:1527–1535.

Franks S. Polycystic ovary syndrome. *N Engl J Med* 1995;**333**:853–861.

Futterweit W, Deligdisch L. Histopathological effects of exogenously administered testosterone in 19 female to male transsexuals. *J Clin Endocrinol Metab* 1986;**62**:16–21.

Gervásio CG, Bernuci MP, Silva-de-Sá MF, Rosa-e-Silva AC. The role of androgen hormones in early follicular development. *ISRN Obstet Gynecol* 2014;**2014**:818010.

Gleicher N, Weghofer A, Barad DH. The role of androgens in follicle maturation and ovulation induction: friend or foe of infertility treatment. *Reprod Biol Endocrinol* 2011;**9**:116.

Goni M, Markussis V, Tolis G. Efficacy of chronic therapy with the gonadotrophin releasing hormone agonist decapeptyl in patients with polycystic ovary syndrome. *Hum Reprod* 1994;**6**:1048–1052.

Grynberg M, Fanchin R, Dubost G, Colau J, Brémont-Weil C, Frydman R, Ayoubi J. Histology of genital tract and breast tissue after long-term testosterone administration in a female-to-male transsexual population. *Reprod Biomed Online* 2010;**20**:553–558.

Hansen KR, Hodnett GM, Knowlton N, Craig LB. Correlation of ovarian reserve tests with histologically determined primordial follicle number. *Fertil Steril* 2011;**95**:170–175.

Hughesdon P. Morphology and morphogenesis of the Stein-Leventhal ovary and of so-called 'hyperthecosis'. *Obstet Gynecol Surv* 1982;**37**:59–77.

Ikeda K, Baba T, Noguchi H, Nagasawa K, Endo T, Kiya T, Saito T. Excessive androgen exposure in female-to-male transsexual persons of reproductive age induces hyperplasia of the ovarian cortex and stroma but not polycystic ovary morphology. *Hum Reprod* 2013;**28**:453–461.

Jayaprakasan K, Hilwah N, Kendall NR, Hopkisson JF, Campbell BK, Johnson IR, Raine-Fenning NJ. Does 3D ultrasound offer any advantage in the pretreatment assessment of ovarian reserve and prediction of outcome after assisted reproduction treatment? *Hum Reprod* 2007;**22**:1932–1941.

Johnstone EB, Rosen MP, Neril R, Trevithick D, Sternfeld B, Murphy R, Addauan-Andersen C, McConnell D, Pera RR, Cedars MI. The polycystic ovary post-Rotterdam: a common, age-dependent finding in ovulatory women without metabolic significance. *J Clin Endocrinol Metabol* 2010;**95**:4965–4972.

Kriplani A, Periyasamy AJ, Agarwal N, Kulshrestha V, Kumar A, Ammini AC. Effect of oral contraceptive containing ethinyl estradiol combined with drospirenone versus desogestrel on clinical and biochemical parameters in patients with polycystic ovary syndrome. *Contraception* 2010;**82**:139–146.

Lam PM, Raine-Fenning N. The role of three dimensional ultrasonography in polycystic ovary syndrome. *Hum Reprod* 2006;**21**:2209–2215.

Lauritsen MP, Bentzen JG, Pinborg A, Loft A, Forman JL, Thuesen LL, Cohen A, Hougaard DM, Nyboe Andersen A. The prevalence of polycystic ovary syndrome in a normal population according to the Rotterdam criteria versus revised criteria including anti-Mullerian hormone. *Hum Reprod* 2014;**29**:791–801.

Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women 1. *J Clin Endocrinol Metabol* 1999;**84**:165–169.

Macleod AF, Wheeler MJ, Gordon P, Lowy C, Sönksen PH, Conaglen JV. Effect of long-term inhibition of gonadotrophin secretion by the

gonadotrophin-releasing hormone agonist, buserelin, on sex steroid secretion and ovarian morphology in polycystic ovary syndrome. *J Endocrinol* 1990;**2**:317–325.

Manikkam M, Steckler TL, Welch KB, Inskeep EK, Padmanabhan V. Fetal programming: prenatal testosterone treatment leads to follicular persistence/luteal defects; partial restoration of ovarian function by cyclic progesterone treatment. *Endocrinology* 2006;**147**:1997–2007.

McGee EA, Hsueh AJ. Initial and cyclic recruitment of ovarian follicles 1. *Endocr Rev* 2000;**21**:200–214.

McGee WK, Bishop CV, Bahar A, Pohl CR, Chang RJ, Marshall JC, Pau FK, Stouffer RL, Cameron JL. Elevated androgens during puberty in female rhesus monkeys lead to increased neuronal drive to the reproductive axis: a possible component of polycystic ovary syndrome. *Hum Reprod* 2012;**27**:531–540.

Mes-Krowinkel MG, Louwers YV, Mulders AG, de Jong FH, Fauser BC, Laven JS. nfluence of oral contraceptives on anthropomorphometric, endocrine, and metabolic profiles of anovulatory polycystic ovary syndrome patients. *Fertil Steril* 2014;**101**:1757–1765.

Mueller A, Haeberle L, Zollver H, Claassen T, Kronawitter D, Oppelt PG, Cupisti S, Beckmann MW, Dittrich R. Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. *J Sex Med* 2010;**7**:3190–3198.

Mueller A, Kiesewetter F, Binder H, Beckmann MW, Dittrich R. Long-term administration of testosterone undecanoate every 3 months for testosterone supplementation in female-to-male transsexuals. *J Clin Endocrinol Metabol* 2007;**92**:3470–3475.

Murray AA, Gosden RG, Allison V, Spears N. Effect of androgens on the development of mouse follicles growing in vitro. *J Reprod Fertil* 1998; **113**:27–33.

Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. *Lancet* 2007;**370**:685–697.

Orsini LF, Venturoli S, Lorusso R, Pluchinotta V, Paradisi R, Bovicelli L. Ultrasonic findings in polycystic ovarian disease. *Fertil Steril* 1985;**5**:709–714.

Overbeek A, van den Berg MH, Kremer LC, van den Heuvel-Eibrink MM, Tissing WJ, Loonen JJ, Versluys B, Bresters D, Kaspers GJ, Lambalk CB. A nationwide study on reproductive function, ovarian reserve, and risk of premature menopause in female survivors of childhood cancer: design and methodological challenges. *BMC Cancer* 2012;**12**:363.

Pache T, Chadha S, Gooren L, Hop W, Jaarsma K, Dommerholt H, Fauser B. Ovarian morphology in long-term androgen-treated female to male transsexuals. A human model for the study of polycystic ovarian syndrome? *Histopathology* 1991;**19**:445–452.

Parisi L, Tramonti M, Derchi LE, Casciano S, Zurli A, Rocchi P. Polycystic ovarian disease: ultrasonic evaluation and correlations with clinical and hormonal data. *J Clin Ultrasound* 1984;**12**:21–26.

Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004; **19**:41–47.

Saxton D, Farquhar C, Rae T, Beard R, Anderson M, Wadsworth J. Accuracy of ultrasound measurements of female pelvic organs. *Br J Obstet Gynaecol* 1990;**97**:695–699.

Scheffer G, Broekmans F, Bancsi L, Habbema J, Looman C, Te Velde E. Quantitative transvaginal two-and three-dimensional sonography of the ovaries: reproducibility of antral follicle counts. *Ultrasound Obstet Gynecol* 2002;**20**:270–275.

Spinder T, Spijkstra JJ, van den Tweel JG, Burger CW, van Kessel H, Hompes PG, Gooren LJ. The effects of long term testosterone administration on pulsatile luteinizing hormone secretion and on ovarian histology in eugonadal female to male transsexual subjects. *J Clin Endocrinol Metab* 1989;**69**:151–157.

Steckler T, Manikkam M, Inskeep EK, Padmanabhan V. Developmental programming: follicular persistence in prenatal testosterone-treated sheep is not programmed by androgenic actions of testosterone. *Endocrinology* 2007;**148**:3532–3540.

Stein IF and Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol 1935;**29**:181–191.

Takahashi K, Eda Y, Abu-Musa A, Okada S, Yoshino K, Kitao M. Transvaginal ultrasound imaging, histopathology and endocrinopathy in patients with polycystic ovarian syndrome. *Hum Reprod* 1994;**9**:1231–1236.

Treloar O, Wolf R, Meyer R. Failure of a single neonatal dose of testosterone to alter ovarian function in the Rhesus monkey. *Endocrinology* 1972; **90**:281–284.

van den Berg MH, van Dulmen-den Broeder E, Overbeek A, Twisk JW, Schats R, van Leeuwen FE, Kaspers GJ, Lambalk CB. Comparison of ovarian function markers in users of hormonal contraceptives during the hormone-free interval and subsequent natural early follicular phases. *Hum Reprod* 2010;**25**:1520–1527.

van Leeuwen FE, Klip H, Mooij TM, van de Swaluw AM, Lambalk CB, Kortman M, Laven JS, Jansen CA, Helmerhorst FM, Cohlen BJ *et al*. Risk of borderline and invasive ovarian tumours after ovarian stimulation for in vitro fertilization in a large Dutch cohort. *Hum Reprod* 2011;**26**: 3456–3465.

van Trotsenburg MA. Gynecological aspects of transgender healthcare. *Int J Transgend* 2009;**11**:238–246.

Vendola KA, Zhou J, Adesanya OO, Weil SJ, Bondy CA. Androgens stimulate early stages of follicular growth in the primate ovary. *J Clin Invest* 1998;**101**:2622–2629.

Walters KA. Role of androgens in normal and pathological ovarian function. *Reproduction* 2015;**149**:R193–R218.

Weil S, Vendola K, Zhou J, Bondy CA. Androgen and follicle-stimulating hormone interactions in primate ovarian follicle development. *J Clin Endocrinol Metabol* 1999;**84**:2951–2956.

Weil SJ, Vendola K, Zhou J, Adesanya OO, Wang J, Okafor J, Bondy CA. Androgen receptor gene expression in the primate ovary: cellular localization, regulation, and functional correlations. *J Clin Endocrinol Metab* 1998;**83**:2479–2485.

Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, Lobo R, Norman RJ, Talbott E, Dumesic DA. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. *J Clin Endocrinol Metabol* 2010;**95**:2038–2049.

Williams IA, Shaw RW, Burford G. An attempt to alter the pathophysiology of polycystic ovary syndrome using a gonadotrophin hormone releasing hormone agonist–Nafarelin. *Clin Endocrinol* 1989;**3**:345–353.

Yang MY, Fortune JE. Testosterone stimulates the primary to secondary follicle transition in bovine follicles in vitro. *Biol Reprod* 2006;**75**:924–932.

PLOS ONE

RESEARCH ARTICLE

Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK

Polly Carmichael[1]*, Gary Butler[1,2,3], Una Masic[1], Tim J. Cole[3], Bianca L. De Stavola[3], Sarah Davidson[1], Elin M. Skageberg[1], Sophie Khadr[3], Russell M. Viner[3]

1 Gender Identity Development Service (GIDS), Tavistock and Portman NHS Foundation Trust, London, United Kingdom, **2** Paediatric Endocrine Service, University College London Hospitals NHS Foundation Trust, London, United Kingdom, **3** UCL Great Ormond Street Institute of Child Health, University College London, London, United Kingdom

* PCarmichael@tavi-port.nhs.uk

Citation: Carmichael P, Butler G, Masic U, Cole TJ, De Stavola BL, Davidson S, et al. (2021) Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. PLoS ONE 16(2): e0243894. https://doi.org/10.1371/journal.pone.0243894

Editor: Geilson Lima Santana, University of Sao Paulo Medical School, BRAZIL

Received: February 3, 2020

Accepted: November 29, 2020

Published: February 2, 2021

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0243894

Data Availability Statement: The data underlying this study are available from the UK Data Service (DOI: 10.5255/UKDA-SN-854413).

Abstract

Background

In adolescents with severe and persistent gender dysphoria (GD), gonadotropin releasing hormone analogues (GnRHa) are used from early/middle puberty with the aim of delaying irreversible and unwanted pubertal body changes. Evidence of outcomes of pubertal suppression in GD is limited.

Methods

We undertook an uncontrolled prospective observational study of GnRHa as monotherapy in 44 12–15 year olds with persistent and severe GD. Prespecified analyses were limited to key outcomes: bone mineral content (BMC) and bone mineral density (BMD); Child Behaviour CheckList (CBCL) total t-score; Youth Self-Report (YSR) total t-score; CBCL and YSR self-harm indices; at 12, 24 and 36 months. Semistructured interviews were conducted on GnRHa.

Results

44 patients had data at 12 months follow-up, 24 at 24 months and 14 at 36 months. All had normal karyotype and endocrinology consistent with birth-registered sex. All achieved suppression of gonadotropins by 6 months. At the end of the study one ceased GnRHa and 43 (98%) elected to start cross-sex hormones.

There was no change from baseline in spine BMD at 12 months nor in hip BMD at 24 and 36 months, but at 24 months lumbar spine BMC and BMD were higher than at baseline (BMC +6.0 (95% CI: 4.0, 7.9); BMD +0.05 (0.03, 0.07)). There were no changes from baseline to 12 or 24 months in CBCL or YSR total t-scores or for CBCL or YSR self-harm indices, nor for CBCL total t-score or self-harm index at 36 months. Most participants reported

Funding: The author(s) received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

positive or a mixture of positive and negative life changes on GnRHa. Anticipated adverse events were common.

Conclusions

Overall patient experience of changes on GnRHa treatment was positive. We identified no changes in psychological function. Changes in BMD were consistent with suppression of growth. Larger and longer-term prospective studies using a range of designs are needed to more fully quantify the benefits and harms of pubertal suppression in GD.

Introduction

Gender dysphoria (GD) describes the experience of incongruence between an individual's experienced gender and the sex they were assigned at birth. GD [1] in children and young people, also known as Gender Incongruence [2] and previously known as Gender Identity Disorder (GID), is associated with considerable distress or impairment in social, school or other important areas of functioning [3,4]. Interventions include psychosocial support, therapy and medical or surgical interventions to align the body with the identified gender [3,5]. Terminology in this field can be challenging [6]. Here we use birth-registered sex to refer to the sex assigned at birth by clinicians based upon external genitalia [6]. Gender identity refers to a young person's personal sense of their gender. We use the terms 'continuation' and 'discontinuation' to refer to GD across childhood and adolescence.

GD in adolescence is highly likely to continue into adult life where gender dysphoria persists after the onset of puberty [3]. Those with earlier onset or more intense GD and those in whom the development of secondary sexual characteristics in puberty is associated with increasing gender dysphoria or psychological distress are more likely to have persistent GD [3,7]. In adolescents with severe and persistent GD, international [8] and national [9–11] guidelines recommend the use of treatments to suppress the rise in sex hormones (oestradiol or testosterone) in young people during puberty. Gonadotropin releasing hormone analogues (GnRHa) are synthetic peptides that work by stimulating gonadotropin release in a tonic fashion which desensitises the gonadotropin receptors, resulting in reversible suppression of sex hormone production.

In GD, GnRHa can be used from the early/middle stages of puberty with the aim of delaying irreversible and unwanted pubertal body changes and giving young people the opportunity to explore their gender identity during a period when puberty is not advancing [3]. This period also allows clinicians more time to assess the stability of young people's gender identity [6]. Despite this treatment being given in mid-puberty it is also called early puberty suppression, where 'early' refers to earlier than the historic practice of suppression after completion of puberty.

Pubertal suppression is currently practised in the majority of international centres across Europe, the Americas and Australasia, as evidenced by a recently published survey of 25 international centres by the European Society of Paediatric Endocrinology (ESPE) [12]. Pubertal suppression with GnRHa as monotherapy is a time-limited strategy, due to the potential for side effects with long-term use. In the UK, for those commencing under age 15 years, use of GnRHa alone ceases after 16 years when young people face a decision to return to the sex hormones produced by their body or begin cross-sex hormones [5]. There are limited data on the outcomes of pubertal suppression in the treatment of young people with GD [3,13]. A recent

systematic review included data on the physical and mental health outcomes of pubertal suppression using GnRHa in over 500 young people [4]. Longer-term follow-up data on pubertal suppression in GD are limited to individuals from four cohorts [14–19].

In 2011 a study was begun to evaluate the proximal outcomes of mid-pubertal suppression using GnRHa in young people with persistent GD (see http://gids.nhs.uk/our-early-intervention-study). Use in the UK began after mid-pubertal suppression had been incorporated into international guidelines [20] and had become available in the USA [21,22], the Netherlands [15], Australia [23] and a number of European countries. The Gender Identity Development Service (GIDS) at the Tavistock and Portman NHS Foundation Trust, London, is a national service for children and young people with GD, drawing from England, Wales and Ireland. Mid-pubertal suppression was offered by the GIDS from 2011 initially only within an ethically approved uncontrolled observational research study with prospective data collection, where all participants received GnRHa. We anticipated that we would recruit 10–15 young people per year for 3 years and follow them up to the end of monotherapy with GnRHa. At the time, a randomised controlled study was not considered feasible due to very small numbers and inability to retain participants in the control arm, as the control treatment would have resulted in progression into near complete puberty and an increasing number of UK families were accessing mid-pubertal suppression internationally. Allocation blinding was also not considered feasible in young people using a product requiring monthly injections.

Here we describe the short-term outcomes of 44 young people with GD from this research cohort, recruited aged 12–15 years and followed to the end of GnRHa monotherapy after age 16 years. This paper describes their medical, psychological and social outcomes during the GnRHa treatment pathway up to the point of decisions about whether or not to undertake further physical treatment. The aims of the study as defined at inception in 2011 were:

1. To evaluate the benefits and risks for physical and mental health and wellbeing of mid-pubertal suppression in adolescents with GD
2. To add to the evidence base regarding the efficacy of GnRHa treatment for young people with GD
3. To evaluate continuation and discontinuation of GD and the continued wish for gender reassignment within this group.

Methods

We undertook an uncontrolled prospective observational study of GnRHa monotherapy in a highly selected group of young people with persistent and severe GD.

Participants

The cohort consisted of 44 sequentially eligible young people, aged 12 to 15 years, who were recruited between April 2011 and April 2014 and who commenced GnRHa treatment between June 2011 and April 2015. They were all recruited from patients referred to the GIDS.

Eligibility criteria were chosen to match those used for a Netherlands cohort [24], namely that the young person:

A. is aged 12–15 years

B. Psychological criteria

1. has been seen by the GIDS for at least 6 months and attended at least 4 interviews for assessment and therapeutic exploration of their gender identity development.

2. psychological stability sufficient to withstand the stresses of medical treatment for GID.
3. fulfils the following criteria relating to GID:
   a. Throughout childhood (defined as over 5 years) the adolescent has demonstrated an intense pattern of cross-gendered behaviours and cross-gender identity.
   b. The adolescent has gender dysphoria that is significantly increased with the onset of puberty. Following assessment the clinician(s) working with the young person deem that there is a high likelihood of the young person experiencing severe psychological distress consequent on experiencing full pubertal development before pubertal suppression is implemented.
4. The young person and their parents/guardians are actively requesting pubertal suppression.
5. is able to give informed consent.

C. Physical/medical criteria

1. is in established puberty:
   - For birth-registered males Tanner (genital and pubic hair (PH)) stage 3 and above.
   - For birth-registered females Tanner (breast and PH) stage 2 and above.
     The rationale for the sex difference was that the pubertal growth spurt which early intervention aims to avoid occurs typically two years earlier in females (Tanner stage 2–3) than in males (Tanner stage 3–4), thus earlier intervention is required in females.
2. has normal endocrine function and karyotype consistent with birth registered sex.

Note that the presence of mildly elevated androgens in birth registered females consistent with polycystic ovarian syndrome is not an exclusion criterion.

Exclusion criteria:

1. Inability to participate with full investigatory protocol e.g. needle phobia, failure to attend for tests and scans.
2. Body mass index (BMI) <2nd centile for age and birth-registered sex [20].
3. Serious psychiatric conditions (e.g. psychosis, bipolar condition, anorexia nervosa, severe body-dysmorphic disorder unrelated to GD).
4. Inability to give informed consent according to the Fraser/Gillick guidelines.
5. Low spine or hip bone mineral density (BMD) on DXA scan: more than 2 SD below expected BMD for age and birth-registered sex. In exceptional circumstances a low BMD was acceptable if:
   i. it was felt to be clinically appropriate by the treating clinicians, who felt that on the balance of risks, pubertal suppression was justified despite the later risk of osteoporosis
   ii. the young person and parents understood the risks of GnRHa treatment for bone density (i.e. potential risks of later osteoporosis)
   iii. The young person and parents consented to more frequent monitoring of BMD (repeat DXA scans 6 months after starting GnRHa and yearly thereafter while on GnRHa) despite the small DXA radiation dose

iv. The young person and parents consented to stopping treatment if raw BMD fell whilst on GnRHa.

The treatment

The treatment under study was suppression of puberty using the GnRHa *triptorelin* together with psychosocial support and therapy, from study entry until the end of the GnRHa monotherapy pathway at age 16 years or older. GnRHa monotherapy ceased when young people either started cross-sex hormones (and continued on GnRHa) or stopped GnRHa. Treatment duration was therefore from 1 to 4 or 5 years depending on age at study entry. Consenting young people were given triptorelin 3.75mg by intramuscular injection every 28 days during the treatment period. Two participants who found monthly injections difficult were moved to a ten-weekly preparation of 11.25mg of triptorelin. The aim of treatment was to suppress gonadotropins and sex hormones to near pre-pubertal levels [13]. Continued regular attendance for psychological support and therapy throughout the study was a precondition of GnRHa prescription. In addition local psychological services provided support for co-occuring difficulties for participants as required.

Procedures and pathway

All young people and families attending the GIDS during the study period were provided with an information leaflet about research underway within the unit. Those wishing to find out more about the study discussed it with their GIDS clinicians and those deemed likely to be eligible were given detailed written study information. Those wanting to participate were invited to a medical clinic at UCLH for an initial discussion. At the first medical clinic, young people and families were seen by a senior paediatric endocrinology clinician together with a senior GIDS clinician, who discussed with the family the then current state of knowledge and rationale for treatment, eligibility criteria and potential risks and benefits of participation. Risks included the anticipated side-effects of GnRHa treatment including symptoms resulting from the withdrawal of sex steroids (headaches, hot flushes), fatigue, loss of libido and low mood, the potential that treatment could influence the continuation of their GD and the potential for unknown risks. It was emphasised that young people needed to continue with both regular medical and psychosocial follow-up during the study and that treatment would cease if they did not comply with the treatment or monitoring requirements. A full medical history was elicited and the clinicians also reviewed a summary of the psychological history and assessment from the GIDS. In this visit information sheets were re-provided if families had lost them or forgotten details of the study. If young people and families remained interested in participation, medical investigations were organised and families were invited for a repeat discussion and a formal evaluation of eligibility at a second medical clinic visit approximately 3 months later. Families were asked to think about the issues raised in the meeting and to discuss with their GIDS clinicians if necessary, in order to discuss further at the second visit.

At the second medical clinic visit, the same clinicians repeated the discussion of risks and benefits and explored understanding with the young person and family. A chaperoned medical examination was undertaken including pubertal assessment and the results of medical investigations were reviewed. Endocrine and GIDS clinicians jointly reviewed eligibility and offered participation in the study to those deemed eligible.

The implications of treatment for fertility were discussed at the first and second medical visits and all young people were urged to consider storing gametes before starting GnRHa. Access to storage depended on regional availability within the NHS. Note that counselling on fertility

continued across the study, and clinicians periodically checked with young people who had decided against storage whether they wished to revisit their decision.

Informed consent was obtained in writing from both the young person and a parent or carer holding parental responsibility. The ability of the young person and parents to give informed consent was assessed jointly by the senior adolescent endocrine and GIDS clinicians, informed by written notes from the GIDS team. The consent forms were read with the young person and the parent by the clinicians to be sure they fully understood the information on the forms before signing.

48 young people and families attended the medical clinics for discussion of participation in the trial, of whom 44 wished to participate. Eight young people (7 birth assigned males) were not eligible for participation at the second medical visit as they were not yet sufficiently advanced in puberty. They were followed up every 3–6 months and entered the study subsequently when sufficiently advanced in puberty (median waiting time 7 months).

The date of signing the consent form was taken as the start of study treatment, although it frequently took one to three months for GnRHa treatment to start due to administrative requirements. Participants were followed up in the endocrine clinic, 3–6 monthly in the first 18 months and 12-monthly thereafter, till the end of the treatment pathway, defined as the date on or after the 16th birthday when a decision was made to either cease GnRHa or start cross-sex hormones. The final participant completed the pathway in February 2019.

Outcomes

The following data were collected:

A. Baseline explanatory variables

1. Sex and gender: Young people were classified by their sex assigned at birth (birth-registered sex) and self-identified gender.
2. Ethnicity: Ethnicity was obtained from clinic records. For analysis, ethnicity was grouped as white, South Asian, black or mixed.
3. Puberty: Pubertal status at baseline was classified using information on genital/breast and pubic hair Tanner stages as appropriate. This was summarized into a single pubertal stage, with the breast/genital stage taking precedence if there was discrepancy between breast/genital and public hair stage.
4. Clinical data: These consisted of a) identification of normal phenotype on physical examination for birth-registered sex; b) venepuncture assessment of endocrinology (gonadotropins, prolactin, oestrogen or testosterone, adrenal androgens, thyroid function; and a short synacthen test in birth-registered females only), karyotype, full blood count, renal and liver function, calcium and vitamin D; and c) imaging including wrist bone age and (in birth-registered females only) pelvic ultrasound scan. Medical assessment at baseline and follow-up was consistent with Endocrine Society guidelines [8,20].

B. Study outcomes

Study outcomes concerned domains including response to treatment, bone health, safety indicators and adverse events, psychological function; participant experience and satisfaction; and decisions regarding treatment following GnRHa. Outcome data were collected at routine clinic visits to GIDS or medical clinics at UCLH and timings therefore varied. For the purposes of these analyses, data for each participant were assigned to baseline (before treatment) and to the closest of the following outcome periods: 12, 24, 36 and 48 months on treatment. For safety and response to pubertal suppression outcomes, data were also examined at 6 months.

1. Response to pubertal suppression

Gonadotropins (LH, FSH), testosterone (in birth-registered males) and oestrogen (birth-registered females) were measured after venepuncture. Height, weight and blood pressure were recorded by trained clinic staff. BMI z-score for age and birth-registered sex was calculated [25]. Menarcheal status and presence/absence of menstrual periods was obtained by report from birth-registered females.

2. Bone health

Bone mineral content (BMC) and bone mineral density (BMD) in the lumbar (L1 to L4) spine and hip (total hip) were measured by dual energy X-ray absorptiometry (DEXA) scans using a Hologic Discovery QDR series model 010–1549 (Hologic Inc, Bedford, MA, USA). BMD z-scores for age and birth-registered sex appropriate to this machine were calculated [26]. BMD z-scores for spine and hip were further adjusted for height (height-adjusted z-scores) using published formulae [27].

3. Safety indicators and adverse events

Blood samples were collected by venepuncture for liver and renal function, full blood count, calcium and vitamin D, prolactin, adrenal androgens and thyroid function. Participants were routinely questioned about adverse events at medical clinic visits, including anticipated events such as headaches, hot flushes or fatigue plus any other unanticipated events.

4. Psychological function

Psychological outcomes included a clinical outcome routinely collected after GIDS appointments and a range of outcomes assessed using questionnaires. A standardised set of psychological questionnaires used in the GIDS clinic was completed at the time young people were deemed potentially eligible and referred to the medical clinic. Questionnaires were completed at home by the young person and parent between GIDS clinical meetings, and a research assistant followed up families to ensure their completion. Questionnaires were repeated approximately every 12 months on treatment.

i. General psychological functioning

The Child Behaviour Checklist (CBCL) (parent report) and Youth Self Report (YSR) (self-report) are general measures of psychological functioning and part of the Achenbach System of Empirically Based Assessment (ASEBA; www.aseba.org). The CBCL consists of 113 questions and is validated for children aged 6–18 years in international population samples [28]. The YSR consists of 112 questions and is validated in international populations of young people aged 11–18 years [29]. Questions in both are scored on a three-point Likert scale (0 = absent, 1 = occurs sometimes, 2 = occurs often), with the time frame for item responses being the past six months. Scoring for both instruments provides a total problems score, an internalizing problems score (items which assess anxious/depressed, withdrawn-depressed, and somatic complaints) and an externalizing score (focusing on rule-breaking and aggressive behaviours). Each questionnaire was scored with Assessment Data Manager Software using ASEBA standard norms and t-scores were generated based on reference data for birth-registered sex and broad age-ranges (here 12–18 years). Higher scores indicate greater morbidity. To account for normative change within our age-range, we used international reference data [29] to transform YSR raw scores into z-scores for year of age. As reference data from the UK were not available, reference data from both Australia and the Netherlands were used.

ii. Self-harm index

Self-harm actions and thoughts were assessed through two questions in each of the CBCL (parent report) and YSR (self-report): Item 18 (I deliberately try to hurt or kill myself) and Item 91 (I think about killing myself). Possible responses for each question were 0 = not true, 1 = somewhat or sometimes true, or 2 = very true or often true. We followed previous studies in calculating a self-harm index score to avoid multiple statistical comparisons across

correlated categorical-response variables. The index was calculated as the sum of the two items in each scale to create an index from 0 to 4 for each of the CBCL and YSR [30–32], a higher score indicating greater self-harm thoughts and behaviour.

iii. Health related quality of life (HRQoL)

This was assessed through separate young person and parent Kidscreen-52 questionnaires, each consisting of 52 items which assess HRQoL across ten dimensions: physical well-being; psychological well-being; moods and emotions; self-perception; autonomy; relations with parents and home life; social support and peers; school environment; social acceptance (bullying); and financial resources. All items use five-point Likert-style scales to assess either the frequency (never-seldom-sometimes-often-always) of certain behaviours/feelings or the intensity of an attitude (not at all–slightly-moderately-very-extremely). The measure was developed for young people aged 8–18 years, with the recall period of one week. The questionnaires provide scores in the form of continuous t-scores for the ten subscales derived from a multinational European sample [33]. Lower scores indicate lower HRQoL, i.e. greater morbidity.

iv. Body image

The Body Image Scale (BIS) is a self-report measure of 30 items used to assess body image satisfaction or dissatisfaction validated for age 12+. The instrument considers 30 body features which the respondent is asked to rate in terms of satisfaction on a five-point scale (1 = very satisfied, 2 = satisfied, 3 = neutral, 4 = dissatisfied, and 5 = very dissatisfied). The BIS provides a total score in the form of a continuous score for the total scale as well as for three subscales assessing primary sexual characteristics, secondary sexual characteristics and 'neutral' characteristics (i.e. non-sexual characteristics, e.g. nose) [34]. Higher scores represent higher degrees of body dissatisfaction.

v. Gender dysphoria

The Utrecht Gender Dysphoria Scale (UGDS) is a self-report measure used to assess the intensity of GD validated for age 12+. It comprises of 12 statements with agreement on a five-point scale (1 = agree completely, 2 = agree somewhat, 3 = neutral, 4 = disagree somewhat, and 5 = disagree completely). There are separate versions for birth-registered males and females. Items are summed to give a single total score, with higher scores indicating greater GD.

vi. Clinical outcomes

The Children's Global Assessment Scale (CGAS) is a rating of functioning in children and young people aged 6–17 years, extensively used as a routine clinical measure in child and adolescent mental health services in the UK. Treating clinicians assign young people a single score between 1 and 100, based on a clinician's assessment of a range of aspects related to a child's psychological and social functioning, with the time period being the previous month. Higher scores indicate better functioning, with categories ranging from 'extremely impaired' (1–10) to 'doing very well' (91–100) [35].

5. Participant experience and satisfaction with GnRHa

Young people were invited to participate in semi-structured qualitative interviews at 6–15 months and 15–24 months after starting GnRHa. Interviews were conducted in person or by telephone with a research assistant. If young people were unavailable, questions were posted to be completed and returned. The interview consisted of 12 questions related to changes young people had experienced in ten domains since starting on GnRHa: life overall, memory, focus, sense of direction, mood, energy levels, relationships with friends, relationships with family, gender role and sexuality. For each domain, young people were asked first about the general direction of change in that domain (whether changes were positive, neutral, negative or mixed positive and negative) and then asked for examples of changes experienced and why they assigned the chosen change rating. At the end of the interview two further questions were asked about change in any other experiences (i.e. allowing open ended responses) and whether

young people wished to continue on GnRHa treatment. Note there was no interview conducted before young people started GnRHa. Interviews were recorded in contemporaneous written notes by the researcher. The questionnaire is provided in the S1 Appendix.

6. Further treatment decisions

Decisions made at the end of the GnRHa pathway were recorded in terms of which if any further treatment for GD young people chose.

Note that other measures of gender dysphoria (Gender Identity Interview; Recalled Childhood Gender Identity Scale) were specified in our original protocol, however they were discontinued during the study as: a) they were historical instruments with poor construct validity and the binary references to male and female roles were challenging for some participants; and b) repeated questioning about gender dysphoria resulted in some distress to respondents. Our protocol had originally included the ASEBA Teacher Report Form (TRF), however we were unable to obtain data from teachers so this outcome was dropped. The Social Responsiveness Scale (SRS) was a baseline only assessment of autistic traits; these data will be analysed in the future.

Analysis plan

Analyses were conducted according to the Statistical Analysis and Dissemination Plan, lodged with the ethics committee that approved the study before the analysis started (see S2 Appendix: Statistical Analysis Plan). The analysis plan was designed to report data on all outcomes but to minimise the likelihood of chance findings due to the large number of outcomes and small sample size. Sample sizes necessarily varied across follow-up as young people were recruited at different ages (12–15 years) but left the study soon after their 16th birthday. All 44 participants had data at 12 months follow-up. As participants necessarily left the study soon after their 16th birthday, numbers reduced after 12 months follow-up as participants could no longer remain in the study. Note this does not represent drop-out. There were 24 left at 24 months, 14 at 36 months and 4 at 48 months. In view of this, outcome reporting was restricted to change from baseline to 12, 24 and 36 months. We made no attempt to account for missing data due to the small sample size and the likelihood of the data missing not at random.

We restricted analyses to primarily descriptive statistics, with formal statistical testing of change across the study restricted to six pre-specified outcomes, i.e.:

1. Overall psychological functioning
    a. parent report: CBCL total t-score
    b. young person self-report: YSR total t-score
2. Self-harm index
    a. parent report: CBCL self-harm index
    b. young person self-report: YSR self-harm index
3. Bone health
    a. BMD and BMC for lumbar spine
    b. BMD and BMC for hip

Assessment of change was through paired t-tests for normally distributed data and the Wilcoxon matched-pairs sign-rank test for non-normal data. The number of formal statistical tests conducted in the study was 16; with overall significance at $p = 0.05$ and a Bonferroni correction, the appropriate threshold for statistical significance is about $p = 0.003$.

In our results and conclusions we refer to change in outcomes only for those that were formally tested. Reporting for other continuous outcomes was restricted to mean and 95% confidence intervals (95%CI) or median and interquartile range (IQR). For categorical outcomes, simple proportions were reported. We reported laboratory tests as normal or abnormal based upon laboratory reference data for age, with the exception of gonadotropins. We did not report data where the sample size was less than 8.

Analysis of potential predictors of outcome was confined a priori to two factors, birth-registered sex and pubertal stage at baseline. Three pre-specified continuous outcomes were examined at 12 months, namely:

1. BMD for lumbar spine
2. YSR total t-score
3. CGAS score

Associations were examined using linear regression of follow-up score on baseline score, adding each baseline factor separately to the model and considering the interaction of predictor with baseline score. All analyses were conducted using Stata 16 (Statacorp, College Station TX).

Responses to the semi-structured interview questionnaires were analysed simply for thematic content in terms of the direction and amount of change that young people experienced in each domain. This involved coding responses about experiences since starting GnRHa into categories; i.e. either positive/improving, negative/deteriorating, both positive and negative, no change or not known. The question on change in sexuality was coded as yes change, no change or not known. Wishes to continue with GnRHa were coded as yes, no or don't know.

To compare our findings with the literature, we drew upon recent reviews [3,4,6,13] and updated a recent review [4] from 1 June 2017 to 31 December 2019 using the same search terms in Medline (see S1 Appendix).

Ethics

Ethical approval for the study was obtained from the National Research Ethics Service (NRES: reference 10/H0713/79) in February 2011. Study consent allowed the use of routinely collected clinical data (medical and psychological) as part of clinical treatment for the study. Study procedures including consent were reviewed by the UK Health Research Authority.

Data sharing. These are highly sensitive data from a small group of vulnerable young people treated in a single service and the risk of identification and disclosure is high. Research ethics permissions at the time the study was undertaken did not include permission to share data. After discussions with the Health Research Authority, UK, an anonymised dataset modified to remove sensitive data and minimise disclosure risk of personal information has been deposited with the UK Data Service.

Results

Participants received psychosocial assessment and support within the GIDS before entering the study for a median of 2.0 years (IQR 1.4 to 3.2; range 0.7 to 6.6). The median time between first medical assessment at UCLH and starting treatment was 3.9 months (IQR 3.0 to 8.4; range 1.6 to 25.7). Median time in the study was 31 months (IQR 20 to 42, range 12 to 59).

Baseline characteristics of the participants by birth-registered sex are shown in Table 1. Median age at consent was 13.6 years (IQR 12.8 to 14.6, range 12.0 to 15.3). A total of 25 (57%) were birth-registered as male and 19 (43%) as female. At study entry, birth-registered males

Table 1. Participant characteristics at baseline.

		Total sample	Birth-registered sex	
		n = 44	male	female
			n = 25	n = 19
Age at consent (years)	Median (IQR)	13.6 (12.8, 14.6)	13.4 (12.7, 14.1)	13.9 (13.5, 14.7)
Ethnic group n (%)	white	39 (89)	24 (96)	15 (79)
	South Asian	1 (2)	1 (4)	0
	black	2 (5)	0	2 (11)
	Mixed ethnicity	2 (5)	0	2 (11)
Pubertal status n (%)	Stage 2	0	0	0
	Stage 3	19 (43)	17 (68)	2 (10)
	Stage 4	16 (36)	5 (20)	11 (58)
	Stage 5	9 (21)	3 (12)	6 (32)
Menarcheal status n (%)	Premenarcheal	-	-	4 (21)
	Post-menarcheal	-	-	15 (79)
Time in study (months)	Median (IQR)	31 (20, 42)	37 (24, 43)	29 (17, 36)
Age at end of pathway (years)	Median (IQR)	16.1 (16.0, 16.4)	16.1 (16.0, 16.5)	16.1 (16.0, 16.3)

At baseline, all participants had normal endocrinology, karyotype, imaging and clinical phenotype on physical examination for birth-registered sex and normal full blood count and liver and renal function. No participants had evidence of disorders of sexual differentiation. Eight participants (18%) had vitamin D insufficiency at baseline and were given vitamin D supplements.

https://doi.org/10.1371/journal.pone.0243894.t001

were predominantly in stage 3 puberty (68%) whilst birth-registered females were predominantly in stages 4 (58%) or 5 (32%) with 79% (15/19) post-menarcheal. 89% of participants were of white ethnicity. Birth-registered females were on average 6 months older than birth-registered males at study entry.

Response to treatment

All participants achieved adequate suppression of gonadotropins and sex hormones by 6 months (mean LH 0.5IU/L; mean FSH 1.4IU/L) and maintained it throughout the study (see Table 2). Liver function, basic haematology and biochemistry were normal in all participants at 3–6 months. All post-menarcheal birth-registered females reported amenorrhoea in the 3 months after starting GnRHa treatment and remained so throughout treatment. No participants reported progression in pubertal development. Height and weight were normal at baseline. Height growth continued through the study but more slowly than expected for age, thus

Table 2. Growth and gonadotropin levels at baseline, 12, 24 and 36 months.

Growth		Baseline		12 months		24 months		36 months	
		n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
Height	z-score	44	0.4 (0.1, 0.7)	44	0.2 (-0.1, 0.4)	24	0.0 (-0.4, 0.4)	14	0.0 (-0.5, 0.5)
Weight	z-score	44	0.8 (0.4, 1.3)	44	0.8 (0.3, 1.3)	24	0.6 (-0.1 1.3)	14	1.0 (0.1, 1.9)
BMI	z-score	44	0.7 (0.2, 1.1)	44	0.7 (0.2, 1.2)	24	0.6 (-0.1, 1.3)	14	1.1 (0.3, 1.9)
Gonadotropins									
LH	IU/L	42*	4.2 (2.8, 5.6)	44	0.60 (0.42, 0.68)	17	0.40 (0.22, 0.60)	7	0.30 (0.14, 0.46)
FSH	IU/L	42*	3.9 (3.2, 4.5)	44	1.3 (1.0, 1.7)	17	1.0 (0.6, 1.5)	7	1.4 (0.7, 2.2)

*In two participants data recorded as normal at baseline were not available.

https://doi.org/10.1371/journal.pone.0243894.t002

height z-score fell over time (Table 2). Weight and BMI z-scores were stable from baseline to 24 months but increased at 36 months.

Three participants had brief periods off GnRHa prior to their 16th birthday. In one, treatment was withdrawn by clinicians due to non-attendance at clinics and restarted 4 months later. Another requested a period off GnRHa to think further about treatment in view of other things happening in their life; they restarted 4 months later. A third, birth-registered male, stopped GnRHa for 9 months to attempt to store sperm, contrary to their earlier decision not to, and restarted afterwards.

Median age at the end of the GnRHa pathway was 16.1 years (Table 1). A quarter of participants made their decision more than six months later, either because they wished to delay due to school exams or other events or because clinicians felt they were not yet ready to make the decision. One young person decided to stop GnRHa and not start cross-sex hormones, due to continued uncertainty and some concerns about side-effects of cross-sex hormones. The remaining 43 (98%) elected to start cross-sex hormones.

Bone mineral density. BMD was available on 44 participants at baseline, 43 at 12 months, 24 at 24 months and 12 at 36 months (Table 3). Numbers were lower for hip than for spine as some hip scans were not done for technical reasons. The table shows mean values at baseline and 12, 24 and 36 months, along with mean baseline values corresponding to the paired samples at each time point. There was no change from baseline in spine or hip at 12 months nor in hip at 24 and 36 months, but at 24 months lumbar spine BMC and BMD were higher than at baseline, as was lumbar BMC at 36 months. Lumbar and hip BMD age-adjusted z-scores were in the normal range at baseline but point-estimates fell at 12 and 24 months but not at 36 months. Point-estimates for height-adjusted z-scores for lumbar and hip BMD also fell at 12 and 24 months but not at 36 months.

Psychological outcomes. For the standardised questionnaires, baseline assessments were conducted at a median of 0.5 (IQR 0.4, 0.8) years before starting treatment, and were available for all 44 participants by self-report and 43 by parental report. Data on the CBCL, YSR, Kidscreen-52, BIS and CGAS were normally distributed whilst those for UGDS and the CBCL and YSR self-harm indices were skewed.

The first psychological follow-up was at a median of 13 (IQR 12, 14) months after start of treatment, with ASEBA data available for 41 participants (parent and self-report). ASEBA data at 24 months (median 25 (21, 28)) were available on 20 young people by parent report and 15 by self-report, and at 36 months (median 36 (29, 39)) on 11 by parent report and 6 by self-report.

Formal testing was undertaken only for key ASEBA outcomes (Table 4). For the CBCL total t-scores, there was no change from baseline to 12, 24 or 36 months. Similarly for the YSR total t-score, there was no change from baseline to 12 or 24 months; YSR data at 36 months (n = 6) were not analysed. There were no significant changes in parent-report CBCL self-harm index scores from baseline to 12, 24 or 36 months, nor for self-report YSR self-harm index scores.

Other psychological outcomes are described in Table 5. Point-estimates of scores on the Kidscreen-52, BIS, UGDS and CGAS showed little change over time."

The pre-specified outcomes of BMD at lumbar spine, YSR total t-score and CGAS score at 12 months, adjusted separately for birth-registered sex and baseline pubertal status, along with the baseline level of the outcome, are shown in Table 6. None of the outcomes were associated with birth-registered sex or pubertal status, and there were no important interactions.

Participant experience, satisfaction and side effects. 41 participants completed interviews at 6–15 months (median 9) and 29 at 15–24 months (median 21); 3 missed both. Fig 1 shows proportions with positive or negative changes for life overall, mood and friendships, with summary data for all questions shown in S1 Appendix (S1 and S2 Tables).

Table 3. Bone mineral density outcomes at baseline, 12, 24 and 36 months.

				12 months					24 months				
		Baseline			Baseline for those followed up	Follow-up	Change	p		Baseline for those followed up	Follow-up	Change	p
		n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)		n	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Lumbar	BMC	44	39.5 (35.9, 43.1)	42	39.6 (35.8, 43.4)	41.2 (38.2, 44.2)	1.6 (0.2, 3.1)	0.03	24	34.1 (30.3, 37.9)	40.1 (36.7, 43.5)	6.0 (4.0, 7.9)	<0.0001
	BMD	44	0.76 (0.71, 0.80)	43	0.76 (0.71, 0.80)	0.77 (0.72, 0.81)	0.01 (-0.00, 0.03)	0.17	24	0.68 (0.63, 0.74)	0.73 (0.68, 0.78)	0.05 (0.03, 0.07)	0.0001
Hip	BMC	43	25.2 (23.2, 27.1)	39	25.5 (23.4, 27.6)	26.1 (24.4, 27.9)	0.7 (-0.2, 1.5)	0.13	22	23.9 (21.2, 26.6)	26.3 (24.1, 28.6)	2.4 (0.7, 4.1)	0.008
	BMD	43	0.80 (0.75, 0.86)	39	0.81 (0.75, 0.87)	0.82 (0.78, 0.86)	0.01 (-0.02, 0.05)	0.6	22	0.76 (0.68, 0.85)	0.79 (0.74, 0.84)	0.03 (-0.04, 0.10)	0.4
BMD z-scores	Spine	44	-0.3 (-0.7, 0.0)	43	-0.3 (-0.7, 0.1)	-1.0 (-1.3, -0.7)			24	-0.5 (-1.1, 0.0)	-1.5 (-2.1, -0.8)		
	HAZ spine	44	-0.5(-0.8, -0.1)	43	-0.4 (-0.8, -0.1)	-1.0 (-1.3, -0.6)			24	-0.7 (-1.2, -0.1)	-1.3 (-1.9, -0.7)		
	Hip	43	-0.5 (-0.9, -0.1)	39	-0.5 (-0.9, -0.1)	-1.0 (-1.3, -0.6)			21	-0.5 (-1.1, 0.1)	-1.4 (-2.0, -0.9)		
	HAZ hip	43	-0.7 (-1.0, -0.3)	39	-0.6 (-1.0, -0.2)	-0.9 (-1.3, -0.5)			21	-0.5 (-1.1, 0.1)	-1.2 (-1.7, -0.6)		
				36 months									
					Baseline for those followed up	Follow-up	Change	p					
				n	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)						
Lumbar	BMC			12	37.05 (31.0, 43.1)	42.4 (37.4, 47.4)	5.3 (2.8, 7.8)	0.0007					
	BMD			12	0.72 (0.65, 0.80)	0.76 (0.70, 0.82)	0.03 (.00, 0.07)	0.05					
Hip	BMC			12	26.1 (22.1, 30.0)	26.8 (21.2, 32.3)	0.7 (-3.8, 5.2)	0.7					
	BMD			12	(0.82, 0.73, 0.91)	0.81 (0.74, 0.88)	-0.009 (-0.05, 0.03)	0.6					
BMD z-scores	Spine			12	-0.2 (-1.0, 0.6)	-1.5 (-2.2, -0.8)							
	HAZ spine			12	-0.4 (-1.2, 0.3)	-1.3 (-2.2, -0.5)							
	Hip			12	-0.3 (-1.3, 0.6)	-1.1 (-1.8, -0.5)							
	HAZ hip			12	-0.5 (-1.5, 0.5)	-1.0 (-1.8, -0.2)							

BMD: bone mineral density; BMC bone mineral content; HAZ height adjusted z-score.

BMD z-scores were not formally tested–see Methods.

https://doi.org/10.1371/journal.pone.0243894.t003

Most participants reported positive or a mix of positive-negative changes in their life at both time points. At 6–15 months 46% reported only positive changes, including feeling happier, relieved, less facial hair or stopping periods. A further 37% reported both positive and negative changes such as feeling happier but also experiencing hot flushes and headaches. In addition 12% reported overall negative changes namely hot flushes, tiredness, and feeling more emotional, while 5% reported no change. At 15–24 months, 55% reported solely positive changes such as feeling happier, no longer experiencing side effects and feeling more

Table 4. ASEBA outcomes at baseline, 12, 24 and 36 months.

				12 months					24 months				
			Baseline		Baseline for those followed up	Follow-up	Change	p		Baseline for those followed up	Follow-up	Change	p
		n	mean (95% CI)	n	mean (95% CI)	mean (95% CI)	mean (95% CI)		n	mean (95% CI)	mean (95% CI)	mean (95% CI)	
Parent report CBCL	Total problems t-score	43	61.6(58.4, 64.7)	41	61.5(58.2, 64.7)	61.8(58.4, 65.1)	0.3(-2.0, 2.6)	0.8	20	61.2(56.5, 65.8)	60.2(54.6, 65.8)	-1.0(-4.0, 2.1)	0.5
	Externalising problems t-score	43	55.8(52.4, 59.3)	41	55.7(52.1, 59.3)	55.4(51.8, 59.0)			20	55.4(49.9, 60.9)	55.2(48.9, 61.5)		
	Internalising problems t-score	43	62.1(58.7, 65.5)	41	61.8(58.3, 65.3)	62.9(59.5, 66.3)			20	60.4(55.7, 65.1)	60.1(54.6, 65.6)		
Self-report YSR	Total problems t-score	44	57.9(55.0, 60.8)	41	57.6(54.5, 60.6)	58.4(54.6, 62.2)	0.8(-3.1, 4.8)	0.7	15	55.1(50.9, 59.2)	56.5(50.6, 62.5)	1.5(-3.4, 6.3)	0.5
	Total problems z-score (ref: Netherlands)	44	1.01(0.67, 1.36)	41	0.97(0.62, 1.33)	0.99(0.55, 1.42)			15	0.66(0.17,1.15)	0.65(-0.05, 1.36)		
	Total problems z-score (ref: Australia)	44	0.72(0.37, 1.06)	41	0.68(0.32, 1.03)	0.68(0.24, 1.12)			15	0.39(-0.11,0.89)	0.37(-0.32, 1.07)		
	Externalising problems t-score	44	52.3(49.2, 55.5)	41	52.3(49.2, 55.4)	52.5(48.7, 56.3)			15	53.1(48.5, 57.6)	52.3(45.3, 59.4)		
	Internalising problems t-score	44	58.0(54.9, 61.2)	41	57.7(54.3, 61.0)	60.1(55.9, 64.3)			15	53.9(49.9, 58.0)	55.9(50.8, 61.1)		
Self-harm scores													
Parent report CBCL	Median (IQR)	43	0(0, 1)	40	0(0, 1)	0(0, 1)		0.3	20	0(0, 1)	0(0, 1)		>0.9
Self-report YSR	Median (IQR)	43	0(0, 1)	39	0(0, 1)	0(0, 2)		0.4	15	0(0, 0)	0(0, 0)		0.3
				36 months									
					Baseline for those followed up	Follow-up	Change	p					
				n	mean (95% CI)	mean (95% CI)	mean (95% CI)						
Parent report CBCL	Total problems t-score			11	62.4(55.1, 69.6)	61.1(52.3, 69.9)	-1.3(-6.6, 4.0)	0.6					
	Externalising problems t-score			11	56.8(48.0, 65.6)	56.2(48.3, 64.1)							
	Internalising problems t-score			11	60.4(53.5, 67.2)	62.5(53.6, 71.5)							
Self-harm scores													
Parent report CBCL	Median (IQR)			11	0(0, 1)	0(0, 1)		0.8					

https://doi.org/10.1371/journal.pone.0243894.t004

comfortable with puberty suspended. A further 17% reported both positive and negative changes including less body hair but continued growth in height, or having clearer skin but also experiencing more hunger, weight gain and tiredness. 17% reported largely negative changes such as mood swings, tiredness and hot flushes whilst 10% reported no change.

Reports of change in mood were mixed. At 6–15 months, the majority reported mood to be improved (49%), mixed changes (such as both feeling happier but experiencing some mood swings; 15%) or no change (7%), however 24% reported negative changes in mood such as

Table 5. Other psychological outcomes at baseline, 12, 24 and 36 months.

		Baseline		12 months		24 months		36 months	
		n	mean (95% CI)	n	mean (95% CI)	n	mean (95% CI)	n	mean (95% CI)
Kidscreen-52 HRQOL									
Parent report CBCL t-scores	Physical wellbeing	42	44.9(41.4, 48.5)	36	40.4(37.5, 43.3)	14	40.5(36.8, 44.2)		
	Psychological Wellbeing	41	39.8(36.7, 42.8)	36	39.0(35.4, 42.6)	14	42.4(36.9, 48)		
	Moods and Emotions	41	40.6(37.6, 43.6)	36	41.2(37.3, 45.1)	14	42.5(36.3, 48.7)		
	Self-perception	42	34.6(32.6, 36.5)	36	34.8(32.0, 37.5)	14	34.8(31.3, 38.2)		
	Autonomy	42	46.2(43.2, 49.2)	36	48.2(45.0, 51.4)	14	46.7(41, 52.4)		
	Parent relations and home life	42	48.1(44.5, 51.6)	35	46.7(42.9, 50.5)	14	49.5(44.1, 54.9)		
	Social support and peers	39	48.0(44.7, 51.4)	36	51.9(48.4, 55.3)	13	51.4(45.6, 57.2)		
	School environment	42	38.2(35.0, 41.4)	35	39.4(35.3, 43.4)	13	43.7(36, 51.3)		
	Social acceptance	39	44.7(40.7, 48.7)	32	42.3(38.1, 46.4)	13	43.5(35.9, 51.2)		
	Financial resources	42	37.9(33.9, 41.9)	36	35.8(31.5, 40.2)	14	36.3(26.4, 46.3)		
Self-report t-scores	Physical wellbeing	42	45.1(41.8, 48.5)	36	41.5(38.0, 45.0)	13	43.9(38.9, 48.9)		
	Psychological Wellbeing	42	43.0(39.6, 46.4)	36	41.1(37.0, 45.2)	14	51(45.8, 56.2)		
	Moods and Emotions	42	46.3(42.7, 49.9)	36	43.9(40.4, 47.3)	14	50.1(45.5, 54.7)		
	Self-perception	42	38.8(36.7, 40.9)	36	37.9(35.1, 40.6)	14	43.1(39.9, 46.2)		
	Autonomy	42	46.6(43.6, 49.6)	36	46.7(42.9, 50.5)	13	51.9(47.4, 56.4)		
	Parent relations and home life	42	49.7(46.2, 53.2)	36	48.7(45.2, 52.3)	14	58.4(53.3, 63.5)		
	Social support and peers	37	45.6(42.5, 48.7)	35	48.1(44.6, 51.6)	14	49.7(44.3,55.1)		
	School environment	41	45.9(42.3, 49.4)	36	44.7(39.7, 49.7)	14	49(43.6, 54.3)		
	Social acceptance	41	47.4(43.5, 51.3)	33	45.5(40.9, 50.1)	13	53.6(46.3, 60.8)		
	Financial resources	42	42.2(38.1, 46.3)	34	43.2(38.2, 48.1)	14	46.3(39.1, 53.5)		
Body image scale	Overall score	42	3.1(2.8, 3.3)	40	3.2(3.0, 3.4)	16	3(2.7, 3.2)	8	3.1(2.4, 3.7)
	Primary characteristics score	42	4.5(4.2, 4.7)	39	4.3(4.2, 4.5)	16	4.5(4.3, 4.7)	8	4.2(3.9, 4.5)
	Secondary characteristics score	41	2.9(2.6, 3.1)	40	3(2.8, 3.3)	16	2.9(2.5, 3.2)	8	2.9(2, 3.8)
	Neutral characteristics score	42	2.5(2.203, 2.707)	40	2.7(2.5, 3.0)	-	-		
Utrecht Gender dysphoria score	Median (IQR)	41	4.8(4.6, 5.0)	40	4.7(4.6, 5.0)	18	4.7(4.3, 5.0)		
Clinical outcome									
CGAS global score	Mean (95% CI)	42	62.9(59.6, 66.2)	35	64.1(59.9, 68.3)	18	65.7(59.6, 71.8)	12	66.0(58.1, 73.9)

Note: Change in outcomes in this Table were not formally tested.

https://doi.org/10.1371/journal.pone.0243894.t005

Table 6. Associations between birth-registered sex and baseline pubertal status and outcomes at 12 months.

		Outcomes at 12 months adjusted for baseline								
		BMD at lumbar spine			YSR total t-score			GCAS score		
		n	Coefficient (95% CI)	p	n	Coefficient (95% CI)	p	n	Coefficient (95% CI)	p
Birth-registered sex										
Main effect (baseline value of outcome)		43	0.86 (0.75, 0.97)	<0.0001	41	0.43 (0.05, 0.82)	0.03	33	0.74 (0.42, 1.06)	<0.0001
Birth-registered sex	Male (ref)		0			0			0	
	Female		-0.02 (-0.05, 0.01)	0.2		2.1 (-5.2, 9.4)	0.6		-3.2 (-10.0, 3.5)	0.3
Pubertal status										
Main effect (baseline value of outcome)		43	0.85 (0.72, 0.97)	<0.0001	41	0.43 (0.01, 0.84)	0.04	33	0.69 (0.37, 1.00)	<0.0001
Pubertal stage at baseline	3		0.008 (-0.03, 0.04)	0.7		0.2 (-8.3, 8.7)	0.9		1.6 (-5.5, 8.8)	0.6
	4 (ref)		0			0			0	
	5		-0.009 (-0.05, 0.03)	0.7		0.4 (-9.9, 10.8)	0.9		-7.9 (-17.6, 1.8)	0.11

https://doi.org/10.1371/journal.pone.0243894.t006

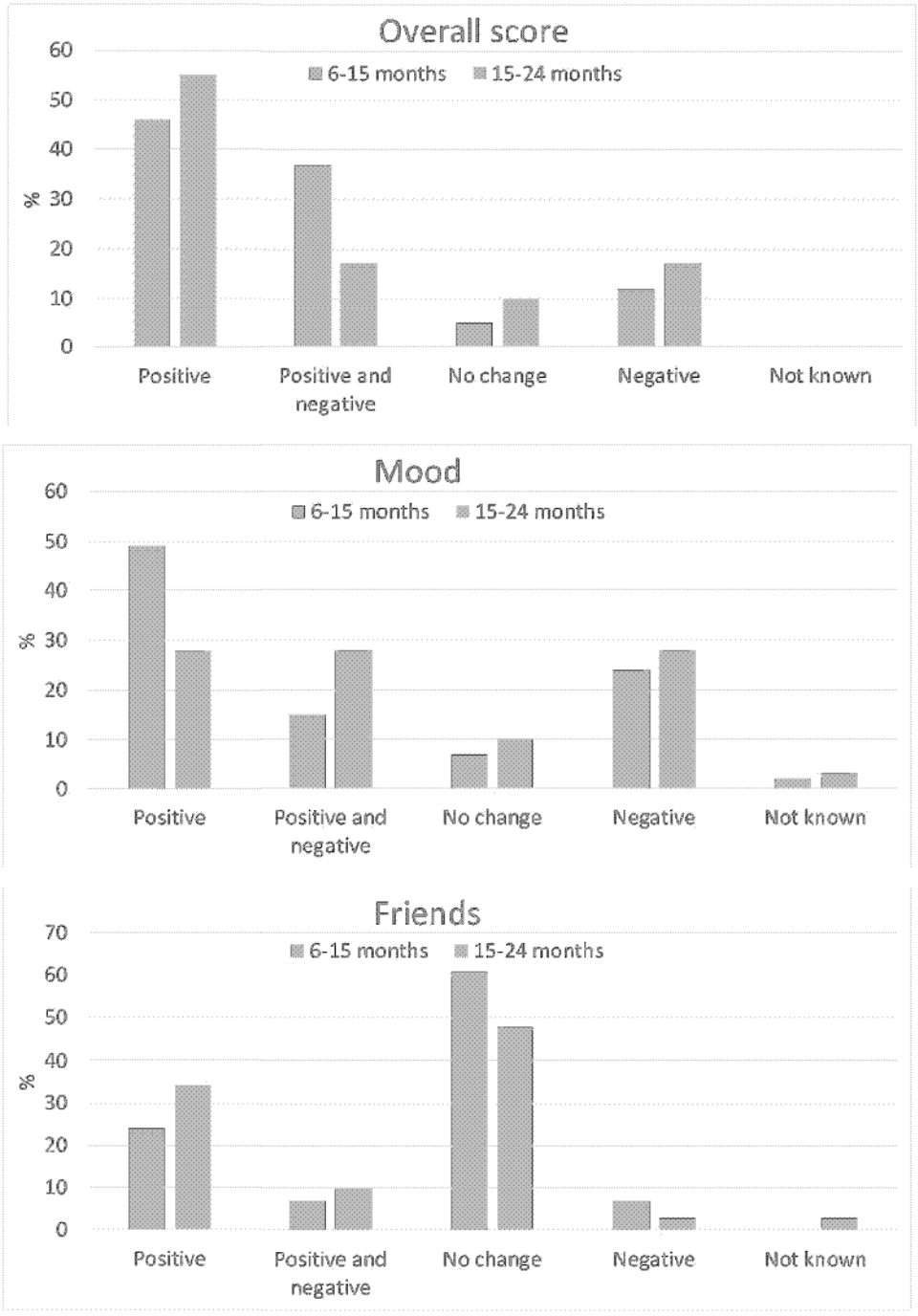


Fig 1. Ratings of change in life overall, mood and friendships at 6–15 months (n = 41) and 15–24 months (n = 29).

https://doi.org/10.1371/journal.pone.0243894.g001

experiencing more mood swings or feeling low. Findings at 15–24 months were similar. The most common negative change was reduced energy levels, reported by 29% at 6-15m and 38% at 15-24m.

Young people's reports of change in family and peer relationships were predominantly positive or neutral at both time points. Positive changes included feeling closer to the family,

Table 7. Adverse events reported across the study.

Participants	0-6m	7-12m	13-24m	25+m
	n = 44	n = 44	n = 36	n = 24
	n (%)	*n (%)*	*n (%)*	*n (%)*
Mild headaches or hot flushes	11 (25%)	10 (23%)	8 (22%)	4 (17%)
Moderate or severe headaches and hot flushes	2 (5%)	4 (9%)	1 (3%)	0
Fatigue—mild	2 (5%)	3 (7%)	3 (8%)	1 (4%)
Fatigue–moderate or severe	0	0	0	0
Mood swings	1 (2%)	0	0	0
Weight gain	1 (2%)	0	1 (3%)	0
Sleep problems	1 (2%)	0	1 (3%)	0
Other events	0	0	0	0
Total events recorded*	18	17	14	5

* individuals may have more than 1 event.

https://doi.org/10.1371/journal.pone.0243894.t007

feeling more accepted and having fewer arguments. Those reporting both positive and negative change reported feeling closer to some family members but not others. At 6–15 months, negative family changes were largely from family members not accepting their trans status or having more arguments. But by 15–24 months only one young person reported this. Improved relationships with peers related to feeling more sociable or confident and widening their circle of friends; negative changes related to bullying or disagreements at school. Again, at 15–24 months only one young person reported negative change, related to feelings of not trusting friends.

At 6–15 months, changes in gender role were reported by 66% as positive, including feeling more feminine/masculine, living in their preferred gender identity in more (or all) areas of life and feeling more secure in their gender identity, with no negative change reported. At 15–24 months, most reported no change although 41% reported positive changes including experimenting more with physical appearance and changing their details on legal documents.

All young people affirmed at each interview that they wished to continue with GnRHa treatment. Note that this was also the case when asked routinely at medical clinics (excepting those who briefly ceased GnRHa as noted above).

Adverse events. Adverse events are shown in Table 7. All adverse events were minor and anticipated, i.e. they were previously described in study participant information and/or noted in the triptorelin medication package inserts. Anticipated adverse events were common in the first two years, particularly mild headaches or hot flushes which were reported in 25% at 0-6m, 23% at 7-12m and 22% at 13-24m. Moderate or severe headaches and/or hot flushes were uncommon. Birth-registered females with distressing headaches or hot flushes were offered 'add-back' oestrogen therapy, and two accepted treatment briefly with very small doses of oestradiol, which was effective in reducing symptoms. Mild fatigue was reported by 5–8% over the first two years and no participants reported moderate or severe fatigue. Sleep problems, mood swings and weight gain were reported by very small numbers and in each case symptoms were mild. Adverse events were less common after 12 months of treatment.

Discussion

We report the short and medium-term outcomes of a prospective cohort of 44 young people with persistent and severe GD treated with GnRHa resulting in pubertal suppression from mid-puberty for 1–4 years. Young people were considered for recruitment after lengthy

assessment, spending an average of 2 years and up to 6 years within the GIDS psychological service before being referred to the endocrine clinic for assessment to enter the study. Medical assessment found no endocrine abnormalities at baseline. GnRHa treatment started in the majority of participants in later stages of puberty, with 57% in puberty stages 4 and 5 and 79% of birth-registered females being post-menarcheal. After starting GnRHa all quickly achieved and maintained suppression of pubertal hormones and none experienced pubertal progression. At the end of the study, 43 (98%) chose to start cross-sex hormones whilst one young person chose to stop GnRHa and continue with puberty consistent with their birth-registered sex.

As anticipated, pubertal suppression reduced growth that was dependent on puberty hormones, i.e. height and BMD. Height growth continued for those not yet at final height, but more slowly than for their peers so height z-score fell. Similarly for bone strength, BMD and BMC increased in the lumbar spine indicating greater bone strength, but more slowly than in peers so BMD z-score fell. These anticipated changes had been discussed with all participants before recruitment to the study. Young people experienced little change in mean weight or BMI z-score in the first two years. The rise in weight and BMI z-score at 36 months may represent a trend towards greater adiposity in those on GnRHa for a prolonged period, or reflect a higher baseline in this group.

Information on side-effects was available through routine reporting in medical clinics and in the participant experience interviews. Anticipated side effects of treatment were common, particularly mild symptoms directly related to suppression of sex hormones. Severe symptoms were uncommon. Fatigue or low energy was reported rarely in medical clinic assessments but frequently at interview (38% at 15-24m). The relationship of symptoms such as headaches, fatigue and sleep disturbance to GnRHa treatment is unclear as they are all very common in early adolescence [36,37], although a conservative perspective would regard them as side-effects of treatment.

Young people experienced little change in psychological functioning across the study. We found no differences between baseline and later outcomes for overall psychological distress as rated by parents and young people, nor for self-harm. Outcomes that were not formally tested also showed little change.

Participant experience of treatment as reported in interviews was positive for the majority, particularly relating to feeling happier, feeling more comfortable, better relationships with family and peers and positive changes in gender role. Smaller numbers reported having mixed positive and negative changes. A minority (12% at 6–15 months and 17% at 15–24 months) reported only negative changes, which were largely related to anticipated side effects. None wanted to stop treatment due to side effects or negative changes. We are not aware of comparative patient experience data from other cohorts.

The median age at consent in our study was very similar to that in the earliest published outcome study of mid-pubertal suppression using GnRHa treatment in Dutch young people (13.6 years) [24]. Similarly to this Dutch cohort, all but one of our participants elected to start cross-sex hormones after completing the GnRHa pathway. However they spent an average of 31 months on GnRHa compared with 23 months in the Dutch cohort [24]. In our study, the successful suppression of puberty and cessation of menses with GnRHa, the impact on height growth [4,16,38] and BMD [4,16] and the normality of liver and renal function through treatment were each consistent with previous reports [4,16].

Our findings that BMD increased over time in the lumbar spine but more slowly than in same age peers, resulting in a fall in z-score, are similar to others [4,14,39,40]. The fall in height-adjusted BMD z-score was consistent with but larger than the fall in height z-score. We found that birth-registered sex and pubertal status at baseline were not associated with later BMD. There is evidence that accretion of bone mass resumes and that BMD increases with the

start of cross-sex hormone therapy [4,14,39,41]. Future research needs to examine longer-term change in BMD in young people treated with mid-pubertal suppression.

We reported a range of adverse events previously described to be associated with pubertal suppression [42], with the exception of mild sleep disturbance although this is a known association with triptorelin use. As anticipated, the withdrawal of sex hormones produces symptoms such as headaches and lack of energy, although in the great majority (11 of 13 at 0–6 months; 10 of 14 at 7–12 months; 8 of 9 at 13–24 months) the symptoms were minor. Symptoms diminished over time as has previously been noted [4], and no young people chose to cease treatment due to the side-effects.

Our finding that 1 participant ceased pubertal suppression and did not commence cross-sex hormones is somewhat similar to the experience of one US cohort and a second Dutch cohort; Kuper et al. described that 2 of approximately 57 young people aged 10–15 years who commenced pubertal suppression treatment stopped this treatment without commencing cross-sex hormones [17]. Brik et al. reported that in a cohort of 137 young people who began GnRHa between 10 and 18 years and were followed until eligible to commence cross-sex hormones, 5 (3.6%) ceased treatment and did not later commence cross-sex hormones [19].

Three longitudinal studies from the Netherlands and the USA have examined psychological function over time in cohorts of young people treated with GnRHa and then cross-sex hormones [17,18,24], although the two US cohorts were of limited size. Our study adopted the same psychological outcome measures as the Dutch cohort, to facilitate comparison [24]. Mean baseline YSR scores in our cohort were similar to those previously reported in 141 young people aged 12–18 years from the London GIDS [43], and baseline CBCL and YSR scores were close to those at baseline from the original Dutch cohort [24]. A number of other studies have shown that young people with GD have higher scores on the CBCL or YSR than same-age population peers, and that they are similar to young people referred to clinical services for a range of mental health problems [44–46]. Population-based studies in America support higher baseline levels of mental health problems amongst young people with GD, with the prevalence of self-harm notably higher than for male or female peers [47,48]. Young people in our study had baseline YSR scores 0.7–1.0 SD higher than norms for age in comparable countries [29,46].

We found no evidence of change in psychological function with GnRHa treatment as indicated by parent report (CBCL) or self-report (YSR) of overall problems, internalising or externalising problems or self-harm. This is in contrast to the Dutch study which reported improved psychological function across total problems, externalising and internalising scores for both CBCL and YSR and small improvements in CGAS [24]. It also contrasts with a previous study from the UK GIDS of change in psychological function with GnRHa treatment in 101 older adolescents with GD (beginning > 15.5 years) which reported moderate improvements in CGAS score over 12 months of GnRHa treatment [49]. CGAS scores in this previous study increased from 61 to 67 with GnRHa treatment, similar to those (63 at baseline, 66 at 24 months) in our study. Follow-up of the Kuper et al. cohort found non-significant changes in depression and anxiety scores in those (n = 25) who had only pubertal suppression treatment, although improvements were seen in the whole sample combining these with those receiving cross-sex hormones [17]. A second US cohort reported that in 23 young people who had received pubertal suppression (using GnRHa or anti-androgens in birth-registered males and either GnRHa or medroxyprogesterone in birth-registered females), there was a reduction in depression scores in birth-registered males but not females.

A recent large US survey found that those who received pubertal suppression in early or mid adolescence had lower odds of lifetime suicidal ideation when studied in adulthood compared with those who did not, regardless of whether they later received cross-sex hormones

and after adjustment for a range of confounding factors [50]. This implies an enduring benefit of pubertal suppression on psychological function, however the cross-sectional design and retrospective exposure classification means the findings require replication. Data are also available from other conditions in which GnRHa is used to suppress puberty during adolescence. A trial of GnRHa suppression of puberty during early adolescence in young people born small-for-gestational-age (SGA) who were also treated with human growth hormone (GH) reported that those treated with GnRHa had similar cognitive and psychological function in adult life to those treated only with GH [51].

The differences between our findings and the previous GIDS study re change in psychological function may relate simply to sample size. But why our findings differ from those of the Dutch study is unclear. They may relate to the timing of assessments; we assessed young people multiple times whereas in the Dutch study the second assessment was shortly before starting cross-sex hormone treatment. Alternatively, there may have been baseline differences in the two cohorts. Whilst some aspects of psychological function were similar, as noted above, the baseline CGAS scores were notably higher in the Dutch group (indicating better function). A previous international comparison study has found that young people aged 12–18 years with GD from the UK have higher scores indicating greater problems on the CBCL and YSR than those from the Netherlands, Belgium and Switzerland [52].

Psychological distress and self-harm are known to increase across early adolescence. Normative data show rising YSR total problems scores with age from age 11 to 16 years in non-clinical samples from a range of countries [29]. Self-harm rates in the general population in the UK and elsewhere increase markedly with age from early to mid-adolescence, being very low in 10 year olds and peaking around age 16–17 years [53–56]. Our finding that psychological function and self-harm did not change significantly during the study is consistent with two main alternative explanations. The first is that there was no change, and that GnRHa treatment brought no measurable benefit nor harm to psychological function in these young people with GD. This is consonant with the action of GnRHa, which only stops further pubertal development and does not change the body to be more congruent with a young person's gender identity. The second possibility is that the lack of change in an outcome that normally worsens in early adolescence may reflect a beneficial change in trajectory for that outcome, i.e. that GnRHa treatment reduced this normative worsening of problems. In the absence of a control group, we cannot distinguish between these possibilities. We aimed to use normative reference data to examine this issue. However age- and gender-standardised t-scores for ASEBA and other outcomes cannot answer this question as they cover a very broad age range (e.g. 12–18 years). We had anticipated that z-scores on the YSR available by calendar year for two comparable countries (Netherlands; Australia) might be informative however confidence intervals were too wide to draw reliable inferences.

Gender dysphoria and body image changed little across the study. This is consistent with some previous reports [24] and was anticipated, given that GnRHa does not change the body in the desired direction, but only temporarily prevents further masculinization or feminization. Other studies suggest that changes in body image or satisfaction in GD are largely confined to gender affirming treatments such as cross-sex hormones or surgery [57]. We found that birth-registered sex and baseline pubertal status were not associated with later psychological functioning on GnRHa, consistent with previous reports [24,49].

These data correct reports from a recent letter by Biggs [58] which used preliminary data from our study which were uncleaned and incomplete data used for internal reporting. In addition there were many statistical comparisons which inflated the risk of type 1 error. Our statistical analysis plan restricted testing all outcomes for differences by sex due to the type 1

error risk. Contrary to Biggs's letter, we found no evidence of reductions over time in any psychological outcomes, and no material differences by sex.

Strengths and limitations

Our study provides comprehensive data on this cohort during follow-up, with an anonymised dataset containing standardised scores deposited to allow other researchers to replicate our findings where data-sharing allows. The study size and uncontrolled design were key limitations. The small sample size limited our ability to identify small changes in outcomes. This was an uncontrolled observational study and thus cannot infer causality. Further, many of the outcomes studied here, including psychological function, self-harm and BMD, undergo normative changes by age and developmental stage during puberty that could confound any observed effect of GnRHa treatment in an uncontrolled study. The analysis plan aimed to take these issues into account as far as possible, however this particularly limits the potential for the study to show benefits or harms from treatment. However, some conclusions can be drawn. It is unlikely that the reported adverse events such as headaches do not relate directly to GnRHa treatment. Equally, given that there were no changes in psychological function and differences in point estimates were minimal for nearly all outcomes, it is unlikely that the treatment resulted in psychological harm. Observational studies are important sources of data on harms of treatment [59–61].

Our data are subject to a number of other limitations. This was an unfunded study undertaken within a clinical service and we were dependent on the clinical service for data collection. There were varying sample sizes for differing tests as some participants did not attend certain investigations and some follow-up medical tests were processed locally to patients; these data are reported as normal or otherwise. Missing items on psychological questionnaires resulted in some unusable data. Some young people found repeated completion of questionnaires about gender issues intrusive and refused to complete them at later follow-ups, as has been reported in other studies [62]. This questionnaire fatigue also affected parent responses. Scoring of psychological questionnaire data was rechecked at the completion of the study however this was not possible in very small numbers of participants in whom only scale scores rather than individual item data were preserved during data migration in hospital clinical information systems. In sensitivity analyses, repeat analysis of ASEBA psychological outcomes restricted to those with rescored data showed highly similar findings to the full sample (see S3 Table in S1 Appendix).

A more detailed qualitative evaluation of participant experience was not possible due to lack of interviewer time, and reporting of interview data was restricted to perceptions of positive or negative change and the giving of examples.

Implications and conclusions

Treatment of young people with persistent and severe GD aged 12–15 years with GnRHa was efficacious in suppressing pubertal progression. Anticipated effects of withdrawal of sex hormones on symptoms were common and there were no unexpected adverse events. BMD increased with treatment in the lumbar spine and was stable at the hip, and BMD z-score fell consistent with delay of puberty. Overall participant experience of changes on GnRHa treatment was positive. We identified no changes in psychological function, quality of life or degree of gender dysphoria.

The great majority of this cohort went on to start cross-sex hormones, as was hypothesized given the severity and continuation of their GD. However one young person did not, providing some evidence that development of gender identity continues on GnRHa treatment and

confirming the importance of continuing supportive psychological therapy to allow further exploration of gender identity and a range of future pathways whilst on GnRHa.

This cohort will be followed up longer term to examine physical and mental health outcomes into early adulthood. However larger and longer-term prospective studies using a range of designs are needed to more fully quantify the harms and benefits of pubertal suppression in GD and better understand factors influencing outcomes [3]. These are beginning to be funded in a number of countries [63].(https://logicstudy.uk) Given that pubertal suppression may be both a treatment in its own right and also an intermediate step in a longer treatment pathway, it is essential for such studies to examine benefits and harms across the longer pathway including pubertal suppression and initiation of cross-sex hormones.

Supporting information

S1 Appendix.
(DOCX)

S2 Appendix. Statistical analysis plan.
(DOCX)

Acknowledgments

We wish to thank the young people and families who participated in the study and the clinical teams at The Tavistock and Portman NHS Foundation Trust and UCL Hospitals NHS Foundation Trust.

We wish to acknowledge the inputs of Harriet Gunn, Claudia Zitz and Domenico di Ceglie for their work in formulating the study, collecting data and advising on the manuscript.

Author Contributions

Conceptualization: Polly Carmichael, Gary Butler, Elin M. Skageberg, Sophie Khadr, Russell M. Viner.

Data curation: Una Masic, Russell M. Viner.

Formal analysis: Tim J. Cole, Bianca L. De Stavola, Russell M. Viner.

Investigation: Gary Butler, Una Masic.

Methodology: Polly Carmichael, Bianca L. De Stavola, Elin M. Skageberg, Russell M. Viner.

Writing – original draft: Polly Carmichael, Gary Butler, Russell M. Viner.

Writing – review & editing: Polly Carmichael, Gary Butler, Una Masic, Tim J. Cole, Sarah Davidson, Sophie Khadr, Russell M. Viner.

References

1. Diagnostic and statistical manual of mental disorders (DSM-V). 5th ed. Arlington, VA: American Psychiatric Association; 2013.
2. International Statistical Classification of Diseases and Related Health Problems (ICD-11). Geneva: World Health Organisation, 2019.
3. Mahfouda S, Moore JK, Siafarikas A, Zepf FD, Lin A. Puberty suppression in transgender children and adolescents. Lancet Diabetes Endocrinol. 2017; 5(10):816–26. Epub 2017/05/27. https://doi.org/10.1016/S2213-8587(17)30099-2 PMID: 28546095.
4. Chew D, Anderson J, Williams K, May T, Pang K. Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. Pediatrics. 2018; 141(4). Epub 2018/03/09. https://doi.org/10.1542/peds.2017-3742 PMID: 29514975.

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Psychosocial Functioning in Transgender Youth after 2 Years of Hormones

Diane Chen, Ph.D., Johnny Berona, Ph.D., Yee-Ming Chan, M.D., Ph.D., Diane Ehrensaft, Ph.D., Robert Garofalo, M.D., M.P.H., Marco A. Hidalgo, Ph.D., Stephen M. Rosenthal, M.D., Amy C. Tishelman, Ph.D., and Johanna Olson-Kennedy, M.D.

ABSTRACT

BACKGROUND

Limited prospective outcome data exist regarding transgender and nonbinary youth receiving gender-affirming hormones (GAH; testosterone or estradiol).

METHODS

We characterized the longitudinal course of psychosocial functioning during the 2 years after GAH initiation in a prospective cohort of transgender and nonbinary youth in the United States. Participants were enrolled in a four-site prospective, observational study of physical and psychosocial outcomes. Participants completed the Transgender Congruence Scale, the Beck Depression Inventory–II, the Revised Children's Manifest Anxiety Scale (Second Edition), and the Positive Affect and Life Satisfaction measures from the NIH (National Institutes of Health) Toolbox Emotion Battery at baseline and at 6, 12, 18, and 24 months after GAH initiation. We used latent growth curve modeling to examine individual trajectories of appearance congruence, depression, anxiety, positive affect, and life satisfaction over a period of 2 years. We also examined how initial levels of and rates of change in appearance congruence correlated with those of each psychosocial outcome.

RESULTS

A total of 315 transgender and nonbinary participants 12 to 20 years of age (mean [±SD], 16±1.9) were enrolled in the study. A total of 190 participants (60.3%) were transmasculine (i.e., persons designated female at birth who identify along the masculine spectrum), 185 (58.7%) were non-Latinx or non-Latine White, and 25 (7.9%) had received previous pubertal suppression treatment. During the study period, appearance congruence, positive affect, and life satisfaction increased, and depression and anxiety symptoms decreased. Increases in appearance congruence were associated with concurrent increases in positive affect and life satisfaction and decreases in depression and anxiety symptoms. The most common adverse event was suicidal ideation (in 11 participants [3.5%]); death by suicide occurred in 2 participants.

CONCLUSIONS

In this 2-year study involving transgender and nonbinary youth, GAH improved appearance congruence and psychosocial functioning. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.)

The authors' affiliations are listed in the Appendix. Dr. Chen can be contacted at dichen@luriechildrens.org or at the Ann and Robert H. Lurie Children's Hospital of Chicago, Potocsnak Family Division of Adolescent and Young Adult Medicine, 225 E. Chicago Ave., Box 161B, Chicago, IL 60611.

N Engl J Med 2023;388:240-50.
DOI: 10.1056/NEJMoa2206297

TRANSGENDER AND NONBINARY YOUTH comprise 2 to 9% of high-school–aged persons in the United States.[1-3] Many transgender and nonbinary youth have gender dysphoria, the persistent distress arising from incongruence between gender identity and external phenotype. Increasingly, transgender and nonbinary youth receive medical care to alleviate gender dysphoria, including gonadotropin-releasing hormone (GnRH) agonists to suppress gender-incongruent puberty and gender-affirming hormones (GAH; testosterone or estradiol) to foster gender-congruent secondary sex characteristics. An important goal of such treatment is to attenuate gender dysphoria by increasing appearance congruence — that is, the degree to which youth experience alignment between their gender and their physical appearance.

The available prospective research indicates that gender-affirming medical care is associated with improvements in psychosocial functioning.[4-9] Previously published studies with modest sample sizes[5,6,9] have examined outcomes for relatively short follow-up periods (approximately 1 year on average),[5,6,9] focused exclusively on outcomes of GnRH agonists,[7,8] or examined outcomes for mixed samples of youth initiating GnRH agonists or GAH,[4,6,9] despite evidence that such cohorts have distinct psychosocial profiles.[10] Evidence has been lacking from longitudinal studies that explore potential mechanisms by which gender-affirming medical care affects gender dysphoria and subsequent well-being.

We characterized the longitudinal course of psychosocial functioning over a period of 2 years after GAH initiation in a prospective cohort of more than 300 transgender and nonbinary young people in the United States. We hypothesized that appearance congruence, positive affect, and life satisfaction would increase and that depression and anxiety symptoms would decrease. We also hypothesized that improvements would be secondary to treatment for gender dysphoria, such that increasing appearance congruence would be associated with concurrent improvements in psychosocial outcomes. We also explored the potential moderating effects of demographic and clinical characteristics, including age, designated sex at birth, racial and ethnic identity, and the initiation of GAH in early as compared with later stages of puberty.

METHODS

STUDY DESIGN AND PARTICIPANT RECRUITMENT

Participants were recruited from gender clinics at the Ann and Robert H. Lurie Children's Hospital of Chicago, UCSF Benioff Children's Hospitals, Boston Children's Hospital, and Children's Hospital Los Angeles from July 2016 through June 2019 for the Trans Youth Care–United States (TYCUS) Study,[11] a prospective, observational study evaluating the physical and psychosocial outcomes of medical treatment for gender dysphoria in two distinct cohorts of transgender and nonbinary youth — those initiating GnRH agonists and those initiating GAH as part of their clinical care. All participating clinics employ a multidisciplinary team that includes medical and mental health providers and that collaboratively determines whether gender dysphoria is present and whether gender-affirming medical care is appropriate. For minors, parental consent is required to initiate medical treatment. Publications by individual study teams provide details on site-specific approaches to care.[12-15]

Study visits occurred at baseline and at 6, 12, 18, and 24 months after treatment initiation. Details on study procedures have been published previously,[11] and the protocol is available with the full text of this article at NEJM.org. The present analyses focus on the GAH cohort; outcomes for the cohort initiating GnRH agonists are being analyzed separately, given differences in baseline functioning between the two cohorts[10] and distinct outcomes of GnRH agonists[8] as compared with GAH treatment.[4] Participants provided written informed consent or assent; parents provided permission for minors to participate. Procedures were approved by the institutional review board at each study site.

The first and second authors analyzed the data and wrote the initial draft of the manuscript. All the authors critically reviewed the manuscript. The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol. There were no agreements regarding confidentiality of the data among the sponsor (Eunice Kennedy Shriver National Institute of Child Health and Human Development), the authors, and the participating institutions. The sponsor had no role in the design of the study; the collection, analysis, or in-

terpretation of data; the writing of the manuscipt; or the decision to submit the manuscript for publication.

MEASURES

Participants reported age, racial and ethnic identity, gender identity, and designated sex at birth (details are provided in the Supplementary Appendix, available at NEJM.org). A small subgroup had been treated with GnRH agonists in early puberty (Tanner stage 2 or 3) (20 participants) or had a relatively late age at onset of endogenous puberty, such that they began receiving GAH in Tanner stage 3 (at 13 to 15 years of age) even without previous treatment with GnRH agonists (4 participants). These 24 participants comprise a subcohort in that they did not undergo extensive gender-incongruent puberty. Participants with a history of GnRH agonist treatment that was initiated in Tanner stage 4 (5 participants) were not included in this subcohort, because their experience of substantial gender-incongruent puberty is more similar to that of youth initiating GAH in Tanner stage 4 or 5.

With respect to longitudinal outcomes, participants completed the Transgender Congruence Scale,[16] the Beck Depression Inventory–II,[17] the Revised Children's Manifest Anxiety Scale (Second Edition),[18] and the Positive Affect and Life Satisfaction measures from the NIH (National Institutes of Health) Toolbox Emotion Battery[19] at each study visit. Scoring information and sample items from each scale are provided in the Supplementary Appendix. Higher scores on these measures reflect greater appearance congruence, depression, anxiety, positive affect, and life satisfaction, respectively.

STATISTICAL ANALYSIS

Trajectories of psychosocial functioning were examined with the use of repeated-measures multivariate analysis of variance and mixed-effects models. Multivariate analysis of variance provided a preliminary omnibus test for significant within-person change over time. Owing to listwise deletion, 150 participants were excluded from the multivariate analysis of variance (the analysis involved 141 participants). Mixed-effects modeling was therefore selected owing to greater flexibility in accommodating missing data and nonnormal distributions and examining parallel processes. Specifically, we used latent growth curve modeling, which uses a structural equation modeling framework to examine changes in mean scores over time.[20] Repeated measures are treated as indicators of latent factors: an intercept factor (estimates of initial levels) and a slope factor (rate of change). Intercept and slope factors can be regressed on covariates in adjusted models to explore moderation effects. In addition, growth curves for two different outcomes can be combined to examine how intercepts and slopes of those constructs correlate with each other. Data were Winsorized at the 95th percentile to reduce the influence of outliers.

Analyses involving latent growth curve modeling proceeded in three steps. First, we modeled trajectories of appearance congruence and psychosocial outcomes (i.e., effects of time only). Second, we adjusted models to estimate the effects of covariates on baseline scores and rates of change over time. Third, because changes in appearance congruence and psychosocial outcomes occur as parallel, simultaneous processes during GAH treatment, we examined how initial levels and rates of change in appearance congruence correlated with those of each psychosocial outcome. Standardized β levels were used as indicators of effect sizes for longitudinal models using conventional ranges (small, 0.20; medium, 0.50; and large, 0.80). Our conceptual model is shown in Figure S1 in the Supplementary Appendix. All statistical analyses were conducted with the use of SPSS software, version 27, and Mplus software, version 8.8.

RESULTS

ANALYTIC SAMPLE

There were a total of 6114 observations from 315 participants, who were assessed up to five times over a period of 2 years (data were available for 81% of all possible observations). Most participants (238 [75.6%]) completed either four study visits (76 participants) or five visits (162 participants). Tables S1 and S2 show the number of completed visits by time point and data coverage for key variables. The analytic sample for longitudinal models included 291 participants with follow-up data on primary outcome variables (Fig. S2). The analytic sample did not differ substantially from the overall sample with respect to age, designated sex at birth, racial and ethnic

identity, initiation of GAH in early puberty, or baseline scores on psychosocial measures (Table S3).

SAMPLE CHARACTERISTICS

We enrolled 315 eligible participants 12 to 20 years of age (mean [±SD], 16±1.9 years) (Table 1). Most were transmasculine (i.e., persons designated female at birth who identify along the masculine spectrum; 60.3%), designated female at birth (64.8%), and non-Latinx or non-Latine White (58.7%). Transmasculine, non-Latinx or non-Latine White, and multiracial participants were overrepresented and nonbinary and Black participants were underrepresented as compared with the study sample in the Williams Institute Executive Report[21] (Table S4); however, the study sample was representative of transgender and nonbinary youth presenting to pediatric subspecialty gender programs[22] and generalizable to this population. Two participants died by suicide during the study (one after 6 months of follow-up and the other after 12 months of follow-up), and 6 participants withdrew from the study. For these eight participants, data that had been collected before death or study withdrawal were included in the analyses. Data on adverse events are provided in Table 2.

APPEARANCE CONGRUENCE AND PSYCHOSOCIAL OUTCOMES OVER TIME

Table S5 depicts mean scores for appearance congruence, depression, anxiety, positive affect, and life satisfaction at baseline and 24 months. Results for multivariate analysis of variance indicated that there were significant within-participant changes over time for all psychosocial outcomes in hypothesized directions (Wilk's lambda, 0.32; F statistic with 20 and 122 degrees of freedom; 12.86; P<0.001). Specifically, scores for appearance congruence, positive affect, and life satisfaction increased significantly, and scores for depression and anxiety decreased significantly.

Means and variances of the variables for latent growth curve modeling, with estimated baseline levels and change over time for both time-only and adjusted models, are provided in Table 3. Scores for appearance congruence increased (annual increase on a 5-point scale, 0.48 points; 95% confidence interval [CI], 0.42 to 0.54; standardized $\beta=1.47$), as did T scores for positive affect (annual increase on a 100-point scale, 0.80 points; 95% CI, 0.08 to 1.54; $\beta=0.19$) and life satisfaction (annual increase on a 100-point scale, 2.32 points; 95% CI, 1.64 to 3.00; $\beta=0.52$). We observed decreased scores for depression (annual change on a 63-point scale, −1.27 points; 95% CI, −1.98 to −0.57; standardized $\beta=-0.29$) and decreased T scores for anxiety (annual change on a 100-point scale, −1.46 points; 95% CI, −2.13 to −0.79; $\beta=-0.35$) over a period of 2 years of GAH treatment.

Unadjusted models can be interpreted on their original scale. For instance, depression scores range from 0 to 63 (ranges of severity, minimal, 0 to 13; mild, 14 to 19; moderate, 20 to 28; and severe, 29 to 63). The model had an intercept (baseline mean) of 15.46 and estimated slope (change per year) of −1.27. Thus, on average, depression started in the mild range and decreased to the subclinical level by 24 months. Table S6 shows the percentages of youth scoring in the clinical range for depression and anxiety at each time point. Of 27 participants with depression scores in the severe range at baseline, 18 (67%) reported a depression score in the minimal or moderate ranges at 24 months. Similarly, 21 of 33 participants (64%) with depression scores in the moderate range at baseline reported a depression score in the minimal or moderate ranges at 24 months (chi-square statistic with 9 degrees of freedom, 49.85; P<0.001). With respect to anxiety, 47 of 122 participants (38.5%) with baseline scores in the clinical range (T scores, >60) were in the nonclinical range at 24 months (chi-square statistic with 1 degree of freedom, 22.05; P<0.001).

ASSOCIATIONS BETWEEN APPEARANCE CONGRUENCE AND PSYCHOSOCIAL OUTCOMES

Figure 1 depicts parallel processes between appearance congruence and each psychosocial outcome as analyzed by means of latent growth curve modeling. As described above, we used linear latent growth curve modeling to estimate baseline scores (intercepts) and linear rates of change (slopes) of each outcome (see Table 3 for details of each model). In parallel-process models, we examined how the components for latent growth curve modeling for appearance congruence related to those for scores for depression (Fig. 1A) and T scores for anxiety (Fig. 1B), positive affect (Fig. 1C), and life satisfaction

Table 1. Demographic and Clinical Characteristics of the Participants.*

Characteristic	Participants (N=315)
	no. (%)
Gender identity†	
Transmasculine	190 (60.3)
Transfeminine	106 (33.7)
Nonbinary	19 (6.0)
Designated sex at birth	
Female	204 (64.8)
Male	111 (35.2)
Racial and ethnic identity	
Non-Latinx or non-Latine White	185 (58.7)
Latinx or Latine non-White	50 (15.9)
Latinx or Latine White	25 (7.9)
Black	11 (3.5)
Asian or Pacific Islander	10 (3.2)
Multiracial	32 (10.2)
Other	1 (0.3)
Unknown	1 (0.3)
Age at baseline	
12 yr	6 (1.9)
13 yr	23 (7.3)
14 yr	38 (12.1)
15 yr	67 (21.3)
16 yr	55 (17.5)
17 yr	51 (16.2)
18 yr	48 (15.2)
19 yr	15 (4.8)
20 yr	12 (3.8)
Tanner stage at GAH initiation‡	
1	2 (0.6)
2	13 (4.1)
3	9 (2.9)
4	29 (9.2)
5	262 (83.2)
Past use of GnRH agonist	
No	290 (92.1)
Yes	25 (7.9)
Tanner stage at initiation of GnRH agonist	
2	12 (3.8)
3	8 (2.5)
4	5 (1.6)
Not applicable	290 (92.1)
Initiation of GAH in early puberty subcohort§	
No	291 (92.4)
Yes	24 (7.6)

* The table does not include demographic and clinical characteristics for one participant who was accidentally enrolled and did not meet criteria for study eligibility. Percentages may not total 100 because of rounding. GAH denotes gender-affirming hormones, and GnRH gonadotropin-releasing hormone.

† Transmasculine refers to persons designated female at birth who identify along the masculine spectrum. Transfeminine refers to persons designated male at birth who identify along the feminine spectrum.

‡ Three participants began receiving GnRH agonists in either Tanner stage 2 or 3 and subsequently had pubertal regression to Tanner stage 1 or 2 by the time of GAH initiation.

§ This subcohort includes 20 participants who began receiving GnRH agonists at Tanner stage 2 or 3 and 4 participants who had not previously received GnRH agonists but had begun receiving GAH in Tanner stage 3 owing to a relatively late onset of puberty (13 to 15 years of age) and thus did not have physical changes associated with later stages of endogenous puberty. This subcohort does not include 5 participants with a history of initiation of GnRH agonists in Tanner stage 4 and who thus did undergo substantial gender-incongruent puberty.

(Fig. 1D). Higher appearance congruence at baseline was associated with lower baseline scores for depression (r=−0.60) and T scores for anxiety (r=−0.40), and increases in appearance congruence were associated with decreases in scores for depression (r=−0.68) and T scores for anxiety (r=−0.52) over time. In addition, higher appearance congruence at baseline was associated with higher baseline T scores for positive affect (r=0.46) and life satisfaction (r=0.72), and increases in appearance congruence were associated with increases in T scores for positive affect (r=0.74) and life satisfaction (r=0.84) over time.

MODERATING EFFECTS OF DEMOGRAPHIC AND CLINICAL COVARIATES

Table 3 shows the effects of covariates on scores for appearance congruence and depression and T scores for anxiety, positive affect, and life satisfaction. Age was not associated with any outcomes at baseline or over time.

Designated Sex at Birth

Depression and anxiety scores decreased among youth designated female at birth but not among those designated male at birth. Similarly, T scores for life satisfaction increased among youth designated female at birth but not among those designated male at birth (Fig. S3). Designated sex at birth was not associated with any other outcomes at baseline or over time.

Table 2. Adverse Events.

Event	No. of Events in Sample
Any event	15
Death by suicide	2
Suicidal ideation reported during study visit	11
Severe anxiety triggered by study visit	2

Effects of Racial and Ethnic Identity

At baseline, youth of color had higher scores for appearance congruence, lower scores for depression, and higher scores for positive affect than non-Latinx or non-Latine White youth. With respect to change over time, non-Latinx or non-Latine White youth had greater decreases in depression scores than youth of color (Fig. S4). Racial and ethnic identity were not associated with any other outcomes at baseline or over time.

Initiation of GAH in Early Puberty

Youth who had initiated GAH in early puberty had higher scores for appearance congruence, positive affect, and life satisfaction at baseline and lower scores for depression and anxiety at baseline than those who had initiated GAH in later puberty. Tables S7, S8, and S9 provide more information regarding differences between youth initiating GAH in early puberty and those initiating GAH in late puberty. With respect to change over time, youth initiating GAH in later puberty had greater improvements in appearance congruence than those initiating GAH in early puberty (Fig. 2).

DISCUSSION

Understanding the effect of GAH on the psychosocial outcomes of transgender and nonbinary youth would appear crucial, given the documented mental health disparities observed in this population,[10,15,23,24] particularly in the context of increasing politicization of gender-affirming medical care.[25] In our U.S.-based cohort of transgender and nonbinary youth treated with GAH, we found decreases in depression and anxiety symptoms and increases in positive affect and life satisfaction as assessed through validated instruments. Our findings are consistent with those of other longitudinal studies involving transgender and nonbinary youth receiving GAH, which showed reductions in depression[6,9] and anxiety[6] and increases in overall well-being[5] with small-to-moderate effects over a follow-up period of up to 1 year. We replicated these findings in a larger sample of racially and ethnically diverse transgender and nonbinary youth recruited from four geographically distinct regions in the United States and found sustained improvements over a period of 2 years.

Increasing appearance congruence is a primary goal of GAH, and we observed appearance congruence improve over 2 years of treatment. This was a moderate effect, and the strongest effect observed across our outcomes, consistent with the effect seen in research involving other samples, which has noted large effects of GAH on body image and small-to-moderate effects on mental health.[6] Appearance congruence was also associated with each psychosocial outcome assessed at baseline and during the follow-up period, such that increases in appearance congruence were associated with decreases in depression and anxiety symptoms and increases in positive affect and life satisfaction. These findings suggest that appearance congruence is a candidate mechanism by which GAH influences psychosocial functioning.

The importance of appearance congruence for psychosocial well-being is further highlighted by the effect of avoiding gender-incongruent pubertal changes. Youth who had not undergone substantial gender-incongruent puberty had higher scores for appearance congruence, positive affect, and life satisfaction and lower scores for depression and anxiety at baseline than youth who had undergone substantial endogenous puberty. These observations align with other published reports that earlier access to gender-affirming medical care is associated with more positive psychosocial functioning.[10,26] Alternatively, youth who first recognize their gender incongruence in adolescence may represent a distinct subgroup of transgender and nonbinary youth who have more psychosocial complexities than youth recognizing gender incongruence in childhood.[27]

The effects of GAH on some psychosocial outcomes varied on the basis of designated sex

Table 3. Variable Estimates for Individual Latent Growth Curve Models of 2-Year Outcomes.*

Model	Appearance Congruence†	Depression‡	Anxiety§	Positive Affect¶	Life Satisfaction‖
			value (95% confidence interval)		
Unconditional model: time					
Intercept mean	2.99 (2.90 to 3.08)	15.46 (14.27 to 16.70)	59.58 (58.22 to 60.68)	42.93 (41.82 to 44.03)	40.12 (38.99 to 41.26)
Intercept variance	0.35 (0.27 to 0.50)	86.23 (68.13 to 106.85)	17.84 (11.38 to 24.54)	63.50 (46.23 to 81.79)	75.21 (59.76 to 93.98)
Slope mean	0.48 (0.42 to 0.54)	−1.27 (−1.98 to −0.57)	−1.46 (−2.13 to −0.79)	0.80 (0.08 to 1.54)	2.32 (1.64 to 3.00)
Slope variance	0.11 (0.07 to 0.15)	19.44 (12.23 to 27.14)	17.84 (11.38 to 24.54)	17.98 (9.25 to 27.57)	20.33 (14.12 to 27.70)
Conditional model					
Time					
Intercept mean	2.59 (1.91 to 3.27)	20.01 (10.79 to 29.48)	60.82 (53.56 to 67.95)	47.27 (38.93 to 55.81)	38.86 (29.90 to 47.75)
Intercept variance	0.32 (0.25 to 0.42)	80.92 (63.35 to 100.47)	114.74 (91.96 to 138.23)	56.96 (41.19 to 74.75)	71.93 (57.15 to 90.22)
Slope mean	0.51 (0.07 to 0.96)	−0.92 (−3.82 to −0.06)	−1.95 (−3.81 to −0.09)	1.79 (0.14 to 3.43)	4.54 (2.66 to 6.43)
Slope variance	0.10 (0.06 to 0.14)	18.81 (11.71 to 26.34)	18.37 (11.78 to 25.63)	17.97 (9.29 to 27.66)	19.74 (13.61 to 27.06)
Time-invariant effects on intercept					
Baseline age	0.02 (−002 to 0.06)	−0.23 (−0.08 to 0.36)	−0.20 (−0.78 to 0.38)	−0.32 (−0.84 to 0.21)	0.06 (−0.49 to 0.62)
Designated sex at birth**	−0.12 (−0.31 to 0.06)	1.74 (−0.69 to 4.09)	0.05 (−2.37 to 2.49)	−1.26 (−3.53 to 0.91)	−2.36 (−4.89 to 0.18)
Racial and ethnic identity††	0.19 (0.03 to 0.36)	−2.60 (−4.82 to −0.32)	−2.22 (−4.48 to 0.06)	2.30 (0.22 to 4.38)	1.70 (−0.58 to 3.98)
Early gender-affirming care‡‡	0.70 (0.35 to 1.04)	−5.88 (−9.67 to −1.96)	−7.41 (−11.30 to −3.52)	5.34 (1.70 to 8.98)	7.55 (2.82 to 12.28)
Time-invariant effects on slope					
Baseline age	0.00 (−0.03 to 0.03)	−0.04 (−0.18 to 0.10)	−0.02 (−0.15 to 0.12)	−0.03 (−0.15 to 0.10)	−0.09 (−0.22 to 0.05)
Designated sex at birth**	0.03 (−0.09 to 0.15)	1.91 (0.33 to 3.50)	1.56 (0.01 to 3.10)	−0.43 (−2.10 to 1.31)	−1.86 (−3.49 to −0.24)
Racial and ethnic identity††	−0.10 (−0.20 to 0.01)	1.70 (0.23 to 3.15)	0.62 (−0.77 to 1.98)	−1.42 (−2.98 to 0.13)	−1.08 (−2.52 to 0.36)
Early gender-affirming care‡‡	−0.42 (−0.66 to −0.19)	−0.73 (−3.41 to 1.93)	0.04 (−2.53 to 2.59)	−0.78 (−3.56 to 2.06)	−1.08 (−4.01 to 1.86)

* Shown are unstandardized variable estimates with 95% confidence intervals. Slope means indicate change over time, and slope variances indicate heterogeneity within the sample.
† Scores on the Appearance Congruence subscale of the Transgender Congruence Scale range from 1 to 5, with higher scores indicating greater appearance congruence.
‡ Scores on the Beck Depression Inventory–II range from 0 to 63, with scores of 20 to 28 indicating moderate depression and scores of 29 to 63 indicating severe depression.
§ T scores on the Revised Children's Manifest Anxiety Scale (Second Edition) have a mean of 50 and a standard deviation of 10, with scores of 60 or more indicating clinical levels of anxiety.
¶ T scores for the Positive Affect measure from the NIH (National Institutes of Health) Toolbox Emotion Battery have a mean of 50 and a standard deviation of 10, with higher scores indicating greater positive affect.
‖ T scores for the Life Satisfaction measure from the NIH Toolbox Emotion Battery have a mean of 50 and a standard deviation of 10, with higher scores indicating greater life satisfaction.
** Coding for designated sex at birth was as follows: 0=assigned female at birth (reference) and 1=assigned male at birth.
†† Coding for racial and ethnic identity was as follows: 0=non-Latinx or non-Latine White (reference) and 1=other racial and ethnic identities.
‡‡ Coding for early gender-affirming care was as follows: 0=initiated GAH in later puberty (Tanner stage 4 or 5) (reference) and 1=initiated GAH in early puberty (Tanner stage 2 or 3).

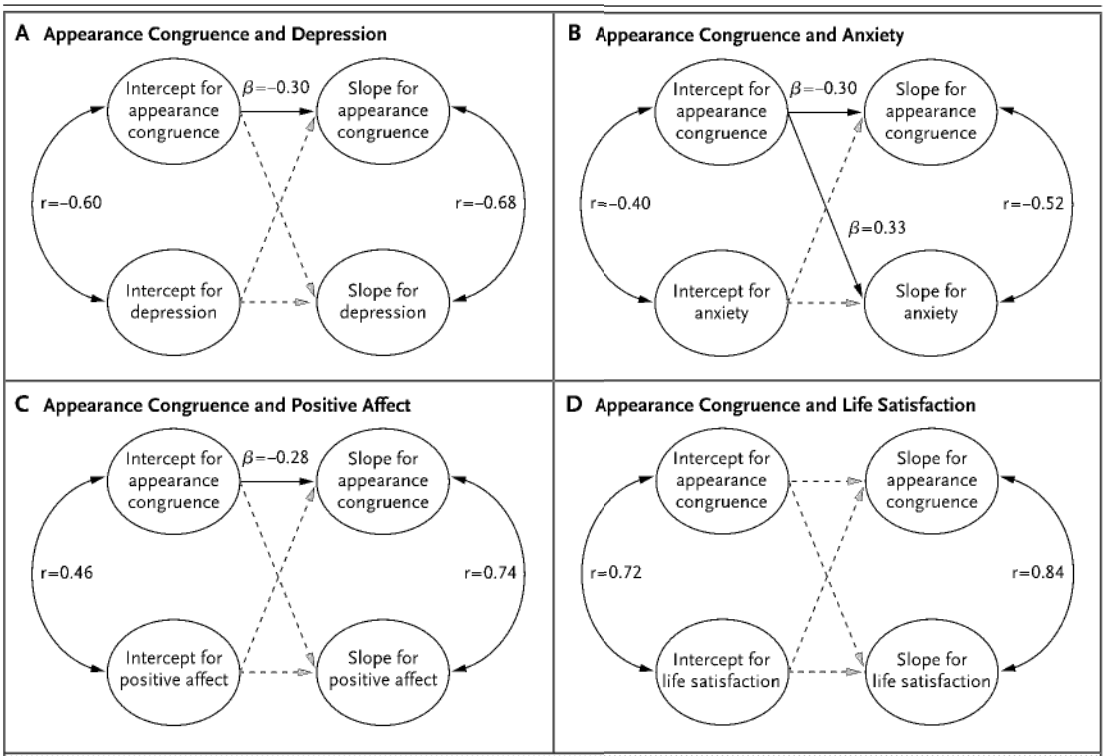


Figure 1. Appearance Congruence and Depression, Anxiety, Positive Affect, and Life Satisfaction.

Parallel-process latent growth curve models are depicted. A linear latent growth curve model was fitted for each outcome, with model-based estimates of baseline scores (intercept) and rates of linear change over time (slope). Parallel-process models can provide tests of how aspects of trajectories relate to each other. Each panel provides estimates for correlations between baseline scores of appearance congruence and each outcome (intercept correlations, arcs displayed on the left side of each panel), correlations between rate of change of appearance congruence and rate of change of each outcome (slope correlations, arcs displayed on the right side of each panel), and effects of baseline scores on slopes (straight lines in the middle of each panel). Solid black lines and arcs indicate significant effects (confidence intervals for variable estimates do not contain 0); nonsignificant effects are shown with dashed gray lines. All models were controlled for age, designated sex at birth, racial and ethnic identity, and early gender-affirming care (not shown for ease of interpretation).

at birth. Depression and anxiety symptoms decreased significantly, and life satisfaction increased significantly, among youth designated female at birth but not among those designated male at birth. Given that some key estrogen-mediated phenotypic changes can take between 2 and 5 years to reach their maximum effect (e.g., breast growth),[28] we speculate that a longer follow-up period may be necessary to see an effect on depression, anxiety, and life satisfaction. Furthermore, changes that are associated with an endogenous testosterone-mediated puberty (e.g., deeper voice) may be more pronounced and observable than those associated with an endogenous estrogen-mediated puberty. Thus, we hypothesize that observed differences in depression, anxiety, and life satisfaction among youth designated female at birth as compared with those designated male at birth may be related to differential experiences of gender minority stress, which could arise from differences in societal acceptance of transfeminine (i.e., persons designated male at birth who identity along the feminine spectrum) as compared with transmasculine persons. Indeed, gender minority stress is consistently associated with more negative mental health outcomes,[29] and research suggests that transfeminine youth may experience more minority stress than transmasculine youth.[30]

Our study has certain limitations. Because participants were recruited from four urban pediatric gender centers, the findings may not be generalizable to youth without access to comprehensive interdisciplinary services or to transgen-

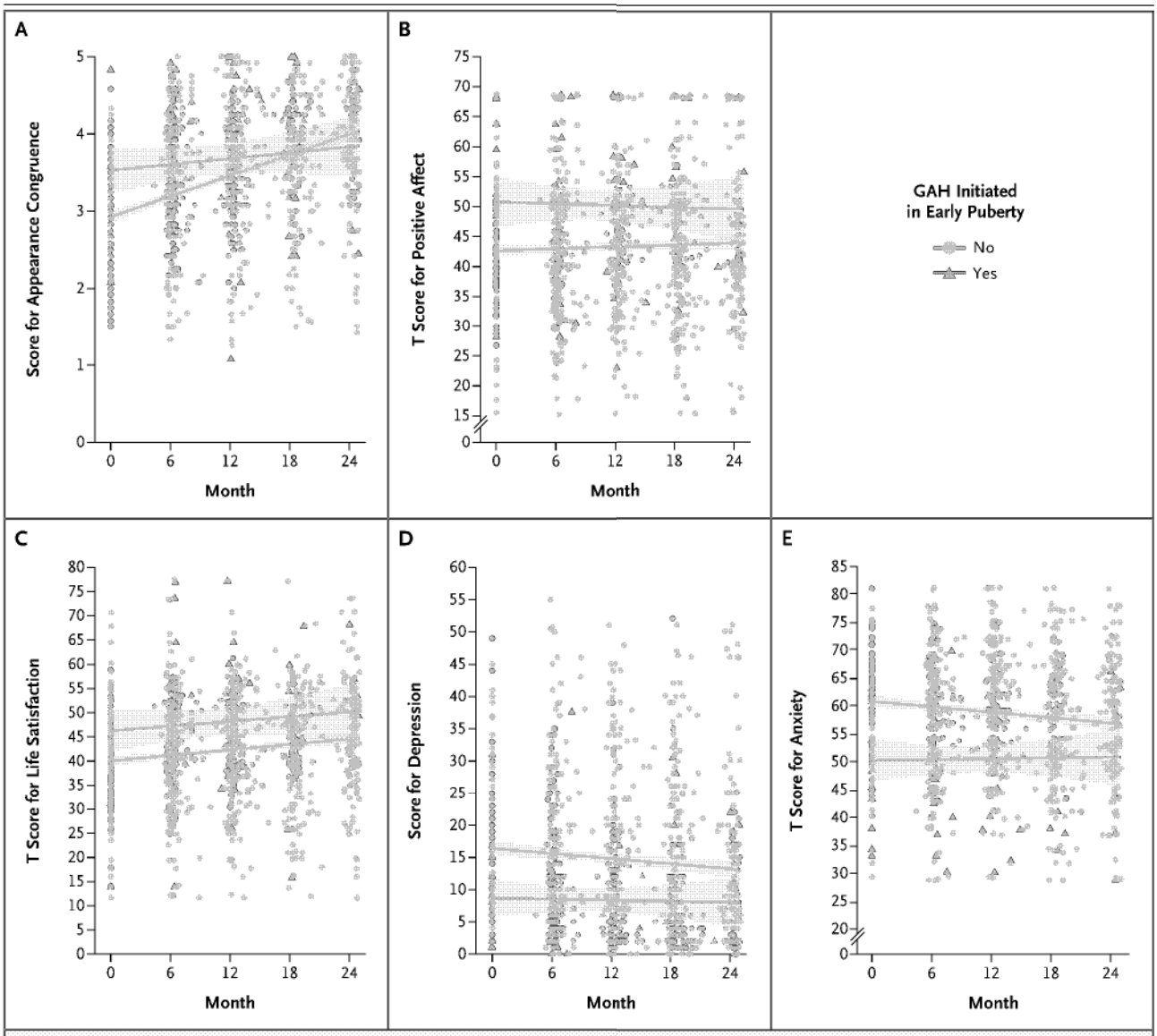


Figure 2. Psychosocial Outcomes during 2 Years of GAH.

Shown are changes in participant-reported measures over a period of 2 years of treatment with gender-affirming hormones (GAH). Scores on the Appearance Congruence subscale of the Transgender Congruence Scale (Panel A) range from 1 to 5, with higher scores indicating greater appearance congruence. T scores for the Positive Affect measure from the NIH (National Institutes of Health) Toolbox Emotion Battery (Panel B) range from 0 to 100, with higher scores indicating greater positive affect. T scores for the Life Satisfaction measure from the NIH Toolbox Emotion Battery (Panel C) range from 0 to 100, with higher scores indicating greater life satisfaction. Scores on the Beck Depression Inventory–II (Panel D) range from 0 to 63, with higher scores indicating greater depression. T scores on the Revised Children's Manifest Anxiety Scale (Second Edition) (Panel D), range from 0 to 100, with higher scores indicating greater anxiety. Individual scores are depicted with orange triangles for youth initiating GAH in early puberty ("Yes") and with blue circles for youth who did not initiate GAH in early puberty ("No"). Lines indicate mean scores for each group, with gray shaded bands for 95% confidence intervals.

der and nonbinary youth who are self-medicating with GAH. In addition, despite improvement across psychosocial outcomes on average, there was substantial variability around the mean trajectory of change. Some participants continued to report high levels of depression and anxiety and low positive affect and life satisfaction, despite the use of GAH. We plan to examine other factors that are known to contribute to psychosocial functioning among transgender and non-

binary youth and may not be affected by GAH, such as parental support,[31,32] in this cohort. Finally, our study lacked a comparison group, which limits our ability to establish causality. However, the large effects in parallel-process models examining associations between improvements in appearance congruence and improvements in psychosocial outcomes provide support for the concept that GAH may affect psychosocial outcomes through increasing gender congruence.

Despite these limitations, our findings showed improvements in psychosocial functioning across 2 years of GAH treatment, which supports the use of GAH as effective treatment for transgender and nonbinary youth. We are now following this cohort to see whether gains in functioning are sustained over a longer follow-up period, and — given substantial variability in outcomes even after controlling for a number of factors — we hope to discover additional predictors of change to identify youth for whom GAH alone is not adequate to address mental health challenges. We intend to initiate further work with this cohort to focus on understanding reasons for discontinuing GAH among the small subgroup of youth who stopped medical treatment. Overall, our results provide evidence that GAH improved appearance congruence and psychosocial functioning in transgender and nonbinary youth.

Supported by a grant (R01 HD082554) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the participants, their families, their referring clinicians, and the many research staff for their contributions in conducting this study, and Norman Spack, one of the original principal investigators, for his contributions to the study.

APPENDIX

The authors' affiliations are as follows: the Gender and Sex Development Program, Potocsnak Family Division of Adolescent and Young Adult Medicine (D.C., R.G.), and the Pritzker Department of Psychiatry and Behavioral Health (D.C.), Ann and Robert H. Lurie Children's Hospital of Chicago, the Departments of Pediatrics (D.C., R.G.) and Psychiatry and Behavioral Sciences (D.C., J.B.), Northwestern University Feinberg School of Medicine, and the Institute for Sexual and Gender Minority Health and Wellbeing, Northwestern University (J.B.) — all in Chicago; the Division of Endocrinology, Department of Pediatrics, Boston Children's Hospital (Y.-M.C.), and the Department of Pediatrics, Harvard Medical School (Y.-M.C.), Boston, and the Department of Psychology and Neuroscience, Boston College, Newton (A.C.T.) — all in Massachusetts; the Department of Pediatrics, Division of Pediatric Endocrinology (D.E., S.M.R.), and the Child and Adolescent Gender Center, Benioff Children's Hospital (D.E., S.M.R.), University of California, San Francisco, San Francisco, and the Gender Health Program, UCLA Health (M.A.H.), and the Division of General Internal Medicine and Health Services Research, Medicine–Pediatrics Section, Department of Medicine, David Geffen School of Medicine (M.A.H.), University of California, Los Angeles, the Center for Transyouth Health and Development, Division of Adolescent and Young Adult Medicine, Children's Hospital Los Angeles (J.O.-K.), and the Department of Pediatrics, Keck School of Medicine, University of Southern California (J.O.-K.), Los Angeles — all in California.

REFERENCES

1. Johns MM, Lowry R, Andrzejewski J, et al. Transgender identity and experiences of violence victimization, substance use, suicide risk, and sexual risk behaivors among high school students — 19 states and large urban school districts, 2017. MMWR Morb Mortal Wkly Rep 2019;68:67-71.
2. Rider GN, McMorris BJ, Gower AL, Coleman E, Eisenberg ME. Health and care utilization of transgender and gender nonconforming youth: a population-based study. Pediatrics 2018;141(3):e20171683.
3. Kidd KM, Sequeira GM, Douglas C, et al. Prevalence of gender-diverse youth in an urban school district. Pediatrics 2021; 147(6):e2020049823.
4. de Vries AL, McGuire JK, Steensma TD, Wagenaar ECF, Doreleijers TA, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 2014; 134:696-704.
5. Allen LR, Watson LB, Egan AM, Moser CN. Well-being and suicidality among transgender youth after gender-affirming hormones. Clin Pract Pediatr Psychol 2019;7:302-11.
6. 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):e20193006.
7. 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; 12:2206-14.
8. 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;8:2276-83.
9. Achille C, Taggart T, Eaton NR, et al. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results. Int J Pediatr Endocrinol 2020;2020:8.
10. Chen D, Abrams M, Clark L, et al. Psychosocial characteristics of transgender youth seeking gender-affirming medical treatment: baseline findings from the trans youth care study. J Adolesc Health 2021;68:1104-11.
11. Olson-Kennedy J, Chan Y-M, Garofalo R, et al. Impact of early medical treatment for transgender youth: protocol for the longitudinal, observational trans youth care study. JMIR Res Protoc 2019;8(7):e14434.
12. Chen D, Hidalgo MA, Leibowitz S, et al. Multidisciplinary care for gender-diverse youth: a narrative review and unique model of gender-affirming care. Transgend Health 2016;1:117-23.
13. Sherer I, Rosenthal SM, Ehrensaft D, Baum J. Child and Adolescent Gender Center: a multidisciplinary collaboration

to improve the lives of gender nonconforming children and teens. Pediatr Rev 2012;33:273-5.
14. Spack NP, Edwards-Leeper L, Feldman HA, et al. Children and adolescents with gender identity disorder referred to a pediatric medical center. Pediatrics 2012; 129:418-25.
15. 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;57:374-80.
16. Kozee HB, Tylka TL, Bauerband LA. Measuring transgender individuals' comfort with gender identity and appearance: development and validation of the Transgender Congruence Scale. Psychol Women Q 2012;36:179-96.
17. Beck AT, Steer RA, Brown GK. BDI-II, Beck depression inventory. San Antonio, TX: Psychological Corporation, 1996.
18. Reynolds CR, Richmond BO. Revised children's manifest anxiety scale (RCMAS-2), second edition. Torrance, CA: Western Psychological Services, 2008.
19. Slotkin J, Nowinski CJ, Hays RD, et al. NIH Toolbox Scoring and Interpretation Guide. Washington, DC: National Institutes of Health, September 18, 2012 (https://repository.niddk.nih.gov/media/studies/look-ahead/Forms/Look_AHEAD_Cognitive_Function/NIH%20Toolbox%20Scoring%20and%20Interpretation%20Manual%209-27-12.pdf).
20. Muthén LK, Muthén BO. Mplus user's guide, version 8. 2017 (https://www.statmodel.com/download/usersguide/MplusUserGuideVer_8.pdf).
21. Herman JL, Flores AR, O'Neill KK. How many adults and youth identify as transgender in the United States? UCLA School of Law, June 2022 (https://williamsinstitute.law.ucla.edu/publications/trans-adults-united-states/).
22. Chen D, Lash B, Kim E, et al. A comparison of demographic and psychosocial characteristics between transgender youth enrolling versus not enrolling in a multisite study. Transgend Health 2020;6:229-34.
23. Reisner SL, Vetters R, Leclerc M, et al. Mental health of transgender youth in care at an adolescent urban community health center: a matched retrospective cohort study. J Adolesc Health 2015;56:274-9.
24. Toomey RB, Syvertsen AK, Shramko M. Transgender adolescent suicide behavior. Pediatrics 2018;142(4):e20174218.
25. American Civil Liberties Union. Legislation affecting LGBT rights across the country. December 17, 2021 (https://www.aclu.org/legislation-affecting-lgbt-rights-across-country).
26. Sorbara JC, Chiniara LN, Thompson S, Palmert MR. Mental health and timing of gender-affirming care. Pediatrics 2020; 146(4):e20193600.
27. de Vries ALC. Challenges in timing puberty suppression for gender-nonconforming adolescents. Pediatrics 2020; 146(4):e2020010611.
28. Coleman E, Bockting W, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. Int J Transgenderism 2012;13:165-232.
29. Delozier AM, Kamody RC, Rodgers S, Chen D. Health disparities in transgender and gender expansive adolescents: a topical review from a minority stress framework. J Pediatr Psychol 2020;45:842-7.
30. Poquiz JL, Coyne CA, Garofalo R, Chen D. Comparison of gender minority stress and resilience among transmasculine, transfeminine, and nonbinary adolescents and young adults. J Adolesc Health 2021;68:615-8.
31. Simons L, Schrager SM, Clark LF, Belzer M, Olson J. Parental support and mental health among transgender adolescents. J Adolesc Health 2013;53:791-3.
32. Pariseau EM, Chevalier L, Long KA, Clapham R, Edwards-Leeper L, Tishelman AC. The relationship between family acceptance-rejection and transgender youth psychosocial functioning. Clin Pract Pediatr Psychol 2019;7:267-77.

European Child & Adolescent Psychiatry
7:246–248 (1998) © Steinkopff Verlag 1998

CASE REPORT

P.T. Cohen-Kettenis
S.H.M. van Goozen

Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent

Accepted: 8 June 1998

P.T. Cohen-Kettenis (✉)
S.H.M. van Goozen
Department of Child and Adolescent Psychiatry of the Utrecht University Hospital, P.O. Box 85500
NL-3508 GA Utrecht
The Netherlands
e-mail: P.T. CohenKettenis@psych.azu.nl

Abstract Early cross-sex hormonal interventions (that is, between 16 and 18) as a treatment for young transsexuals are often considered to be risky. However, the delay of such treatment until after the development of secondary sex characteristics has obvious drawbacks for transsexual individuals. This paper reports a postoperative follow-up case-study of a female-to-male transsexual who was treated with a combination of an LHRH agonist (which delayed her secondary sex characteristics development) and psychotherapy at age 13, and subsequently underwent sex reassignment at 18.

Key words Gender identity disorder – transsexualism – adolescence – sex reassignment – hormone treatment

Introduction

Sex reassignment for individuals with extreme gender identity disorder (GID) has long been restricted to adults. Prospective studies have shown that most GID children under 12 will not grow up to become transsexuals (5, 13, 14). Because of this, hormonal or any other medical intervention is never considered in prepubertal children. However, for some adolescents applying for sex reassignment, medical interventions may be a treatment option. Until recently, clinicians have been reluctant to start hormone treatment before the age of 18 or 21. It was felt that only in adulthood gender identity could be consolidated enough to allow for decisions regarding invasive interventions such as hormone and surgical therapy. Such a relatively late treatment start, however, has it drawbacks. Some individuals who have shown a pattern of extreme cross-sex identification from toddlerhood onwards may develop psychiatric disorders, e.g., depression, anorexia or social phobias, as a consequence of their hopelessness. Social and intellectual development may be adversely influenced. Also, the physical treatment outcome following interventions in adulthood is far less satisfactory than when treatment is started at an age at which secondary sex characteristics have not yet been fully developed. This is obviously an enormous and life-long disadvantage. Ross and Need (11) found that postoperative psychopathology was primarily associated with factors that made it difficult for postoperative transsexuals to pass successfully as their new gender or that continued to remind them of their transsexualism. Furthermore, follow-up studies show that unfavorable postoperative outcome seems to be related to a late rather than an early start of the sex reassignment surgery (SRS) procedure (for reviews, see 6, 10). Age at time of assessment also emerged as a factor differentiating two groups of male-to-female transsexuals with and without postoperative regrets (7).

In some gender identity clinics a selected group of transsexual adolescents are now being treated hormonally before they are legal adults (age 18), but still after the age of 16. A careful diagnostic procedure includes more rigorous eligibility criteria than used for adults and a prolonged diagnostic procedure. The first follow-up study of adolescent transsexuals showed that 1–5 years after surgery the now young adults functioned socially and psychologically

satisfactory and that none had regrets in their decision. They functioned psychologically better than a group of transsexuals, who was treated in adulthood and evaluated with partly the same instruments (2). Despite these initial positive results, even younger adolescents (between 12 and 16 years) who wish to apply for sex reassignment have no other option than to wait for several years.

This paper reports a case of a female-to-male transsexual who attended the gender clinic at age 16. It appeared that she was already under treatment by pediatric endocrinologist with a luteinizing hormone-releasing hormone (LHRH) agonist, depot triptorelin, since the age of 13. This substance binds so strongly to the pituitary that endogenous LHRH can no longer exert its effects. The pituitary secretion of LH and FSH stops and the gonadal production of sex steroids stops therefore as well. As a result, when administered before puberty, puberty will not occur. Given after puberty, pubertal development will not proceed. The treatment does not appear to influence final adult height (4).

Case report

B came to the gender clinic requesting sex reassignment surgery at age 16. From interviews with her parents it appeared that she had always been a classical tomboy in her play activities and toy and peer preference and that she wished to be a boy from early on. Also, she showed boisterous and antagonistic behavior and was often in conflict with her father. At school she did well. At seven she had psychotherapy for a year, because of her oppositional and disobedient behavior, but without any success. When she was 12 her mother found a suicidal note, telling that she did not want to live any longer if she would enter puberty. Again she was treated by means of psychotherapy at the local mental health institute. Despite some improvement in her depressed mood her cross-sex behavior, interests, and identification remained. Her psychiatrist and a pediatric endocrinologist decided therefore to delay B's puberty by triptorelin treatment. By then she was 13 years old. Using this hormone she started to feel better about herself, thus, allowing her therapist to explore gender issues for an extended period, without being pressured by any physical developments.

When it appeared that B's gender identity would not change she ended her psychotherapy. However, being a transsexual was very shameful to her and she had great difficulties picturing herself to be one of 'them'. As the situation at home grew worse, her parents, who were not happy with the idea of sex reassignment, sought help again. They were referred to our gender clinic by their general practitioner. Cognitive testing revealed that B had an IQ (WAIS) of 128 (verbal IQ: 133, performance IQ: 116; (12)). Personality assessment (the Dutch shortened MMPI (NVM) (8), the Dutch Personality Inventory (NPV), (9), Symptom Checklist-90 (SCL-90) (1), Rorschach (Comprehensive System, (3)) showed that she also had excellent problem-solving capabilities with respect to emotional matters. Vulnerable aspects of her psychological functioning were that she felt insecure about herself and moderately depressed, but no serious psychopathology was found: the majority of her questionnaire scores was in the average range, as compared to a large Dutch normative sample. Her shame concerning her transsexualism made her highly selective in her friendships and guarded in her contacts with new people. She felt close to her mother, but had many conflicts with her father. His Mediterranean background made acceptance of his daughter's masculinity very difficult. Following the regular clinical procedure (2) much time was spent exploring feelings of shame in individual sessions. A family therapist focused on conflicts between father and daughter, and father and mother. Occasional sessions with a small group of FM adolescents helped B in realizing that transsexuals can be just like other peers. When no psychological obstacles remained, cross-sex hormone treatment could start. However B chose to start at age 18, after she had graduated from high school.

Androgen treatment had a quick positive effect on B. At home she became more easy-going and friendly. After graduation from high school (age 18) she underwent a subcutaneous mastectomy (she had only developed a pseudogynaecomastia) and ovariectomy/uterus removal. Several months later she had her birth certificate changed.

In a follow-up interview one year after the ovariectomy and mastectomy, B reported no gender dysphoria at all. He said that he had found the adjustment to the male role to be very easy and expressed no doubts on the adequacy of his masculine behavior. He never felt any regrets about his decision and had never contemplated to live as a girl again. Knowing now what sex reassignment implied, he would do it all over again. B was happy with his life and did not feel lonely. He was currently studying to become a physician.

On the psychological questionnaires (the SCL-90, (1); the Dutch shortened MMPI, (8); and the Dutch Personality Questionnaire, (9)) he scored chiefly in the average range compared with scores of a normative Dutch sample. The only significant pre-post treatment change was a drop in his feelings of inadequacy. The majority of the other scores had slightly improved compared with the pretreatment situation. With regard to his social life, nobody had ever approached him as a woman after the development of secondary sex characteristics. B had not yet undergone metaidoioplasty (i.e., transformation of the hypertrophic

European Child & Adolescent Psychiatry, Vol. 7, No. 4 (1998)

clitoris into a micropenis) with a neoscrotum and implanted testes, but he intended to do so. He was therefore cautious in social activities such as sleeping over and showering after sports, but spent quite some time with close friends. As a result of his transsexualism he had not lost contact with family members or friends. B still did not easily engage in sexual encounters, because he disliked telling his partners about his physical incompleteness. Yet he was interested in sex and masturbated regularly. The frequency had increased since the start of his androgen treatment.

Most of his expectations on the physical changes had come true. Only his beard had grown much more slowly than he had expected; he also would have liked to be taller than he actually was. He looked and sounded, however, convincingly male.

B had found the time period between the start of treatment and the legal changes rather long but he was satisfied with other aspects of the sex reassignment procedure. He was very grateful that he had been given the opportunity to be treated this early.

When contacting B for approval of publication of his case, he wrote that he had undergone metaidoioplasty and was very satisfied with the results.

Discussion

The case of B is the first we know of to show that pubertal delay and subsequent hormonal and surgical intervention in a consistently cross-sex identified person has resulted in a positive outcome. In recent meetings of clinicians who treat adolescent transsexuals the minimum age of the start o[redacted] i[redacted] b[redacted] w[redacted] t[redacted] o[redacted] incidence of transsexuals with postoperative regrets. This holds especially for male-to-female transsexuals, because beard growth and voice breaking give so many of them a never disappearing masculine appearance. The most important advantage of pubertal delay over cross-sex hormone treatment is that no irreversible steps are taken. The therapist and transsexual can explore problems which possibly underlie the cross gender identity or clarify gender confusion under less time pressure. Although the physical side effects are few (4), this option also has its risks. Adolescents may consider this step a guarantee of sex reassignment, and it could make them therefore less rather than more inclined to engage in introspection. Furthermore, pubertal delay could widen the already existing social gap between transsexuals and their peers, which could increase the risk of pestering.

However, this case illustrates that pubertal delay as an additional tool in the diagnosis and treatment of young adolescents with GID should not be dismissed beforehand. For certain selected cases with a life-long consistent and extreme GID it may be a physical and psychological beneficial way to intervene.

References

1. Arrindell WA, Ettema JHM (1986) SCL-90. Handleiding bij een multidimensionele psychopathologie-indicator. Lisse: Swets en Zeitlinger
2. Cohen-Kettenis PT, Van Goozen SHM (1997) Sex reassignment of adolescent transsexuals: A follow-up study. Journal of the American Academy of Child and Adolescent Psychiatry 36:263–271
3. Exner JE, Weiner IB (1982) The Rorschach: A Comprehensive System. Volume 3: Assessment of Children and Adolescents. New York: Wiley
4. Gooren LJG, Delemarre-van de Waal H (1996) The feasibility of endocrine interventions in juvenile transsexuals. Journal of Psychology and Human Sexuality 8:69–74
5. Green R (1987) The "sissy boy syndrome" and the development of homosexuality. New Haven: Yale University Press
6. Green R, Fleming DT (1990) Transsexual surgery follow-up: Status in the 1990s. Annual Review of Sex Research 1:163–174
7. Lindemalm G, Körlin D, Uddenberg N (1987) Prognostic factors vs. outcome in male-to-female transsexualism: A follow-up of 13 cases. Acta Psychiatrica Scandinavica 74:268–274
8. Luteyn F, Kok AR, Van der Ploeg FAE (1980) NVM. Nederlandse Verkorte MMPI, Handleiding. Lisse: Swetz en Zeitlinger
9. Luteyn F, Starren J, Van Dijk H (1985) Handleiding bij de NPV. Lisse: Swetz en Zeitlinger
10. Pfäfflin F, Junge A (1992) Geschlechtsumwandlung: Abhandlungen zur transsexualität. Stuttgart: Schattauer
11. Ross MW, Need JA (1989) Effects of adequacy of gender reassignment surgery on psychological adjustment: A follow-up of fourteen male-to-female patients. Archives of Sexual Behavior 18 145–153
12. Stinissen J, Willems PJ, Coetsier P, Hulsman WLL (1970) Handleiding WAIS, Nederlandstalige bewerking. Amsterdam: Swetz en Zeitlinger
13. Zuger B (1984) Early effeminate behaviour in boys: Outcome and significance for homosexuality. Journal of Nervous and Mental Disease 172:90–97
14. Zucker KJ, Bradley SJ (1995) Gender identity disorder and psychosexual problems in children and adults. New York: Guilford Press

ORIGINAL RESEARCH—INTERSEX AND GENDER IDENTITY DISORDERS

Hormonal Treatment Reduces Psychobiological Distress in Gender Identity Disorder, Independently of the Attachment Style

Marco Colizzi, MD, Rosalia Costa, MD, Valeria Pace, PsyD, and Orlando Todarello, MD, PhD

Department of Neuroscience and Sense Organs, University of Bari, Bari, Italy

DOI: 10.1111/jsm.12155

ABSTRACT

Introduction. Gender identity disorder may be a stressful situation. Hormonal treatment seemed to improve the general health as it reduces psychological and social distress. The attachment style seemed to regulate distress in insecure individuals as they are more exposed to hypothalamic–pituitary–adrenal system dysregulation and subjective stress.
Aim. The objectives of the study were to evaluate the presence of psychobiological distress and insecure attachment in transsexuals and to study their stress levels with reference to the hormonal treatment and the attachment pattern.
Methods. We investigated 70 transsexual patients. We measured the cortisol levels and the perceived stress before starting the hormonal therapy and after about 12 months. We studied the representation of attachment in transsexuals by a backward investigation in the relations between them and their caregivers.
Main Outcome Measures. We used blood samples for assessing cortisol awakening response (CAR); we used the Perceived Stress Scale for evaluating self-reported perceived stress and the Adult Attachment Interview to determine attachment styles.
Results. At enrollment, transsexuals reported elevated CAR; their values were out of normal. They expressed higher perceived stress and more attachment insecurity, with respect to normative sample data. When treated with hormone therapy, transsexuals reported significantly lower CAR ($P < 0.001$), falling within the normal range for cortisol levels. Treated transsexuals showed also lower perceived stress ($P < 0.001$), with levels similar to normative samples. The insecure attachment styles were associated with higher CAR and perceived stress in untreated transsexuals ($P < 0.01$). Treated transsexuals did not expressed significant differences in CAR and perceived stress by attachment.
Conclusion. Our results suggested that untreated patients suffer from a higher degree of stress and that attachment insecurity negatively impacts the stress management. Initiating the hormonal treatment seemed to have a positive effect in reducing stress levels, whatever the attachment style may be. **Colizzi M, Costa R, Pace V, and Todarello O. Hormonal treatment reduces psychobiological distress in gender identity disorder, independently of the attachment style. J Sex Med 2013;10:3049–3058.**

Key Words. Gender Identity Disorder; Hormonal Sex-Reassignment Therapy; Cortisol Awakening Response; Perceived Stress; Adult Attachment; Transsexualism

Introduction

Cross-sex hormone treatment is an important component in the medical treatment of transsexual people and is desired by patients to successfully live as a member of their identified gender. It provides some relief from the dichotomy between body habitus and gender identity. For this reason, hormone therapy seems to give a feeling of social re-adaptation that alleviates the suffering of transsexuals and to facilitate the distress reduction [1]. This is particularly important for those transsexuals who experience insecure relations and are more vulnerable to the stress system dysregulation. In fact, the conditions that promote the development of an insecure attachment in relations are also associated with the dysregulation of the stress response

The gender identity disorder (GID) is characterized by a strong and persistent identification with the opposite sex and persistent discomfort with one's own biological sex or the roles assigned to it [3]. GID or transsexualism may also be suspected in children; therefore, in adolescents and young adults, this condition may be a continuation of a previous condition or develop de novo. A distinction should be made between transsexualism and other conditions that are not characterized by a persistent desire of a permanent sex change. Transsexualism cannot be diagnosed if the individual has a concurrent physical intersex condition such as androgen insensitivity syndrome or congenital adrenal hyperplasia. Transient and stress-related cross-dressing behavior, as well as a persistent preoccupation with castration or penectomy without a desire to acquire the sex characteristics of the other sex, is not sufficient to diagnose transsexualism either. All these conditions are diagnosed as GID not otherwise specified [3].

For most patients, transsexualism may be a stressful condition and may cause clinical distress or impairment in important areas of functioning [4,5]. Several studies, including a meta-analysis, indicated that cross-sex hormonal intervention improves quality of life and overall happiness among transsexual individuals [6,7]. Hormones contributed to optimizing the real life process in the sex identity, improving the well-being, and decreasing the psychiatric comorbidities often associated with a lack of hormone treatment [1]. Motmans et al. showed that hormonal treatment has improved transsexuals' general health, while there was no significant difference in the quality of life between transsexuals who had undergone genital or breast surgery and transsexuals who did not have these surgeries, suggesting the centrality of hormonal treatment [8]. Specifically, a recent study has shown that patients under cross-sex hormonal treatment reported a lower prevalence of perceived social distress than patients who had not initiated hormone therapy, suggesting a positive effect of hormonal treatment in the management of psychological and sociological distress in transsexual patients [9].

The normal function of attachment is to regulate distress and stressful situations stimulate the attachment system thus activating physiological responses [10,11]. The quality of the parental style, as well as the family life events during infancy, determines the attachment style [12] and outlines durable cognitive schemes of care expectancy that persist in adult life [10,13,14]. A connection between the subjective differences in coping with the stressful situations and with the psychological distress [14], and the attachment styles has been proved by studies.

The hypothalamic–pituitary–adrenal (HPA) axis abnormality has been reported to be a characteristic consequence of frequently repeated or chronic environmental stress challenges. Chronic stress-induced stimulation of HPA activity alters adrenocorticotropic hormone (ACTH) secretagogue expression and hypothalamic afferent activity to maintain adrenocortical responsiveness [15]. Dysregulation of these control mechanisms ensues. The consequent overriding function of a pathological HPA axis determines a persistent increase of cortisol awakening response (CAR) and of daily cortisol plasmatic levels, especially in individuals with an insecure style of attachment (anxious or avoidant), and for this reason unable to face stressful situations [16–18]. Stress-induced hypercortisolism seemed to establish risk factor for a variety of diseases and increase the all-cause mortality risk of affected subjects by twofold to threefold, curtailing their life expectancy by several years [19,20].

There have been several studies into the possible positive effects of surgical therapy [21,22]; in contrast, the literature on the effect of cross-sex hormone therapy on psychobiological parameters is more limited.

To our knowledge, quantitative data on perceived and biological stress and differences in its regulation related to the hormonal treatment have not been previously reported. Moreover, no research has been carried out to investigate attachment among adults with transsexualism and, more specifically, the presence of insecure conditions with regard to psychobiological distress.

If transsexualism seems to be a stressful condition, insecure attachment and hormonal therapy may determine a clinically increase or reduction of CAR and perceived stress levels, respectively, with important consequences for therapeutic interventions.

The objective of the present study was to evaluate the presence of current psychobiological distress in transsexuals attending a gender identity unit through the CAR and perceived stress measurement. We compared these values with regard to the hormonal intervention. On the basis of previous research and of our own clinical experience, we suggested a significant reduction of CAR and perceived stress in transsexuals after the beginning of hormonal treatment. Within a theoretical framework and inspired by the attachment theory, we also suggested the insecure attachment styles be significantly associated with higher CAR and perceived stress if compared with the secure style. Finally, we

tested the interaction between attachment styles and hormone therapy on CAR and perceived stress to see whether stress levels in different attachment styles in untreated and treated transsexual patients differ.

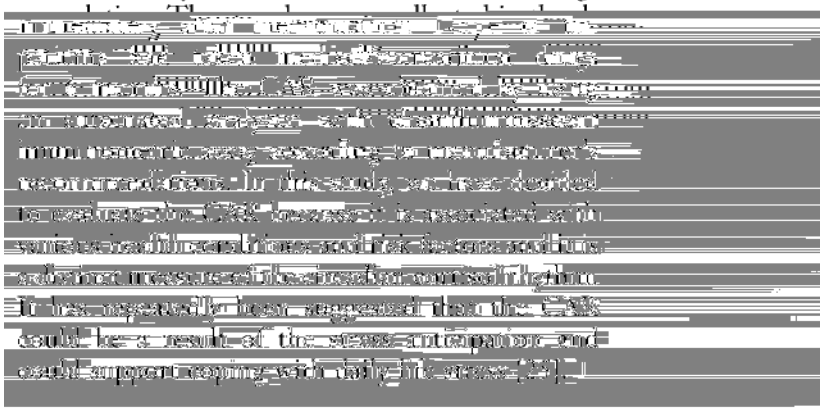
Materials and Methods

Participants

Seventy consecutive patients have visited the Gender Identity Unit of the University of Bari Psychiatric Department between 2008 and 2011. Each patient has been visited by two psychiatrists with a special interest in this topic, one of whom is author of this study (O.T.). Each patient has received psychological counseling and has been interviewed according to the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) as he manifested all the Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision (DSM-IV-TR) diagnostics criteria for GID in adults. The presence of any neurologic or psychiatric pathology and of any metabolic or intersexual pathology (as diagnosed by the endocrinologist and accompanied by hematologic and chromosome profile evaluations) has been considered an exclusion principle. All patients have signed the informed consent for data treatment. Forty-five (64%) belonged to the male to female (MtF) type. Hormonal treatment for MtF transsexuals consisted of transdermal estradiol gel (1.77 ± 0.46 mg/day), in association with oral cyproterone acetate (100 mg/day). The androgen administration schedule in female to male (FtM) patients consisted of testosterone administered as intramuscular injections of a testosterone esters depot (250 mg every 27.12 ± 2.64 days). All the patients in this study received hormonal therapy. The unit has adopted the standards of care guidelines of the World Professional Association for Transgender Health [23]. No patient had undergone any type of surgical intervention.

Measurement of CAR

CAR was measured by taking a blood sample of 20 mL per patient at 8:00 AM, 1 hour after wake up, for 3 consecutive days, once before the onset of hormone therapy (phase 1), and once after about 12 months (52.14 weeks ± 17.1 days) of hormone therapy (phase 2). All the patients performed these evaluations. For each patient, in phase 1 and in phase 2, a mean of the three CARs was calculated. At the moment of each blood taking, all patients had fasted for at least 8 hours, had not drunk caffeine or alcohol nor smoked since the previous night, and neither had they practiced any hard physical exercise during the 3 days before. While awakening cortisol levels seemed to be comparable across the female menstrual cycle phases, without significant differences in the CAR between the follicular and luteal phase, researches have shown a net increase during ovulation, presumably mediated by elevated sex steroid levels during the ovulation period [24]. For this reason, at the time of the evaluation, the FtM patients did not have the menstrual cycle and were far from the timing of



Measurement of Perceived Stress

All the patients performed a self-reported evaluation of perceived stress. They assessed this evaluation in phase 1 (before), when they were still waiting for hormone therapy approval, and in phase 2 (after hormone therapy). Each of these two investigations was conducted before the first cortisol measurement. The perceived stress has been evaluated by the 10-item Perceived Stress Scale (PSS) [26]. It is the most commonly used measure of perceived stress. Answers to the 10-item PSS were summed for each participant, yielding scores that ranged from 0 (*low perceived stress*) to 40 (*high perceived stress*). A recent study has reviewed several articles related to the psychometric properties of the PSS. This search has found that internal consistency reliability, factorial validity, and hypothesis validity of the PSS were well reported. The test–retest reliability and criterion validity were evaluated too, though to a lesser extent. The 10-item version is suggested as it has maximum reliability. In this study, we used the 10-item PSS whose psychometric properties also were found to be superior to those of the 14-item PSS, while those of the four-item scale fared the worst [27]. Appropriate application of this instrument in epidemiological and clinical research, as well as in

inpatient care, can aid the detection of psychosocial stress and ensure accurate identification of individuals who would benefit from specific psychotherapeutic interventions [28].

Measurement of Attachment

The attachment styles have been assessed through the Adult Attachment Interview (AAI) [29] by one of the authors who is an expert psychologist–psychotherapist with certification (V.P.). Only 50 participants were well disposed toward this particular interview. The AAI is a semistructured interview that explores the representation of attachment in the adult by a backward investigation in the relations between the child and the parental figures. The AAI is audio recorded and transcribed verbatim. This transcript has made it possible to classify the current mental state of an adult in relation to his/her attachment history by evaluating the coherence between emotions and thoughts. The AAI helps distinguish four styles of attachment: secure (safe and balanced), avoidant (the importance given to relation is minimum), anxious (worry, ambivalence, and rage), and unresolved/disorganized (due to traumas coming from loss or abuse). In this study, we have decided to use the AAI first because attachment represents the person's early experiences that are crucial in the development of the stress system and then because it shows relative stability from infancy to adulthood and is fundamental in stress management and HPA axis regulation [10,11,30,31]. Subjects with the avoidant or the anxious attachment style are both considered insecure. The unresolved/disorganized attachment style, instead, is used if the interview shows signs of unresolved experiences of trauma usually involving the loss of attachment figures. Therefore, this style is superimposed on the three main classifications [32]. Rigorous psychometric testing and meta-analyses of the AAI demonstrate stability and discriminant and predictive validity in both clinical and nonclinical populations [33,34] and in Italian samples too [35]. The test–retest stabilities of the secure, avoidant, and anxious categories are 77–90% across 1- to 15-month periods [33,36] and are not attributable to interviewer effects [37].

Statistical Analysis

Statistical analysis was conducted using STATA 10 (Stata Corp, Georgetown, TX, USA). The difference of the proportion of MtF and FtM transsexual patients among occupational status, as well as the proportion of transsexual patients and normative samples among attachment styles, was evaluated using the chi square. The comparison of age and level of education between MtF and FtM, as well as the comparison of CAR and perceived stress between treated and untreated transsexuals, was performed using independent sample *t*-tests. *t*-Tests were used to compare the perceived stress between treated/untreated transsexual patients and normative sample. Interactions of hormonal treatment and attachment styles on CAR/perceived stress were evaluated using two-way analysis of variance. Fisher's post hoc description was applied if differences were found. The significance level was set at $P < 0.05$.

Ethics

The study was approved by the Ethics Committee of the Medical Faculty, University of Bari.

Results

The Demographic Variables

The average age of the sample did not show significant differences between MtF (mean = 29.25 years, standard deviation [SD] = 9.87) and FtM patients (mean = 26.78 years, SD = 8.09) ($t = 0.90$; $P = 0.37$). No significant differences emerged between the level of education of MtF (mean = 11.6 years of study, SD = 1.21) and FtM (mean = 10.3 years of study, SD = 1.61) ($t = 7.83$; $P = 0.49$) and between their occupational status (31 MtF [69%] and 18 FtM [72%] employed) ($\chi^2 = 0.07$, $P = 0.79$).

CAR

In phase 1, patients showed elevated CAR (mean = 28.98 μg/dL, SD = 20.82 μg/dL); in fact, the values were out of the normal range (normal value: 9–23 μg/dL). There were no significant differences between untreated MtF (mean = 31.71 μg/dL, SD = 16.48 μg/dL) and untreated FtM (mean = 27.78 μg/dL, SD = 26.76 μg/dL). In phase 2, patients expressed significantly lower CAR (mean = 15.72 μg/dL, SD = 6.54 μg/dL) ($t = 4.25$, $P < 0.001$). There were no significant differences between treated MtF (mean = 15.94 μg/dL, SD = 6.42 μg/dL) and treated FtM (mean = 15.23 μg/dL, SD = 6.74 μg/dL) (Table 1).

Perceived Stress

In phase 1, patients expressed elevated levels of perceived stress, as evidenced by a high average total PSS score (mean = 27.70, SD = 6.11). There

Table 1 Means, standard deviations, and statistical comparisons with *t*-test of the relationship between cortisol and transsexual patients

Transsexuals under hormonal treatment (N = 70) M (SD)	*t*-Test	
	t	*P*
15.72 (6.54)	4.25	0.001

MtF (mean = 29.13, SD = 6.05) and untreated FtM (mean = 25.37, SD = 5.71). When comparing the perceived stress found in our sample with the available normative data [26], it was clear that, in transsexual patients, perceived stress was considerably higher than in nonclinical samples of the same age (mean = 14.2, SD = 6.2) ($t = -17.53$; $P < 0.001$). In phase 2, transsexual patients showed a significantly lower perceived stress (mean = 14.96, SD = 4.89) ($t = 11.51$, $P < 0.001$), coinciding almost perfectly with that found in nonclinical samples of the same age ($t = -1.2$; $P = 0.12$). There were no significant differences between treated MtF (mean = 14.67, SD = 4.83) and treated FtM (mean = 15.42 SD = 5.08) (Table 2).

Attachment Patterns

Transsexual patients showed a high percentage of insecure attachment (70%). Twenty-three patients showed avoidant attachment (46%), 11 the anxious type (22%), 1 the unresolved/disorganized type superimposed on the anxious type (2%), and only 15 the secure type (30%). Moreover, when comparing the attachment styles found in our sample with the available normative data about nonclinical young adults and clinical groups of the same age [32], we found that the percentage of insecure conditions in the group of participants with transsexualism was considerably higher than that usually found in nonclinical samples ($\chi^2 = 9.91$, $P = 0.002$) and clinical groups ($\chi^2 = 4.81$, $P = 0.03$). When classifying participants with transsexualism on the basis of one of the three attachment styles (secure, avoidant, and anxious), the distribution of percentages also differed significantly from that found in nonclinical ($\chi^2 = 9.45$, $P = 0.009$) and clinical samples ($\chi^2 = 6.12$, $P = 0.046$). The main difference was in the percentage of those with a secure attachment style, which is lower in the case of participants with transsexualism (30%) as compared with clinical (46%) and nonclinical samples (56%) (Table 3). Only one patient has shown an unresolved/disorganized attachment (phase 1: PSS 27, CAR 14.2; phase 2: PSS 23, CAR 13.2) and has been excluded from the analysis.

Interaction of Attachment Styles and Hormonal Treatment on CAR

There was a significant interaction between the attachment patterns and the hormone therapy on CAR ($F = 3.97$, $P = 0.02$) (Figure 1). In phase 1, anxious patients showed significantly higher CAR (M = 42.94 μg/dL, SD = 33.77 μg/dL) than avoidant (M = 26.73 μg/dL, SD = 14.74 μg/dL) ($F = 5.39$, $P = 0.003$) and secure patients (M = 22.21 μg/dL, SD = 10.96 μg/dL) ($F = 5.83$, $P < 0.001$). In phase 2, there were no significant differences in CAR by attachment. In contrast to anxious (M = 14.69 μg/dL, SD = 4.81 μg/dL) and avoidant patients (M = 15.69 μg/dL, SD = 7.28 μg/dL), secure patients (M = 16.51 μg/dL, SD = 6.75 μg/dL) did not show significant differences in CAR between phase 1 and phase 2.

Table 2 Means and standard deviations of the perceived stress measured with the Perceived Stress Scale in transsexual patients without and under cross-sex hormonal treatment and in normative samples, and statistical comparisons with *t*-test

	Transsexuals without hormonal treatment (N = 70) M (SD)	Transsexuals under hormonal treatment (N = 70) M (SD)	Normative samples (N = 645) M (SD)	*t*-Test	
				t	*P*
PSS (0–40)	27.70 (6.11)	14.96 (4.89)	14.2 (6.2)	−17.53*	<0.001
				11.51†	<0.001
				−1.2‡	0.12

*Comparison between transsexuals without hormonal treatment and normative samples
†Comparison between transsexuals without and under hormonal treatment
‡Comparison between transsexuals under hormonal treatment and normative samples
M = mean; PSS = Perceived Stress Scale; SD = standard deviation

Table 3 Prevalence of attachment styles and overall insecure attachment (anxious and avoidant styles) measured with Adult Attachment Interview in transsexual patients, in normative clinical and nonclinical groups, and statistical comparisons with chi square

	Transsexuals (N = 70) N (%)	Normative clinical group (N = 1,023) N (%)	Normative nonclinical group (N = 861) N (%)	Chi square	
				χ^2	*P*
Attachment styles				6.12*	0.046
				9.45†	0.009
Secure	15 (30%)	471 (46%)	482 (56%)		
Anxious	12 (24%)	133 (13%)	146 (17%)		
Avoidant	23 (46%)	419 (41%)	233 (27%)		
Insecure attachment (anxious and avoidant)	35 (70%)	552 (54%)	379 (44%)		
				4.81*	0.03
				9.91†	0.002

*Comparison between transsexuals and normative clinical group
†Comparison between transsexuals and normative nonclinical group

Interaction of Attachment Styles and Hormonal Treatment on Perceived Stress

There was a significant interaction between the attachment conditions and the hormone therapy on perceived stress ($F = 4.98$, $P < 0.01$) (Figure 2). In phase 1, anxious patients expressed significantly higher perceived stress (M = 33.09, SD = 5.28) if compared with avoidant (M = 28.17, SD = 4.65) ($F = 1.85$, $P = 0.009$) and secure patients (M = 23.26, SD = 5.61) ($F = 2.00$, $P < 0.001$). Also avoidant patients showed significantly higher perceived stress than secure patients ($F = 1.67$, $P = 0.004$). In phase 2, there were no significant differences in perceived stress by attachment (anxious style: M = 15.27, SD = 4.71; avoidant style: M = 15.30, SD = 5.04; secure style: M = 14.4, SD = 5.13). All the three attachment styles showed significant differences in perceived stress between phase 1 and phase 2 (anxious style: $F = 2.15$, $P \leq 0.001$; avoidant style: $F = 1.49$, $P \leq 0.001$; secure style: $F = 1.84$, $P \leq 0.001$).

Discussion

The study aimed at describing the presence of psychobiological distress and attachment insecurity in transsexual patients.

Results from this study indicated that these patients show HPA dysregulation and appear to notably differ from the normative samples in terms

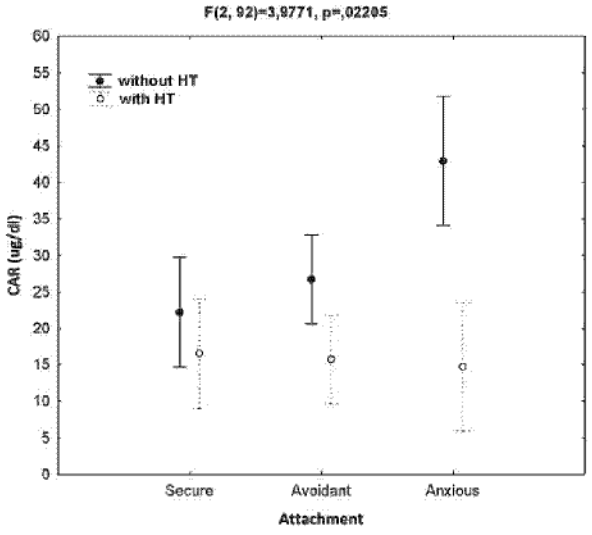


Figure 1 Interaction between hormonal treatment and attachment styles on cortisol awakening response in transsexual patients. CAR = cortisol awakening response; HT = hormonal treatment

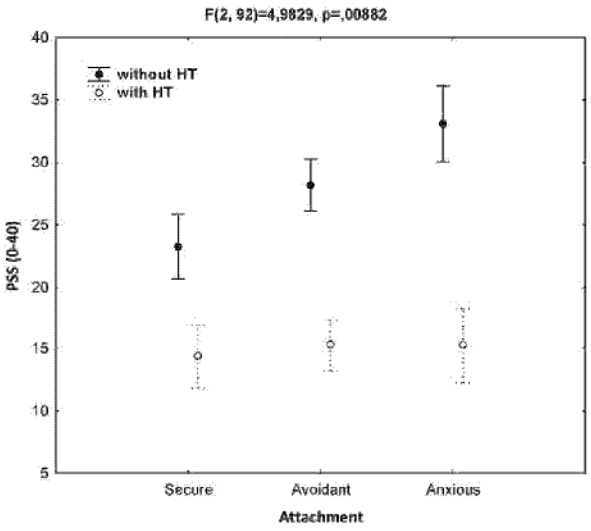


Figure 2 Interaction between hormonal treatment and attachment styles on perceived stress in transsexual patients. HT = hormonal treatment; PSS = Perceived Stress Scale

of mean levels of perceived stress and percentage of attachment insecurity. They showed elevated CAR, with cortisol levels above the normal range, and elevated perceived stress, confirming the literature data on distress related to transsexualism [4,5]. They expressed also a high percentage of attachment insecurity.

An important result of our study was that when treated with cross-sex hormone therapy, transsexuals reported significantly lower CAR, falling within the normal range for cortisol levels in the morning, and lower perceived stress, with levels similar to normative samples.

Another result from this study was that, as shown in the literature about healthy subjects, attachment insecurity and especially the anxious style seemed to be associated with CAR and perceived stress and consequently with psychobiological stress management [16,18].

The last and most interesting result from this study was that after about 12 months of hormonal treatment we did not find significant differences in perceived stress and CAR by attachment groups, suggesting that transsexual patients can improve their stress levels whatever the attachment style may be. Our data suggested that untreated patients suffer from a higher degree of stress and that attachment insecurity, especially the anxious pattern, negatively impacts the stress management. Interestingly enough, instead, secure patients did not show differences in CAR between phase 1 and phase 2 in both cases showing values in the normal range, and this finding suggested a protective effect of secure attachment against HPA dysregulation.

Despite the importance attributed to the problems connected to the attachment insecure styles in structuring numerous psychobiological alterations, there is little quantitative and categorical work about the attachment and the experience of social or emotional distress in children, adolescents, and adults with transsexualism. Some researches have been restricted to transsexual children and the parents of transsexual children. In particular, only one study has shown the existence of a prevalence of ambivalent attachment styles among children with this condition [38]. A research program has been conducted on the parents of transsexual children founding in the vast majority of cases parents with an insecure attachment style (avoidant or anxious) [39]. In addition, highly stressful factors or traumas were found in the primary attachment figures' history operating just before or during early childhood of transsexual patients [40]. Moreover, transsexual children have shown, on average, more behavior and emotional problems than their siblings and controls [41]; they have also shown a high rate of traumatic experiences that may relate to specific transgenerational dynamics [42,43].

Frequent early-life stress like, for example, inadequate parental care and the subsequent insecure attachment style can have enduring effects on stress reactivity and on HPA system regulation, as evidenced by different studies [44–46]. Insecure early care-giving experiences stimulate up-regulation or down-regulation of adult cortisol stress responses resulting in dysregulation of stress responsivity [47]. The quality of parental caretaking is considered to be particularly crucial while brain systems critically involved in the regulation of the HPA axis such as the hippocampus or the prefrontal cortex are developing [48,49]. Accordingly, while high parental responsiveness and sensitivity during this period attenuates HPA reactivity throughout the life span [50,51] and promotes adequate biobehavioral regulation and well-being of the offspring in general [52–54], adverse early rearing conditions such as insensitive and unresponsive care [55] have been linked to increased HPA reactivity and poor biobehavioral regulation throughout the life span. Secure individuals, therefore, are generally able to develop efficient strategies to cope with stress. Instead, insecure patients with high levels of anxiety or avoidant attitude tend to adopt dysfunctional strategies. The insecure individuals are more likely to show emotional uneasiness because of stressful experiences. The HPA axis is activated in response to stressful situations having a strong emotional impact on an interpersonal level [56]. A difficult management of the stress and of the negative emotions ensues, and this is proved by a steady presence of high cortisol levels also a long time after the exposure to stress [57]. Moreover, the insecure behavior has been associated with a higher sense of solitude and social isolation and to greater relational difficulties [58]. The sense of solitude and the self-reported difficulty in managing stress have been connected with the CAR increase [59].

Over the course of the past decade, CAR as part of the circadian rhythm has extensively been investigated. It typically constitutes the circadian peak of cortisol secretion and has been identified as a reliable marker for studying individual differences [60]. Although the CAR has found to be related to a number of factors such as age, time of awakening, sleep quality, and genetic differences, the determinants of CAR have not been fully explained yet.

There is considerable evidence that the cortisol increase after awakening is reduced in individuals scoring high on personality dimensions that have been associated with high levels of attachment security [18]. According to our results, there appears to be an association between hormonal treatment and lower stress levels, also in insecure individuals. This result may have several explanations. First, the stress differences might be a direct effect of hormone therapy. As previously reported in only one study in MtF subgroup, estrogens may reduce cortisol levels in transsexuals: Mueller et al. found that cortisol levels were reduced by 43% after 12 months of estrogenic therapy in MtF patients [61]. According to the authors, cortisol serum levels may be decreased due to estrogen-induced increase in corticoid-binding globulin. We did not find researches about the effect of androgenic therapy in FtM patients. However, some studies suggested that testosterone levels are significantly associated with several measures of stress in women, perceived stress included [62]. Therefore, one would expect that treated MtF transsexuals might display lower cortisol and perceived stress levels than treated FtM. Nevertheless, our study did not find differences between MtF and FtM when gender was included in the statistical analyses. Therefore, our results could not support this hypothesis, and, in accordance with Kuiper and Cohen-Kettenis, there appears to be no direct relation between the hormone therapy itself and the patients' subjective well-being [63]. In any case, data are too limited to express conclusively. Second, stress in transsexuals may be considered as a reaction to the nonsatisfaction connected to their incongruent body image and, as hormone therapy induces desired changes in body features and shape, this could translate into a better quality of life for the patient himself. Thanks to the body changes obtained, transsexuals could experience a reduction of self-reported distress [9,64]. Third, the initiation of the hormonal treatment could have a psychological meaning which per se could be fundamental in reducing stress.

Further researches are needed to resolve these issues. Understanding these mechanisms is extremely important if one wants to grant early enough interventions to transsexuals who seem to live a very stressful condition. This article has showed the potential for early hormonal treatment intervention to reduce the deleterious effects of stress on the brain, behavior, and cognition. After years of research on the negative effects of stress, it is now time to turn our attention to the potential positive impact of early interventions, especially in vulnerable patients. These results could help us develop health policies that treat the problem of early-life stress by promoting therapeutic actions that increase the patients' supportive experiences and sense of attachment security. As reported in previous studies, our clinical experience suggests that transsexual patients attending a gender unit are pleased in the knowledge that the hormonal therapy will be performed within a reasonable time and refer a distress reduction [63,64]; instead, transsexuals and in particular the insecure patients express distress when treatments are delayed because of their health problems. In fact, we suspect that findings would likely be different if therapy were discontinued or in patients who have no possibility of being attended by a gender unit.

A limit of our study was that we did not evaluate the cortisol levels in the rest of the day. A second limit of our research was that the normative data about perceived stress are collected in a sample from the USA, which may be not comparable with an Italian sample. Moreover, the generalization of our results may be limited by the fact that patients were recruited from a specialized gender unit in Italy where the care pathway provides continuous psychological support. We cannot exclude a positive effect of psychological treatment on stress management. A major strength of this study is that it is a longitudinal study and it is the first to investigate stress levels and their relation with cross-sex hormonal treatment and attachment.

In few words, the study provides information on HPA dysregulation, perceived stress, and attachment patterns of transsexual patients. Untreated transsexual patients expressed elevated CAR, together with perceived stress and attachment insecurity. The insecure attachment styles (anxious and avoidant) were associated with higher CAR and perceived stress in untreated transsexuals. Finally, there appeared to be a relationship between cross-sex hormone therapy and lower CAR and perceived stress in transsexuals, independently of the attachment style.

Acknowledgment

Special thanks for voluntary support in translation to Professor Caterina Farina.

Corresponding Author: Marco Colizzi, MD, Department of Neuroscience and Sense Organs, University of Bari, Bari 70124, Italy. Tel: +39-3289222551; Fax: +39-0805593058; E-mail: marco.colizzi@hotmail.it

Conflict of Interest: The authors report no conflicts of interest.

Statement of Authorship

Category 1

(a) Conception and Design
Marco Colizzi; Rosalia Costa; Valeria Pace; Orlando Todarello

(b) Acquisition of Data
Marco Colizzi; Rosalia Costa; Valeria Pace

(c) Analysis and Interpretation of Data
Marco Colizzi

Category 2

(a) Drafting the Article
Marco Colizzi; Rosalia Costa

(b) Revising It for Intellectual Content
Marco Colizzi; Rosalia Costa; Valeria Pace; Orlando Todarello

Category 3

(a) Final Approval of the Completed Article
Marco Colizzi; Rosalia Costa; Valeria Pace; Orlando Todarello

References

1 Moreno-Pérez O, Esteva De Antonio I, Grupo de Identidad y Diferenciación Sexual de la SEEN (GIDSEEN). Clinical practice guidelines for assessment and treatment of transsexualism. SEEN Identity and Sexual Differentiation Group (GIDSEEN). Endocrinol Nutr 2012;59:367–82.
2 Maunder RG, Hunter JJ. Attachment relationships as determinants of physical health. J Am Acad Psychoanal Dyn Psychiatry 2008;36:11–32.
3 American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4th edition. Washington, DC: APA; 2000.
4 Gómez-Gil E, Trilla A, Salamero M, Godás T, Valdés M. Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. Arch Sex Behav 2009;38:378–92.
5 Sohn M, Bosinski HA. Gender identity disorders: Diagnostic and surgical aspects. J Sex Med 2007;4:1193–207; quiz 1208.
6 Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, Erwin PJ, Montori VM. Hormonal therapy and sex reassignment: A systematic review and meta-analysis of quality of life and psychosocial outcomes. Clin Endocrinol (Oxf) 2010; 72:214–31.
7 Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Gebleux S, Penochet JC, Pringuey D, Albarel F, Morange I, Loundou A, Berbis J, Auquier P, Lançon C, Bonierbale M. Is hormonal therapy associated with better quality of life in transsexuals? A cross-sectional study. J Sex Med 2012;9:531–41.
8 Motmans J, Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: Socioeconomic and medical differences. J Sex Med 2012;9:743–50.
9 Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone-treated transsexuals report less social distress, anxiety and depression. Psychoneuroendocrinology 2012;37: 662–70.
10 Bowlby J. Attachment and loss. Attachment. Vol. 1. New York: Basic Books; 1969.
11 Mikulincer M, Shaver PR, Pereg D. Attachment theory and affect regulation: The dynamics, development, and cognitive consequences of attachment-related strategies. Motiv Emot 2003;27:77–102.
12 Kokcu F, Kesebir S. The relationship between attachment style, and temperament, personality and bipolar symptoms: A controlled study on bipolar patients and their children. Turk Psikiyatri Derg 2010;21:309–18.
13 Hazan C, Shaver P. Romantic love conceptualized as an attachment process. J Pers Soc Psychol 1987;52:511–24.
14 Bartholomew K, Horowitz LM. Attachment styles among young adults. A test of a four category model. J Pers Soc Psychol 1991;61:226–44.
15 Jacobson L. Hypothalamic–pituitary–adrenocortical axis regulation. Endocrinol Metab Clin North Am 2005;34:271–92.
16 Maunder RG, Lancee WJ, Nolan RP, Hunter JJ, Tannenbaum DW. The relationship of attachment insecurity to subjective stress and autonomic function during standardized acute stress in healthy adults. J Psychosom Res 2006;60:283–90.
17 Taylor SE. Mechanisms linking early life stress to adult health outcomes. Proc Natl Acad Sci U S A 2010;107:8507–12.
18 Oskis A, Loveday C, Hucklebridge F, Thorn L, Clow A. Anxious attachment style and salivary cortisol dysregulation in healthy female children and adolescents. J Child Psychol Psychiatry 2011;52:111–8.
19 Rosmond R, Björntorp P. The hypothalamic–pituitary–adrenal axis activity as a predictor of cardiovascular disease, type 2 diabetes and stroke. J Intern Med 2000;247:188–97.
20 Chrousos GP. The role of stress and the hypothalamic–pituitary–adrenal axis in the pathogenesis of the metabolic syndrome: Neuro-endocrine and target tissue-related causes. Int J Obes Relat Metab Disord 2000;24(suppl 2):S50–5.
21 Lawrence AA. Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. Arch Sex Behav 2003;32:299–315.
22 Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller MD, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. Fertil Steril 2009;92: 1685–9.e3.
23 Devor A, Bockting W, Brown G, Brownstein M, Cohen-Kettenis P, DeCuypere G, DeSutter P, Feldman J, Fraser L, Lev AI, Levine S, Meyer W, Meyer-Bahlburg H, Monstrey S, Schechter L, van Trotsenburg M, Winter S, Zucker K. World Professional Association for Transgender Health, Standards of Care (SOC) for the Health of Transsexual, Transgender, and Gender Nonconforming People, 7th version, 2012.
24 Wolfram M, Bellingrath S, Kudielka BM. The cortisol awakening response (CAR) across the female menstrual cycle. Psychoneuroendocrinology 2011;36:905–12.
25 Powell DJ, Schlotz W. Daily life stress and the cortisol awakening response: Testing the anticipation hypothesis. PLoS ONE 2012;7:e52067.
26 Cohen S, Williamson G. Perceived stress in a probability sample of the United States. In: Spacapan S, Oskamp S, eds. Social psychology of health. Newbury Park, CA: Sage; 1988:31–68.
27 Eun-Hyun L. Review of the psychometric evidence of the perceived stress scale. Asian Nurs Res 2012;6:121–7.
28 Kopp MS, Thege BK, Balog P, Stauder A, Salavecz G, Rózsa S, Purebl G, Ádám S. Measures of stress in epidemiological research. J Psychosom Res 2010;69:211–22.

30 Fraley RC. Attachment stability from infancy to adulthood: Meta-analysis and dynamic modeling of developmental mechanisms. Pers Soc Psychol Rev 2002;6:123–51.
31 Simpson JA, Collins WA, Tran S, Haydon KC. Attachment and the experience and expression of emotions in romantic relationships: A developmental perspective. J Pers Soc Psychol 2007;92:355–67.
32 Van IJzendoorn MH, Bakermans-Kranenburg MJ. Attachment representations in mothers, fathers, adolescents, and clinical groups: A meta-analytic search for normative data. J Consult Clin Psychol 1996;64:8–21.
33 Cassidy J, Shaver PR. The Adult Attachment Interview: Protocol, method of analysis, and empirical studies. In: Cassidy J, Shaver PR, eds. Handbook of attachment. New York: The Guilford Press; 2008:552–98.
34 Roisman GI, Holland A, Fortuna K, Fraley RC, Clausell E, Clarke A. The Adult Attachment Interview and self-reports of attachment style: An empirical rapprochement. J Pers Soc Psychol 2007;92:678–97.
35 Ammaniti M, Van Ijzendoorn MH, Speranza AM, Tambelli R. Internal working models of attachment during late childhood and early adolescence: An exploration of stability and change. Attach Hum Dev 2000;2:328–46.
36 Van Ijzendoorn MH, Bakermans-Kranenburg MJ. The distribution of adult attachment representations in clinical groups: A meta-analytic search for patterns of attachment in 105 AAI studies. In: Steele H, Steele M, eds. Clinical applications of the Adult Attachment Interview. New York: Guilford Press; 2008:69–96.
37 Ravitz P, Maunder R, Hunter J, Sthankiya B, Lancee W. Adult attachment measures: A 25-year review. J Psychosom Res 2010;69:419–32.
38 Birkenfeld-Adams A. Quality of attachment in young boys with gender identity disorder: A comparison to clinical and nonreferred control boys. Unpublished doctoral dissertation, York University, Downsview, Canada. 1999.
39 Cook C. Parental contributions to the aetiology of gender identity disorder: A study of attachment, affect regulation and gender conflict. Unpublished master's thesis, The City College of the City University of New York. 1999.
40 Coates SW, Moore MS. The complexity of early trauma: Representation and transformation. In: Di Ceglie D, in collaboration with Freedman D eds. A stranger in my own body. London: H. Karnac Books; 1998:39–62.
41 Zucker KJ, Bradley SJ. Gender identity disorder and psychosexual problems in children and adolescents. New York: Guilford Press; 1995.
42 Di Ceglie D. Gender identity disorder in young people. Adv Psychiatr Treat 2000;6:458–66.
43 Gehring D, Knudson G. Prevalence of childhood trauma in a clinical population of transsexual people. Int J Transgenderism 2000;8:23–30.
44 Heim C, Nemeroff CB. The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. Biol Psychiatry 1999;46(11):1509–22.
45 Heim C, Newport DJ, Bonsall R, Miller AH, Nemeroff CB. Altered pituitary–adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. Am J Psychiatry 2001;158:575–81.
46 Buss C, Lord C, Wadiwalla M, Hellhammer D, Lupien SJ, Meaney M, Pruessner J. Maternal care modulates the relationship between prenatal risk and hippocampal volume. J Neurosci 2007;27:2592–5.
47 Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effect of stress throughout the lifespan on the brain, behaviour and cognition. Nature 2009;10:434–45.
48 Sanchez MM, Ladd CO, Plotsky PM. Early adverse experience as a developmental risk factor for later psychopathology: Evidence from rodent and primate models. Dev Psychopathol 2001;13:419–49.
49 Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP, Kim DM. The neurobiological consequences of early stress and childhood maltreatment. Neurosci Biobehav Rev 2003;27:33–44.
50 Spangler G, Schieche M, Ilg U, Maier U, Ackermann C. Maternal sensitivity as an external organizer for biobehavioral regulation in infancy. Dev Psychobiol 1994;27:425–37.
51 Gunnar MR. Quality of early care and buffering of neuroendocrine stress reactions: Potential effects on the developing human brain. Prev Med 1998;27:208–11.
52 Gunnar MR. Integrating neuroscience and psychological approaches in the study of early experiences. Ann N Y Acad Sci 2003;1008:238–47.
53 Gunnar M. Attachment and stress in early development: Does attachment add to the potency of social regulators of infant stress? In: Carter CS, Ahnert L, Grossmann KE, Hrdy SB, Lamb ME, Porges SW, Sachser N, eds. Attachment and bonding. Cambridge, MA: The MIT Press; 2005:245–56.
54 Gunnar MR, Donzella B. Social regulation of the cortisol levels in early human development. Psychoneuroendocrinology 2002;27:199–220.
55 De Wolff M, van IJzendoorn MH. Sensitivity and attachment: A meta-analysis on parental antecedents of infant attachment. Child Dev 1997;68:571–91.
56 Kirschbaum C, Klauer T, Filipp SH, Hellhammer DH. Sex specific effects of social support on cortisol and subjective response to acute psychological stress. Psychosom Med 1995;57:23–31.
57 Van Ijzendoorn MH, Schuengel C, Bakermans-Kranenburg MJ. Disorganized attachment in early childhood: Meta-analysis of precursors, concomitants, and sequelae. Dev Psychopathol 1999;11:225–49.
58 Larose S, Bernier A. Social support processes: Mediators of attachment state of mind and adjustment in late adolescence. Attach Hum Dev 2001;3:96–120.
59 Steptoe A, Owen N, Kunz-Ebrecht SR, Brydon L. Loneliness and neuroendocrine, cardiovascular, and inflammatory stress responses in middle-aged men and women. Psychoneuroendocrinology 2004;29:593–611.
60 Pruessner JC, Wolf OT, Hellhammer DH, Buske-Kirschbaum A, von Auer K, Jobst S, Kaspers F, Kirschbaum C. Free cortisol levels after awakening: A reliable biological marker for the assessment of adrenocortical activity. Life Sci 1997;61:2539–49.
61 Mueller A, Binder H, Cupisti S, Hoffmann I, Beckmann MW, Dittrich R. Effects on the male endocrine system of long-term treatment with gonadotropin-releasing hormone agonists and estrogens in male-to-female transsexuals. Horm Metab Res 2006;38:183–7.
62 King JA, Rosal MC, Ma Y, Reed GW. Association of stress, hostility and plasma testosterone levels. Neuro Endocrinol Lett 2005;26:355–60.
63 Kuiper B, Cohen-Kettenis P. Sex reassignment surgery: A study of 141 Dutch transsexuals. Arch Sex Behav 1988;17:439–57.
64 Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. Psychopathology 2008;41:96–100.

ORIGINAL RESEARCH

Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria

Rosalia Costa, MD,*† Michael Dunsford, PsyD,* Elin Skagerberg, PhD,* Victoria Holt, MRCPsych,* Polly Carmichael, PhD,*‡ and Marco Colizzi, MD†‡‡

*Gender Identity Development Service, Tavistock and Portman NHS Foundation Trust, Tavistock Centre, London, UK; †Department of Medical Basic Sciences, Neuroscience and Sense Organs, University of Bari "A. Moro," Bari, Italy; ‡Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

DOI: 10.1111/jsm.13034

ABSTRACT

Introduction. Puberty suppression by gonadotropin-releasing hormone analogs (GnRHa) is prescribed to relieve the distress associated with pubertal development in adolescents with gender dysphoria (GD) and thereby to provide space for further exploration. However, there are limited longitudinal studies on puberty suppression outcome in GD. Also, studies on the effects of psychological support on its own on GD adolescents' well-being have not been reported.

Aim. This study aimed to assess GD adolescents' global functioning after psychological support and puberty suppression.

Methods. Two hundred one GD adolescents were included in this study. In a longitudinal design we evaluated adolescents' global functioning every 6 months from the first visit.

Main Outcome Measures. All adolescents completed the Utrecht Gender Dysphoria Scale (UGDS), a self-report measure of GD-related discomfort. We used the Children's Global Assessment Scale (CGAS) to assess the psychosocial functioning of adolescents.

Results. At baseline, GD adolescents showed poor functioning with a CGAS mean score of 57.7 ± 12.3. GD adolescents' global functioning improved significantly after 6 months of psychological support (CGAS mean score: 60.7 ± 12.5; $P < 0.001$). Moreover, GD adolescents receiving also puberty suppression had significantly better psychosocial functioning after 12 months of GnRHa (67.4 ± 13.9) compared with when they had received only psychological support (60.9 ± 12.2, $P = 0.001$).

Conclusion. Psychological support and puberty suppression were both associated with an improved global psychosocial functioning in GD adolescents. Both these interventions may be considered effective in the clinical management of psychosocial functioning difficulties in GD adolescents. **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;12:2206–2214.**

Key Words. Gender Dysphoria; Adolescents; Psychosocial Functioning; Puberty Suppression

Introduction

Gender dysphoria (GD) individuals experience a marked incongruence between their assigned gender and their experienced gender [1]. GD refers to this stressful condition resulting in clinically significant distress or impairment in

‡Joint last authors.
The study was conducted in the Gender Identity Development Service, Tavistock and Portman NHS Foundation Trust, Tavistock Centre, 120 Belsize Lane, London NW3 5BA.

important areas of functioning [2,3]. When supporting and treating children and adolescents with GD, health professionals should broadly conform to the Standards of Care of the World Professional Association for Transgender Health (WPATH) [4]. These guidelines indicate that psychological support should focus on exploring gender identity, role, and expression; addressing the negative impact of GD and stigma on mental health; alleviating internalized transphobia; enhancing social and peer support; improving body image; promoting resilience. Psychological interventions such as individual, couple, family, or group therapy should be provided within a multidisciplinary gender identity specialty service [4].

Studies indicate that cross-sex hormonal treatment (CSHT) improves well-being in GD adults [5,6]. However, it has been observed that despite many years of psychotherapy the GD of most adolescents does not often abate. Rather, once these young persons, who are already experiencing considerable distress over their gender identity, undergo the pubertal development of their biological sex, their psychological well-being deteriorates significantly [7]. Because this risk can be so great, the need for an early intervention has become paramount.

Delemarre-van de Waal and Cohen-Kettenis have proposed an early intervention approach, the Dutch model [8], which aims to eliminate the exposure to unwanted pubertal hormones, limit GD, and improve the ability to "pass" as the desired gender in adulthood. It considers adolescents, after a comprehensive psychological evaluation with many sessions over a longer period of time, eligible for puberty suppression, cross-sex hormonal treatment (CSHT), and gender reassignment surgery (GRS) at the respective ages of 12, 16, and 18 years when there is a history of GD; no psychosocial problems interfering with assessment or treatment; adequate family or other support; and good comprehension of the impact of medical interventions. According to this protocol, suppressing puberty and allowing young individuals the opportunity to explore their gender identity would provide some relief from the distress associated with the development of secondary characteristics [8]. Consistently, some studies indicate that puberty suppression leads to a better psychosocial outcome [2,9].

Since the release of the Dutch model, there has been disagreement about the appropriateness of treatment in minors. Some practitioners have questioned the ethics and safety of this intervention. Conversely, other health care professionals have argued they have an obligation to alleviate suffering and it would be unethical to allow a patient to suffer through the distress of pubertal development when there is a way of preventing it [10]. Anyway, puberty suppression by gonadotropin-releasing hormone analogs (GnRHa) has increasingly become accepted in clinical management of adolescents with GD. Even if further studies are needed, GnRHa are considered a safe and putatively reversible intervention which should be provided to people in need of it, especially if allowing puberty to progress appears likely to harm the young person [7].

There are limited longitudinal studies on the psychosocial functioning of GD adolescents after puberty suppression [2,9]. Also, studies on the effects of psychological support on its own on GD adolescents' psychosocial functioning have not been reported.

Aims

The aim of this study was to assess GD adolescents' psychosocial functioning in follow-up evaluations. Based on previous literature [2,9] and our clinical experience, we hypothesized a poor general functioning at baseline, an improvement after psychological support, and a further improvement after the beginning of the GnRHa.

Methods

Study Design and Participants

This longitudinal study was conducted at the Gender Identity Development Service (GIDS) in London. The health care pathway provided at the GIDS is described in Figure 1. A consecutive series of 436 adolescents (mean age = 15.74 ± 1.38 years; natal male/natal female ratio = 1:1.7) were referred between 2010 and 2014 to the GIDS. 201 adolescents (mean age = 15.52 ± 1.41 years; natal male/natal female ratio = 1:1.6) completed the diagnostic procedure (about 6 months) and were invited to take part in the follow-up evaluations. No GD adolescent refused to participate and all participants and their parents gave informed consent. By clinical interview, all adolescents fulfilled DSM-IV-TR criteria in use at the time for Gender Identity Disorder. The GIDS has adopted the WPATH Standards of Care [4]. There were no significant differences in socio-demographic characteristics as well as baseline CGAS scores

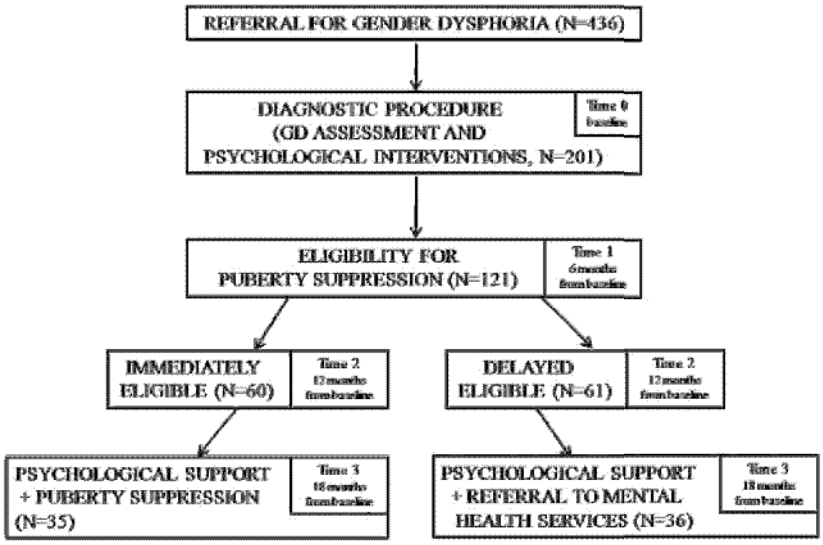


Figure 1 Health care pathway at the Gender Identity Development Service (GIDS)

between adolescents with a GD diagnosis enrolled in this study (N = 201) and adolescents who did not complete the diagnostic procedure (N = 235; all $P > 0.1$).

Psychological Support

The GIDS has developed a standardized psychological assessment which is part of the diagnostic procedure, in accordance with the WPATH guidelines [4]. This model emphasizes the early recognition and non-judgmental acceptance of gender identity problems as well as the importance of ameliorating associated behavioral, emotional and relationship difficulties [11]. Ample room is given to adolescents to explore different options for gender expression. Together with their families GD adolescents are supported in making difficult decisions regarding the extent to which they are allowed to express a gender role that is consistent with their gender identity. Also the timing of changes in gender role and possible social transition are extensively explored. This ensures that decisions about gender expression and the treatment of GD are thoughtfully and recurrently considered. Health care professionals help families to make decisions regarding the timing and process of any gender role changes for their young children. Information is provided to parents to weigh the potential benefits and challenges of choices.

The aims outlined are achieved through various psychotherapeutic interventions, ranging from individual to family and group therapy, which are carried out on a regular basis (at least once a month). Social and educational interventions are also provided if necessary. All these interventions are well coordinated and integrated in a comprehensive management plan agreed with local services (The Network Model). Moreover, the care pathway provides continuous psychological support to the patients' emotional and behavioral changes that may occur during the puberty suppression treatment. All adolescents received psychological support for the entire duration of the study.

Eligibility for Puberty Suppression

In accordance with the WPATH Standards of Care [4], adolescents were able to commence puberty suppression with GnRHa if they met the following criteria: (i) a presence of GD from early childhood on; (ii) an increase of the GD after the first pubertal changes; (iii) an absence of psychiatric comorbidity that interferes with the diagnostic work-up or treatment; (iv) adequate psychological and social support during treatment; and (v) a demonstration of knowledge and understanding of the effects of GnRHa, cross-sex hormone treatment, surgery, and the social consequences of sex reassignment. All GD adolescents were considered eligible for puberty suppression. Eligible adolescents were divided into two groups: immediately eligible and delayed eligible adolescents, consistently with Cohen-Kettenis and colleagues [12]. Immediately eligible adolescents started GnRHa at the end of the diagnostic procedure (0.75 ± 0.59 years from baseline). On the contrary, some adolescents were considered delayed eligible and continued to receive psychological support without

any type of physical intervention until they felt ready to make a decision in collaboration with their families and the clinicians. In those specific cases clinicians needed more time to make the decision of starting GnRHa because of possible comorbid psychiatric problems and/or psychological difficulties. If concomitant problems were observed (e.g., psychiatric problems, substantial problems with peers, or conflicts with parents or siblings), the young person was referred to a local mental health service. All possible medical and/or psychosocial interventions were well coordinated, integrated in a comprehensive management plan agreed with local services, and tended to be individualized in relation to the psychopathology/difficulty. The primary aim was for the child and the family to function better. After being assessed and, if necessary, treated for a psychiatric comorbidity, all delayed eligible GD individuals received puberty suppression. The interval from the start of the diagnostic procedure to the start of puberty suppression took about 1.5 years (1.5 ± 0.63 years from baseline). None of the delayed eligible individuals received puberty suppression at the time of this study.

Main Outcome Measures

Socio-Demographic Information

The data collected included: natal gender (male–female ratio), age (at assessment, at start of GnRHa), education level (yes/no), living arrangement (both parents, one parents, other), living in the chosen gender (partly, i.e., by wearing clothing and having a hairstyle that reflects gender identity/completely, i.e., by also using a name and pronouns congruent with gender identity/no), and change of name (yes/no).

GD-Related Discomfort

The Utrecht GD Scale (UGDS) was used to measure adolescents' GD-related discomfort. This is a 12-item questionnaire specifically developed to measure GD in a dimensional way. In particular, the UGDS focuses on core aspects of GD and gender identity. The adolescents are asked to rate their agreement on a 5-point scale. The total score ranges from 12 to 60. Higher UGDS total scores indicate high level of GD [13]. The scale has shown a high reliability (a Cronbach's alpha of 0.66–0.80 in one sample, and 0.78–0.92 in another); as reported by the authors, the lower alphas on the scale were only found among control subjects, which may be related to the lower variability of GD in these groups [13]. Cronbach's alpha for UGDS in our sample was 0.76–0.88. The UGDS has also shown a good discriminant validity, when adolescents and adults with and without a GD diagnosis were compared.

Measure of Global Psychosocial Functioning

The Children's Global Assessment Scale (CGAS) was used to assess adolescents' psychosocial functioning. The CGAS is one of the most widely used rating scales designed to measure how children and adolescents function psychosocially in daily life [14]. This clinical-rated instrument is divided into 10-point intervals and ranges from 1 to 100, with higher scores indicating better psychosocial functioning. The CGAS is useful to assess psychosocial/psychiatric outcomes, socio-cognitive competence and changes because of treatment [15]. In particular, it has been used in several longitudinal and epidemiological studies in clinical and non-clinical populations, naturalistic cohorts [16], and young GD individuals [9]. The inter-rater reliability was tested by Shaffer and his colleagues [14] before publication of CGAS, in order to minimize variation because of clinician background. Test–retest has been described in different studies with raters' consistence over time [16].

All CGAS were administered by qualified psychologists, psychotherapists, and psychiatrists who attended training and intra-class correlation assessment ($0.76 \leq$ Cronbach's $\alpha \leq 0.94$). Participants were assessed at baseline (Time 0) and every following 6 months, for a total of four evaluations over an 18-month period. Follow-up evaluations were performed 6 months from the baseline (Time 1: after 6 months of psychological support); 12 months from the baseline (Time 2: after 12 months of psychological support for delayed eligible GD adolescents, and after 12 months of psychological support + 6 months of puberty suppression for immediately eligible GD adolescents); 18 months from the baseline (Time 3: after 18 months of psychological support for delayed eligible GD adolescents, and after 18 months of psychological support + 12 months of puberty suppression for immediately eligible GD adolescents).

Participants were compared with a sample of young individuals without observed psychological/psychiatric symptoms ($N = 169$), using the same methodology of this study, the CGAS scale [16]. This sample was part of a large naturalistic cohort

of children/adolescents who attended child and adolescent mental health services (CAMHS; N = 12,613) in Stockholm in order to be evaluated for their psychosocial functioning.

Statistical Analysis

Chi-squared and independent *t*-tests were used to test for possible differences in socio-demographic characteristics and CGAS scores between natal men and natal women; adolescents who did not complete the diagnostic procedure and adolescents who received a GD diagnosis; immediately eligible and delayed eligible individuals. Dependent and independent *t*-tests were used to test for possible differences in CGAS scores between baseline and follow-up evaluations, in both immediately eligible and delayed eligible individuals.

Finally, independent *t*-tests were used to compare GD adolescents' CGAS scores with CGAS scores from a sample of children/adolescents without observed psychological/psychiatric symptoms [16].

Ethics

The study received ethical approval from the National Research Ethics Service (NRES) Committee London-Camden and Islington.

Results

Socio-Demographic Characteristics of the Sample

Socio-demographic characteristics of the sample (N = 201) are reported in Table 1. The majority of GD adolescents were living with one parent, were in education, were living as a member of the desired gender, and had changed their names. However, compared with natal women, a higher proportion of natal men did not live with their biological parents, had left school, were not living as a member of the desired gender, and had not changed their names. Moreover, natal women reported a significantly higher GD-related discomfort than natal men. Natal men and women did not differ in their age, both at assessment and when GnRHa was started (Table 1).

Table 1 General characteristics of 201 adolescents with gender dysphoria

Age in years, M (SD)	All participants	Natal men	Natal women	Statistical comparisons *t*-test; *P* value
Baseline	15.52 (1.41)	15.61 (1.70)	15.46 (1.22)	0.73; 0.47
Range	12–17	12–17	12–17	
At start of GnRHa	16.48 (1.26)	16.64 (1.22)	16.39 (1.28)	0.74; 0.46
Range	13–17	13–17	13–17	
Living arrangement, N (%)				χ^2; *P*
Both parents	78 (41.5)	25 (33.7)	53 (44.2)	8.95; 0.01
One parent	100 (53.2)	35 (51.5)	65 (54.2)	
Other*	10 (5.3)	8 (11.8)	2 (1.6)	
No details	13	8	5	3.47; 0.06
Education				
Yes	168 (89.8)	56 (83.6)	112 (93.3)	20.52; <0.001
No	19 (10.2)	11 (16.4)	8 (6.7)	
No details	14	9	5	
Living in role				
Completely	117 (62.6)	29 (42.6)	88 (73.9)	23.14; <0.001
Partly	27 (14.4)	12 (17.7)	15 (12.6)	
No	43 (23.0)	27 (39.7)	16 (13.5)	
No details	14	8	6	
Change name				
Yes	107 (57.5)	23 (33.8)	84 (71.2)	
No	79 (42.5)	45 (66.2)	34 (28.8)	
No details	15	8	7	
	Mean (SD)	Mean (SD)	Mean (SD)	*t*-test; *P* value
UGDS†	54.7. (6.8)	51.6 (9.7)	56.1 (4.3)	4.07; <0.001
CGAS at baseline	57.7 (12.3)	55.4 (12.7)	59.2 (11.8)	2.15; 0.03

*Living in children's home, living with other family's members
†Data available in 160 individuals, 50 natal men (31.25%), 110 natal women (68.75%)
M (SD) = mean (standard deviation); UGDS = Utrecht Gender Dysphoria Scale; CGAS = Children's Global Assessment Scale; GnRHa = gonadotropin-releasing hormone analogs

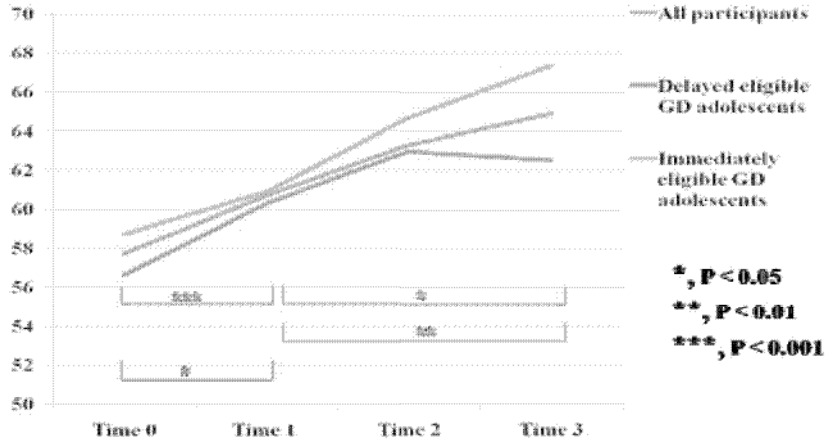


Figure 2 Gender dysphoria adolescents' psychosocial functioning (CGAS) at baseline, after psychological support, and after puberty suppression
CGAS, Children's Global Assessment Scale; Time 0, baseline; Time 1, 6 months from baseline (after 6 months of psychological support); Time 2, 12 months from baseline (delayed eligible gender dysphoria [GD] adolescents, after 12 months of psychological support; immediately eligible GD adolescents, after 12 months of psychological support + 6 months of puberty suppression); Time 3, 18 months from baseline (delayed eligible GD adolescents, after 18 months of psychological support; immediately eligible GD adolescents, after 18 months of psychological support + 12 months of puberty suppression)

CGAS at Baseline

GD adolescents' CGAS at baseline (Time 0, $M = 57.7 \pm 12.3$) revealed a score suggestive of

of the following evaluations (Figure 2). In particular, CGAS scores were significantly higher after 6 months of psychological support (Time 0 vs. Time 1, $P < 0.001$). Also there was a further significant improvement 18 months from baseline (Time 1 vs. Time 3, $P = 0.02$; Table 2).

Delayed eligible GD adolescents, who received only psychological support for the entire duration of the study, had a significantly better psychosocial functioning after six months of psychological support (Time 0 vs. Time 1, $P = 0.05$). However, despite scoring better at the following evaluations they did not show any further significant improvement in their psychosocial functioning (Table 2). Also, the delayed eligible group continued to score lower than a sample of children/adolescents without observed psychological/psychiatric symptoms [16], even after 18 months of psychological support (Time 3, $t = 2.0$, $P = 0.04$).

On the contrary, the immediately eligible group, who at baseline had a higher, but not significantly different psychosocial functioning than the delayed eligible group, did not show any significant improvement after 6 months of psychological support. However, immediately eligible adolescents had a significantly higher psychosocial functioning after 12 months of puberty suppression compared with when they had received only psychological support (Time 1 vs. Time 3 $P = 0.001$; Table 2). Also, their CGAS scores after 12 months of puberty suppression (Time 3) coincided almost perfectly with those found in a sample of children/adolescents without observed psychological/psychiatric symptoms ($t = 0.01$, $P = 0.99$) [16].

There were no significant differences in CGAS scores between GD natal men and women in all the follow-up evaluations (all $P > 0.1$). Also delayed eligible and immediately eligible GD adolescents did not differ in their demographic variables (all $P > 0.1$). Finally, even if at the end of the

Table 2 Gender dysphoria adolescents' psychosocial functioning (CGAS) at baseline, after psychological support, and after puberty suppression

	Time 0 N M/F ratio M (SD)	Time 1 N M/F ratio M (SD)	Time 2 N M/F ratio M (SD)	Time 3 N M/F ratio M (SD)	Statistical comparisons *t*-test; *P* value
All participants	N = 201 1:1.6 57.73 (12.27)	N = 201 1:1.6 60.68 (12.47)	N = 121 1:1.6 63.31 (14.41)	N = 71 1:1.6 64.93 (13.85)	4.87*; <0.001 3.70†; <0.001 4.11‡; <0.001 1.73§; 0.08 2.40¶; 0.02 0.76**; 0.45
Delayed eligible GD adolescents	N = 100 1:1.6 56.63 (13.14)	N = 100 1:1.6 60.29 (12.81)	N = 61 1:1.6 62.97 (14.10)	N = 36 1:1.6 62.53 (13.54)	1.99*; 0.05 2.89†; 0.005 2.29‡; 0.02 1.24§; 0.22 0.89¶; 0.37 0.15**; 0.88
Immediately eligible GD adolescents	N = 101 1:1.7 58.72 (11.38)	N = 101 1:1.7 60.89 (12.17)	N = 60 1:1.7 64.70 (13.34)	N = 35 1:1.7 67.40 (13.93)	1.31*; 0.19 3.02†; 0.003 3.66‡; <0.001 1.85§; 0.07 2.63¶; 0.001 0.94**; 0.35
Statistical comparisons *t*-test; *P* value	1.21††; 0.23	0.34††; 0.73	0.69†; 0.49	1.49†; 0.14	

*Comparison between baseline and Time 1
†Comparison between baseline and Time 2
‡Comparison between baseline and Time 3
§Comparison between Time 1 and Time 2
¶Comparison between Time 1 and Time 3
**Comparison between Time 2 and Time 3
††Comparison between delayed eligible GD adolescents and immediately eligible GD adolescents
CGAS = Children's Global Assessment Scale; M/F = natal male/natal female; M (SD) = mean (standard deviation)

follow-up study (Time 3) the immediately eligible group had a 5-point higher CGAS score than the delayed eligible group, this difference failed to reach significance, possible because of sample size (Table 2).

Discussion

Results from this study indicate that psychological support is associated with a better psychosocial functioning in GD adolescents, especially if presenting psychological/psychiatric problems. Moreover, puberty suppression was associated with a further improvement in global functioning. Finally, global functioning improved steadily over time in GD adolescents receiving both psychological support and GnRHa.

Medical and surgical interventions are considered to be necessary components of effective management in GD adults. These partially reversible/irreversible treatments aim to align the individuals' physical appearance with their internal gender identity and have been shown to improve the patients' psychosocial well-being [3,5,6]. GD adolescents may experience psychosocial problems at puberty onset because of an intensification of feelings of incongruence between self-perception and their natal gender [2,9]. Therefore, in the prepubertal population, the suppression of puberty using continuous GnRHa is a fully reversible treatment which has the fundamental benefit for children of gaining time to reflect over their gender identity, have a real-life experience living as the other gender (i.e., in dress and behavior) and determine whether or not they desire the transition [12,13]. Preventing the development of a body contrary to the experienced gender, puberty suppression allows GD adolescents to experience a smooth transition into their desired gender role. This translates into an improvement in many aspects of their psychosocial functioning, such as mood improvement and school integration [2,9]. Consistently, these results underline the importance of puberty suppression for GD adolescents' well-being.

The GD adolescents' improved global functioning after only 6 months of psychological support may have different explanations. First, it

could indicate that the timely addressing of psychosocial problems contributes to enhanced psychological well-being. Second, as also reported in previous studies among both GD adults and adolescents [2,3,5,9], our clinical experience suggests that patients attending a gender unit are pleased in the knowledge that the puberty suppression will be performed within a reasonable time and refer a distress reduction because of their accepted and understood requirements. Moreover, the initiation of the puberty suppression may have a psychological meaning which *per se* could be fundamental in reducing distress. In any case, data are too limited to express conclusively.

Both natal men and women benefited from the clinical approach, although natal men had a significantly worse functioning than natal women at baseline. It is even more important if we consider that natal men reported more social difficulties than natal women (higher dropout from school and more frequently not living with their parents). Interestingly, natal women reported significantly more GD-related discomfort than natal men. As already suggested [2], with a mean of 15 years most natal women had developed their breasts and had their menarche, which are likely to be associated with higher levels of distress. Therefore, natal men and women may need to be thought about separately and may require different interventions. Also, as the revised Dutch model [8] encourages considering GD individuals eligible for puberty suppression when they are 12 years old, studies are ongoing at our service to explore the possible benefit of further reducing the age for being eligible for puberty suppression. Even if the absence of a control group in our study does not allow us to pronounce conclusively on these comparisons, GD adolescents undergoing puberty suppression in addition to the psychological support result in psychosocial functioning levels that are impossible to differentiate from a sample of peers. These additional findings further indicate the effectiveness of both psychological support and puberty suppression in enabling young GD individuals to reach a satisfactory psychosocial functioning.

In the present study, there are some limitations. Even if psychosocial functioning is of crucial importance to identify clinical or sociocognitive difficulties [17], we focused only on a measure of psychosocial well-being. Also, the study sample was relatively small and came from only one clinic. Most importantly, despite the findings seem to suggest a cumulative and increasing over time positive effect of psychological support and GnRHa on young GD patients' well-being, results could have also different explanations because of the study design. For instance, getting older has been positively associated with maturity and well-being [18]. Ideally, a blinded randomized controlled trial design should have been performed. However, it is highly unlikely that adolescents would be motivated to participate. Also, disallowing puberty suppression, resulting in irreversible development of secondary sex characteristics, may be considered unethical [2]. Moreover, we cannot be conclusive on the higher GD-related distress in natal women compared with natal men. There are different versions of the UGDS scale for men and women, with specific items reversely coded because of gender. These differences do not allow drawing strong conclusions from the gender difference analysis.

Conclusions

In conclusion, this study confirms the effectiveness of puberty suppression for GD adolescents. Recently, a long-term follow-up evaluation of puberty suppression among GD adolescents after CSHT and GRS has demonstrated that GD adolescents are able to maintain a good functioning into their adult years [2]. The present study, together with this previous research [2], indicate that both psychological support and puberty suppression enable young GD individuals to reach a psychosocial functioning comparable with peers.

Corresponding Author: Rosalia Costa, MD, Gender Identity Development Service, Tavistock and Portman NHS Foundation Trust, Tavistock Centre, 120 Belsize Lane, London NW3 5BA, UK. Tel: +447947213589; Fax: + 39-0805593058; E-mail: rcosta@tavi-port.nhs.uk

Conflict of Interest: The author(s) report no conflicts of interest.

Statement of Authorship

Category 1

(a) **Conception and Design**
Rosalia Costa, Michael Dunsford, Elin Skagerberg, Victoria Holt, Polly Carmichael, Marco Colizzi

(b) **Acquisition of Data**
Rosalia Costa, Michael Dunsford, Elin Skagerberg, Victoria Holt, Polly Carmichael, Marco Colizzi

(c) **Analysis and Interpretation of Data**
Rosalia Costa, Polly Carmichael, Marco Colizzi

Category 2

(a) **Drafting the Article**
Rosalia Costa, Polly Carmichael, Marco Colizzi

(b) **Revising It for Intellectual Content**
Rosalia Costa, Michael Dunsford, Elin Skagerberg, Victoria Holt, Polly Carmichael, Marco Colizzi

Category 3

(a) **Final Approval of the Completed Article**
Rosalia Costa, Michael Dunsford, Elin Skagerberg, Victoria Holt, Polly Carmichael, Marco Colizzi

References

1 American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th edition. Washington, DC: American Psychiatric Association; 2013.
2 de Vries AL, McGuire JK, Steensma TD, Wagenaar EC, Doreleijers TA, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 2014;134:696–704.
3 Colizzi M, Costa R, Pace V, Todarello O. Hormonal treatment reduces psychobiological distress in gender identity disorder, independently of attachment style. J Sex Med 2013;10:3049–58.
4 Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfaefflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha W, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. Standards of care (SOC) for the health of transsexual, transgender, and gender nonconforming people, 7th version. Int J Transgender 2012;13:165–232.
5 Colizzi M, Costa R, Todarello O. Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: Results from a longitudinal study. Psychoneuroendocrinology 2014;39:65–73.
6 Colizzi M, Costa R, Todarello O. Dissociative symptoms in individuals with gender dysphoria: Is the elevated prevalence real? Psychiatry Res 2015;226:173–80.
7 Giordano S. Lives in a chiaroscuro. Should we suspend the puberty of children with gender identity disorder? J Med Ethics 2008;34:580–4.
8 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(suppl 1):S131–7.
9 De Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: A prospective study. J Sex Med 2011;8:2276–83.
10 Kreukels BP, Cohen-Kettenis PT. Puberty suppression in gender identity disorder: The Amsterdam experience. Nat Rev Endocrinol 2011;7:466–72.
11 Di Ceglie D. Management and therapeutic aims with children and adolescents with gender identity disorders and their families. In: Di Ceglie D, Freedman D, eds. A stranger in my own body: Atypical gender identity development and mental health. London: Karnac; 1998:185–97.
12 Cohen-Kettenis PT, Delemarre-van de Waal HA, Gooren LJ. The treatment of adolescent transsexuals: Changing insights. J Sex Med 2008;5:1892–7.
13 Cohen-Kettenis PT, van Goozen SHM. Sex reassignment of adolescent transsexuals: A follow-up study. J Am Acad Child Adolesc Psychiatry 1997;36:263–71.
14 Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwahlia S. A Children's Global Assessment Scale (CGAS). Arch Gen Psychiatry 1983;40:1228–31.
15 Schorre BE, Vandvik IH. Global assessment of psychosocial functioning in child and adolescent psychiatry. A review of three unidimensional scales (CGAS, GAF, GAPD). Eur Child Adolesc Psychiatry 2004;13:273–86.
16 Lundh A, Forsman M, Serlachius E, Lichtenstein P, Landén M. Outcomes of child psychiatric treatment. Acta Psychiatr Scand 2013;128:34–44.
17 Prince M, Glozier N, Sousa R, Dewey M. Measuring disability across physical, mental and cognitive disorders. In: Regier DA, Narrow WE, Kuhl EA, Kupfer DJ, eds. The conceptual evolution of DSM-5. Washington, DC: American Psychiatric Publishing; 2011:189–227.
18 Sheldon KM, Kasser T. Getting older, getting better? Personal striving and psychological maturity across the life span. Dev Psychol 2001;37:491–501.

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.

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

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

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.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-2958

doi:10.1542/peds.2013-2958

Accepted for publication Jul 7, 2014

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

(Continued on last page)

Transgender adolescents experience an incongruence between their assigned gender and their experienced gender and may meet the Diagnostic and Statistical Manual of Mental Disorders 5 criteria for gender dysphoria (GD).[1] Fifteen years ago, pubertal delay was introduced as an aid in the treatment of a gender dysphoric adolescent.[2] Although not without debate, blocking pubertal development has rapidly become more widely available[3–7] and is now part of the clinical management guidelines for GD.[8–12]

Gonadotropin-releasing hormone analogs (GnRHa) are a putatively fully reversible[13] medical intervention intended to relieve distress that gender dysphoric adolescents experience when their secondary sex characteristics develop. A protocol designed by Cohen-Kettenis and Delemarre-van de Waal[14] (sometimes referred to as "the Dutch model")[4,7] considers adolescents, after a comprehensive psychological evaluation with many sessions over a longer period of time, eligible for puberty suppression, cross-sex hormones (CSH), and gender reassignment surgery (GRS) at the respective ages of 12, 16, and 18 years when there is a history of GD; no psychosocial problems interfering with assessment or treatment, for example, treatment might be postponed because of continuous moving from 1 institution to another or repeated psychiatric crises; adequate family or other support; and good comprehension of the impact of medical interventions.[12] Puberty suppression is only started after the adolescent actually enters the first stages of puberty (Tanner stages 2–3), because although in most prepubertal children GD will desist, onset of puberty serves as a critical diagnostic stage, because the likelihood that GD will persist into adulthood is much higher in adolescence than in the case of childhood GD.[15,16]

Despite the apparent usefulness of puberty suppression, there is only limited evidence available about the effectiveness of this approach. In the first cohort of adolescents who received GnRHa, we demonstrated an improvement in several domains of psychological functioning after, on average, 2 years of puberty suppression while GD remained unchanged.[16] The current study is a longer-term evaluation of the same cohort, on average, 6 years after their initial presentation at the gender identity clinic. This time, we were not only interested in psychological functioning and GD, but added as important outcome measures objective and subjective well-being (often referred to as "quality of life"), that is, the individuals' social life circumstances and their perceptions of satisfaction with life and happiness.[17–19] After all, treatment cannot be considered a success if GD resolves without young adults reporting they are healthy, content with their lives, and in a position to make a good start with their adult professional and personal lives.[20] Because various studies show that transgender youth may present with psychosocial problems,[21,22] a clinical approach that includes both medical (puberty suppression) and mental health support (regular sessions, treatment when necessary, see Cohen-Kettenis et al[12]) aims to improve long-term well-being in all respects.

In the present longitudinal study, 3 primary research questions are addressed. Do gender dysphoric youth improve over time with medical intervention consisting of GnRHa, CSH, and GRS? After gender reassignment, how satisfied are young adults with their treatment and how do they evaluate their objective and subjective well-being? Finally, do young people who report relatively greater gains in psychological functioning also report a higher subjective well-being after gender reassignment?

METHODS

Participants and Procedure

Participants included 55 young adults (22 transwomen [natal males who have a female gender identity] and 33 transmen [natal females who have a male gender identity]) of the first cohort of 70 adolescents who had GD who were prescribed puberty suppression at the Center of Expertise on Gender Dysphoria of the VU University Medical Center and continued with GRS between 2004 and 2011. These adolescents belonged to a group of 196 consecutively referred adolescents between 2000 and 2008, of whom 140 had been considered eligible for medical intervention and 111 were prescribed puberty suppression (see de Vries et al[16]). The young adults were invited between 2008 and 2012, when they were at least 1 year past their GRS (vaginoplasty for transwomen, mastectomy and hysterectomy with ovariectomy for transmen; many transmen chose not to undergo a phalloplasty or were on a long waiting list). Nonparticipation (n = 15, 11 transwomen and 4 transmen) was attributable to not being 1 year postsurgical yet (n = 6), refusal (n = 2), failure to return questionnaires (n = 2), being medically not eligible (eg, uncontrolled diabetes, morbid obesity) for surgery (n = 3), dropping out of care (n = 1), and 1 transfemale died after her vaginoplasty owing to a postsurgical necrotizing fasciitis. Between the 55 participants and the 15 nonparticipating individuals, Student's t tests revealed no significant differences on any of the pretreatment variables. A similar lack of differences was found between the 40 participants who had complete data and the 15 who were missing some data.

Participants were assessed 3 times: pre-treatment (T0, at intake), during treatment (T1, at initiation of CSH), and post-treatment (T2, 1 year after GRS). See Table 1 for age at the different time points. The VU University Medical Center medical ethics committee approved the study, and all participants gave informed consent.

TABLE 1 Age at Different Treatment Milestones and Intelligence by Gender

Variable	All Participants[a] ($N = 55$)		Transwomen (Natal Males) ($N = 22$)	Transmen (Natal Females) ($N = 33$)
Age, y	Mean (SD)	Range	Mean (SD)	Mean (SD)
At assessment PreT	13.6 (1.9)	11.1–17.0	13.6 (1.8)	13.7 (2.0)
At start of GnRHa	14.8 (1.8)	11.5–18.5	14.8 (2.0)	14.9 (1.9)
At start of CSH	16.7 (1.1)	13.9–19.0	16.5 (1.3)	16.8 (1.0)
At GRS	19.2 (0.9)	18.0–21.3	19.6 (0.9)	19.0 (0.8)
At assessment PostT	20.7 (1.0)	19.5–22.8	21.0 (1.1)	20.5 (0.8)
Full-scale intelligence[b]	99.0 (14.3)	70–128	97.8 (14.2)	100.4 (14.3)

PostT, post-treatment; PreT, pre-treatment.

[a] Comparisons between those who had complete data ($n = 40$) and those who had missing data on the CBCL/ABCL ($n = 15$) reveal no significant differences between the groups in age at any point in the study or in natal sex.

[b] WISC-R, the WISC-III, or the WAIS-III at first assessment, depending on age and time.[45–47]

Measures

Time was the predominate independent variable. Other demographic characteristics were incorporated in some models, including, age, natal sex, Full Scale Intelligence, and parent marital status; where significantly different they are reported.

Gender Dysphoria/Body Image

There was 1 indicator measuring GD (Utrecht Gender Dysphoria Scale [UGDS]) and 3 indicators measuring body image (Body Image Scale [BIS] with primary, secondary, and neutral subscales). Higher UGDS (12 items, 1–5 range, total score ranging from 12–60) total scores indicate higher levels of GD, for example, "I feel a continuous desire to be treated as a man/woman."[23] There are separate versions of the UGDS for males and females with mostly different items, permitting no gender difference analyses. BIS (30 items, 1–5 range) higher scores indicate more dissatisfaction with primary sex characteristics (important gender-defining body characteristics, eg, genitals, breasts), secondary sex characteristics (less obvious gender-defining features, eg, hips, body hair), and neutral (hormonally unresponsive) body characteristics (eg, face, height).[24] The male and the female BIS are identical except for the sexual body parts. The UGDS and the BIS of the natal gender were administered at T0 and T1. At T1, we chose the UGDS of the assigned gender, because no physical changes had occurred yet and some were still treated as their assigned gender. This way, however, decreased GD caused by social transitioning was not measured. At T2 young adults filled out the versions of their affirmed gender.

Psychological Functioning

There were 10 indicators assessing psychological functioning. To assess global functioning, the Children's Global Assessment Scale (CGAS) was used.[25] The Beck Depression Inventory (BDI; 21 items, 0–3 range) indicates presence and severity of depressive symptoms.[26] Spielberger's Trait Anger (TPI) and Spielberger's Trait Anxiety (STAI; 10 and 20 items, respectively, 1–4 range) scales of the State-Trait Personality Inventory were administered to assess the tendency to respond with anxiety or anger, respectively, to a threatening or annoying situation.[27,28]

Behavioral and emotional problems were assessed by the total, internalizing, and externalizing T scores as well as clinical range scores for these 3 indices (T score >63) of the Child/Adult Behavior Checklist (CBCL at T0 and T1, ABCL at T2), the Youth/Adult Self-Report (YSR at T0 and T1, ASR at T2).[29–31] Items referring to GD in the CBCL/YSR and ABCL/ASR were scored as 0 (for more explanation, see Cohen-Kettenis et al[32]).

Objective and Subjective Well-Being (T2 Only)

A self-constructed questionnaire was used to ask the young adults about their current life circumstances, such as living conditions, school and employment, and social support (objective well-being), and satisfaction with treatment (subjective well-being). Three instruments further assessed subjective well-being. To measure quality of life, the WHOQOL-BREF (quality of life measure developed by the World Health Organization) was administered (24 items, 4 domains: Physical Health, Psychological Health, Social Relationships, and Environment, 1–5 range with higher scores indicating better quality of life).[17] The Satisfaction With Life Scale (SWLS, 5 items, 5–35 range, 20 being neutral) was used to assess life satisfaction.[18] Higher scores on the Subjective Happiness Scale (SHS, 4 items, 7-point Likert scale, average score 1–7) reflect greater happiness.[19]

Data Analyses

General Linear Models examined the repeated measures with an analysis of variance-based model, incorporating continuous and categorical predictors, and correcting for the unbalanced cell sizes. Linear and quadratic effects of the 14 indicators across 3 time points, with time as the within-subjects factor, and sex as a between-subjects factor in a second set of analyses are reported in Tables 2 and 3 and Fig 1. A linear effect signifies an overall change across T0 to T2. A quadratic effect signifies that the change was not continuous, such as when an indicator does not improve from T0 to T1 but improves from T1 to T2. It is possible to have both a significant linear and quadratic effect on the same

TABLE 2 Gender Dysphoria and Body Image of Adolescents at Intake (T0), While on Puberty Suppression (T1), and After Gender Reassignment (T2)

	N[a]	T0	T1	T2	T0–T2	Time	Time × Sex
					t test	Linear Effect Quadratic Effect	Linear Effect Quadratic Effect
		Mean (SD)	Mean (SD)	Mean (SD)	*P*	*P*	*P*
UGDS	33	53.51 (8.29)	54.39 (7.70)	15.81 (2.78)	<.001		
MtF	11	47.07 (11.05)	48.95 (10.80)	17.27 (2.57)	<.001	<.001 <.001	n/a
FtM	22	56.74 (3.74)	57.11 (3.40)	15.08 (2.64)	<.001	<.001 <.001	n/a
Body Image (BIS)							
Primary sex characteristics	45	4.13 (0.59)	4.05 (0.60)	2.59 (0.82)	<.001	<.001 <.001	.01 .45
MtF	17	4.03 (0.68)	3.82 (0.56)	2.07 (0.74)	<.001		
FtM	28	4.18 (0.53)	4.13 (0.60)	2.89 (0.71)	<.001		
[illegible]	[illegible]	[illegible]	[illegible]	[illegible] 07 (0.56)	<.001	<.001 <.001	.10 <.001
[illegible]	[illegible]	[illegible]	[illegible]	[illegible] 3 (0.63)	<.001		
[illegible]	[illegible]	[illegible]	[illegible]	[illegible] 8 (0.40)	.05		
[illegible]	MtF	17	[illegible]	[illegible] 3 (0.49)	.29	.29	.007
[illegible]	FtM	[illegible]	[illegible]	[illegible]		.01	.01
[illegible]	[illegible]	[illegible]	[illegible]	[illegible] 9 (0.56)	.014		
[illegible]	[illegible]	[illegible]	[illegible]	[illegible] 2 (0.44)	.40		

[illegible] ere added to the study later, yielding fewer total participants for those scales.

[illegible] RESULT

[illegible] ia and Body

cluded owing to a lack of relationship with the 14 indicators at T0. The 1 exception, age predicting secondary sex characteristics, is described below in the findings. We compared T2 sample means to population norms for subjective well-being using 1-sample *t* tests from previously published validation studies. Finally, we examined T2 subjective well-being correlations with residual change scores from T0 to T2 on the 14 indicators (an indicator of who improved relatively more or less over time).

All measures used were self-reported, except the CGAS (attending clinician) and the CBCL/ASR (parents). Each participant was given all measures at each of 3 assessments. Numbers varied across indicators owing to the later inclusion of the YSR, CGAS, BDI, TPI, and STAI, yielding 8 persons who had missing data at T0 and a clinician error yielding missing data at T1 for 10 participants on the UGDS. Dutch versions were used (see de Vries et al[16]).

Figure 1 and Table 2 show that GD and body image difficulties persisted through puberty suppression (at T0 and T1) and remitted after the administration of CSH and GRS (at T2) (significant linear effects in 3 of 4 indicators, and significant quadratic effects in all indicators). Time by sex interactions revealed that transwomen reported more satisfaction over time with primary sex characteristics than transmen and a continuous improvement in satisfaction with secondary and neutral sex characteristics. Transmen reported more dissatisfaction with secondary and neutral sex characteristics at T1 than T0, but improvement in both from T1 to T2. Age was a significant covariate with secondary sex characteristics (the only significant demographic covariate with any outcome indicator in the study), indicating that older individuals were more dissatisfied at T0, but the age gap in body satisfaction narrowed over time ($F(1, 42) = 8.18$; $P < .01$).

Psychological Functioning

As presented in Table 3, significant linear effects showed improvement over time in global functioning (CGAS), CBCL/ABCL total, internalizing and externalizing *T* scores, and YSR/ASR total and internalizing *T* scores. Quadratic effects revealed decreases from T0 to T1 followed by increases from T1 to T2 in depression and YSR/ASR internalizing *T* scores. Quadratic trends revealed decreases from T0 to T1, followed by increases from T1 to T2 in depression and YSR/ASR internalizing *T* scores. For all CBCL/ABCL and YSR/ASR indicators except YSR/ASR externalizing, the percentage in the clinical range dropped significantly (McNemar's test, *P* value <0.05) from T0 to T1, from T0 to T2, or from T1 to T2.

Over time, transmen showed reduced anger, anxiety, and CBCL/ABCL externalizing *T* scores, whereas transwomen showed stable or slightly more symptomatology on these measures. Transwomen improved in CBCL/ABCL total *T* scores in a quadratic fashion (all the improvement between T1 and T2),

TABLE 3 Psychological Functioning of Adolescents at Intake (T0), While on Puberty Suppression (T1), and After Gender Reassignment (T2)

	N^a	T0	T1	T2	T0–T2	Time	Time × Sex
					t test	Linear Effect Quadratic Effect	Linear Effect Quadratic Effect
		Mean (SD)	Mean (SD)	Mean (SD)	*P*	*P*	*P*
Global functioning (CGAS)	32	71.13 (10.46)	74.81 (9.86)	79.94 (11.56)	<.001	<.001	.89
						.61	.68
MtF	15	74.33 (7.53)	78.20 (9.56)	82.40 (8.28)	<.001		
FtM	17	67.65 (11.87)	70.65 (9.89)	76.29 (14.48)	.02		
Depression (BDI)	32	7.89 (7.52)	4.10 (6.17)	5.44 (8.40)	.21	.23	.66
						.04	.49
MtF	12	4.73 (4.20)	2.25 (3.54)	3.38 (4.40)	.12		
FtM	20	10.09 (8.34)	5.05 (7.08)	6.95 (9.83)	.32		
Anger (TPI)	32	17.55 (5.72)	17.22 (5.61)	16.01 (5.28)	.20	.15	.04
						.52	.12
MtF	12	14.17 (3.01)	14.00 (3.36)	5.58 (3.92)	.18		
FtM	20	19.55 (5.96)	19.25 (5.69)	16.56 (6.06)	.05		
Anxiety (STAI)	32	39.57 (10.53)	37.52 (9.87)	37.61 (10.39)	.45	.42	.05
						.47	.52
MtF	12	31.87 (7.42)	31.71 (8.36)	35.83 (10.22)	.14		
FtM	20	44.41 (9.06)	41.59 (9.03)	39.20 (10.53)	.12		
CBCL–ABCL							
Total *T* score	40	60.20 (12.66)	54.70 (11.58)	48.10 (9.30)	<.001	<.001	.25
% Clinical		38_x	20_y	5_y		.68	.03
MtF	15	57.40 (12.76)	49.67 (12.29)	48.13 (12.58)	.002		
FtM	25	61.88 (12.56)	57.72 (10.23)	48.08 (6.95)	<.001		
Int *T* score	40	60.83 (12.36)	54.42 (10.58)	50.45 (10.04)	<.001	<.001	.91
% Clinical		30_x	12.5_y	10_y		.42	.33
MtF	15	59.40 (10.03)	50.93 (11.15)	48.73 (12.61)	<.001		
FtM	25	61.68 (13.70)	56.52 (9.86)	51.48 (8.25)	<.001		
Ext *T* score	40	57.85 (13.73)	53.85 (12.77)	47.85 (8.59)	<.001	<.001	.19
% Clinical		40_x	25_x	2.5_y		.43	.12
MtF	15	52.53 (14.11)	47.87 (12.07)	46.33 (10.95)	.10		
FtM	25	61.04 (12.71)	57.44 (12.01)	48.76 (6.89)	<.001		
YSR-ASR							
Total *T* score	43	54.72 (12.08)	49.16 (11.16)	48.53 (9.46)	.005	.005	.28
% Clinical		30_x	14_{xy}	7_y		.07	.75
MtF	17	50.65 (12.19)	45.94 (12.24)	47.24 (12.28)	.28		
FtM	26	57.38 (11.47)	51.27 (10.08)	49.38 (7.21)	.01		
Int *T* score	43	55.47 (13.08)	48.65 (12.33)	50.07 (11.15)	.03	.03	.87
% Clinical		30_x	9.3_y	11.6_{xy}		.008	.73
MtF	17	54.00 (12.31)	47.59 (14.26)	48.12 (12.54)	.04		
FtM	26	56.42 (13.86)	49.35 (11.13)	51.35 (10.19)	.17		
Ext *T* score	43	52.77 (12.47)	49.44 (9.59)	49.44 (9.37)	.14	.14	.005
% Clinical		21_x	11.6_x	7_x		.09	.14
MtF	17	46.00 (11.58)	44.71 (9.53)	50.24 (11.18)	.17		
FtM	26	57.16 (11.14)	52.54 (8.43)	48.92 (8.18)	.006		

FtM, female to male transgender; MtF, male to female transgender.

$_{xy}$ Percent clinical range, shared subscripts indicate no significant difference in values. In no case was an increase in percent in the clinical range significant from 1 time point to any other time point, indicating an overall decline or stability of clinical symptoms over time.

[a] Participants who had complete data at all 3 waves were included. Some assessments were added to the study later, yielding fewer total participants for those scales.

whereas transmen improved steadily across the 3 time points (linear effect only).

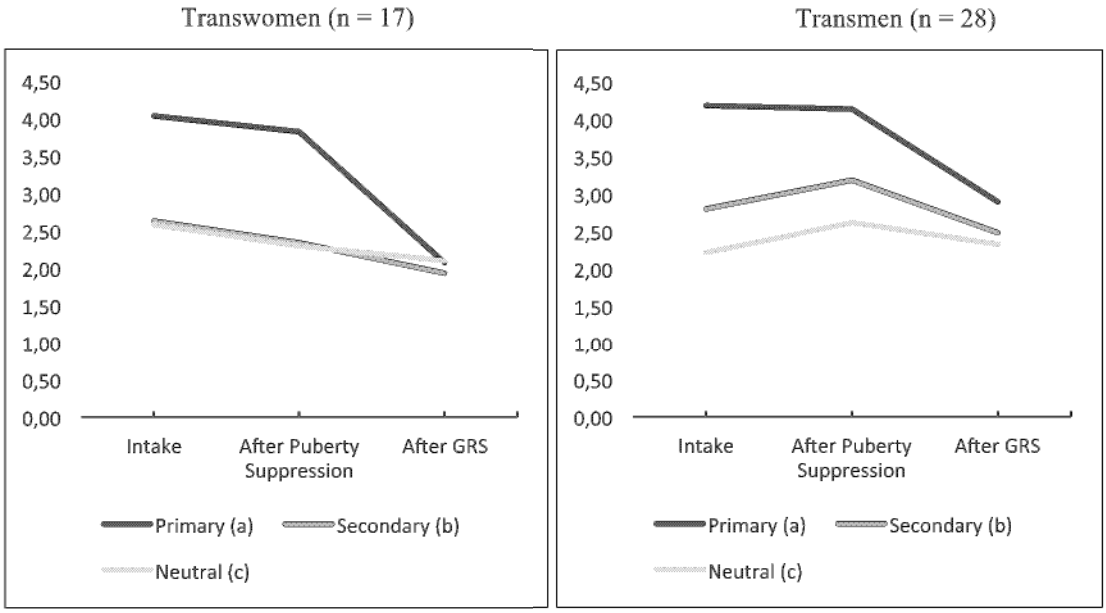
Objective Well-Being

At T2, the participants were vocationally similar to the Dutch population except they were slightly more likely to live with parents (67% vs 63%), and more likely, when studying, to be pursuing higher education (58% vs 31%).[33]

Families were supportive of the transitioning process: 95% of mothers, 80% of fathers, and 87% of siblings. Most (79%) young adults reported having 3 or more friends, were satisfied with their male (82%) and female peers (88%), and almost all (95%) had received support from friends regarding their gender reassignment. After their GRS, many participants (89%) reported having been never or seldom called names or harassed. The majority (71%) had experienced social transitioning as easy.

Subjective Well-Being

None of the participants reported regret during puberty suppression, CSH



Eta Squared for Linear and Quadratic Effects

(a) Primary sex characteristics
Time: .79 ($P < .001$), .66 ($P < .001$),
Time × sex: .14 ($P = .01$), .01 ($P = .45$),

(b) Secondary sex characteristics
Time: .31($P < .001$), .30 ($P < .001$),
Time × sex: .06 ($P = .10$), .22 ($P < .001$)

(c) Neutral body characteristics
Time: .07($P < .001$), .09 ($P = .29$)
Time × sex: .16 ($P = .007$), .15 ($P = .01$)

FIGURE 1
BIS[23] for transwomen and transmen at T0 (pretreatment, at intake), T1 (during treatment, at initiation of cross-gender hormones), and T2 (post-treatment, 1 year after GRS).

treatment, or after GRS. Satisfaction with appearance in the new gender was high, and at T2 no one reported being treated by others as someone of their assigned gender. All young adults reported they were very or fairly satisfied with their surgeries.

Mean scores on WHOQOL-BREF, the SWLS, and the SHS are presented in Table 4, together with scores from large validation and reliability studies of these measures,[17,19,34] revealing similar scores in all areas except WHOQOL-Environment subdomain, which was higher for the participants than the norm. There were some differences across gender; transwomen scored higher than transmen on the SWLS (mean = 27.7; SD = 5.0 vs mean = 23.2; SD = 6.0; t (52) = 2.82; $P < .01$) and on the psychological subdomain of the WHOQOL (mean = 15.77; SD = 2.0 vs mean = 13.92; SD = 2.5; t (53) = 2.95; $P < .01$).

Correlations With Residual Change Scores

The residual change scores of secondary sex characteristics, global functioning, depression, anger, anxiety, and YSR total, internalizing and externalizing from T0 to T2, were significantly correlated with the 6 T2 quality of life indicators. Most correlation coefficients were within the moderate to large magnitude (eg, 0.30–0.60), except depression, which was highly correlated (0.60–0.80) (see Table 5).

DISCUSSION

Results of this first long-term evaluation of puberty suppression among transgender adolescents after CSH treatment and GRS indicate that not only was GD resolved, but well-being was in many respects comparable to peers.

The effectiveness of CSH and GRS for the treatment of GD in adolescents is in line with findings in adult transsexuals.[35,36] Whereas some studies show that poor surgical results are a determinant of postoperative psychopathology and of dissatisfaction and regret,[37,38] all young adults in this study were generally satisfied with their physical appearance and none regretted treatment. Puberty suppression had caused their bodies to

TABLE 4 Subjective Well-Being: Quality of Life, Satisfaction With Life, and Subjective Happiness Mean Scores With Scores From Validation Studies

	N	Mean (SD)	Range	Validation Studies Scores Mean (SD)	Comparison *P*
WHOQOL[a] Physical	55	15.22 (2.49)	8.6–20.0	15.0 (2.9)[b]	.56
WHOQOL Psychological	55	14.66 (2.44)	6.67–20.0	14.3 (2.8)[b]	.24
WHOQOL Social Relations	55	14.91 (2.35)	9.3–20.00	14.5 (3.4)[b]	.18
WHOQOL Environment	55	15.47 (2.06)	10.5–20.00	13.7 (2.6)[b]	<.001
SWLS	54	24.98 (6.0)	9.0–35.0	26.18 (5.7)[c]	.16
SHS	54	4.73 (0.77)	2.75–6.0	4.89 (1.1)[d]	.17

[a] WHOQOL, Bref, Skevington et al.[16]
[b] International field trial, ages 21 to 30 years, Skevington et al.[18]
[c] Dutch young adults, Arindell et al.[33]
[d] US Public College Students, Lyubomirsky.[18]

not (further) develop contrary to their experienced gender.

Psychological functioning improved steadily over time, resulting in rates of clinical problems that are indistinguishable from general population samples (eg, percent in the clinical range dropped from 30% to 7% on the YSR/ASR[30]) and quality of life, satisfaction with life, and subjective happiness comparable to same-age peers.[17,19,34] Apparently the clinical protocol of a multidisciplinary team with mental health professionals, physicians, and surgeons gave these formerly gender dysphoric youth the opportunity to develop into well-functioning young adults. These individuals, of whom an even higher percentage than the general population were pursuing higher education, seem different from the transgender youth in community samples with high rates of mental health disorders, suicidality and self-harming behavior, and poor access to health services.[21,22,39,40]

In this study, young adults who experienced relatively greater improvements in psychological functioning were more likely to also report higher levels of subjective postsurgical well-being. This finding suggests value to the protocol that involves monitoring the adolescents' functioning, physically and psychologically, over many years, and providing more support whenever necessary.

This clinic-referred sample perceived the Environmental subdomain (with items like "access to health and social care" and "physical safety and security") of the WHOQOL-BREF as even better than the Dutch standardization sample.[17] Whereas in some other contexts transgender youth may experience gender-related abuse and victimization,[22,41,42] the positive results may also be attributable to supportive parents, open-minded peers, and the social and financial support (treatment is covered by health insurance) that gender dysphoric individuals can receive in the Netherlands.

Both genders benefitted from the clinical approach, although transwomen showed more improvement in body image satisfaction (secondary sex characteristics) and in psychological functioning (anger and anxiety). None of the transmen in this study had yet had a phalloplasty because of waiting lists or

TABLE 5 Correlations Between Residual Change in Psychological Functioning Over Time and Young Adult Subjective Well-Being

	WHOQOL BREF					
	Physical	Psychological	Social	Environment	SWLS	SHS
Gender dysphoria (UGDS)	0.01 (.97)	0.05 (.75)	−0.09 (.57)	−0.02 (.89)	0.06 (.71)	0.30 (.04)
Body image subscales (BIS)						
Primary sex characteristics	−0.22 (.14)	−0.25 (.09)	−0.35 (.02)	−0.04 (.78)	−0.22 (.14)	−0.21 (.17)
Secondary sex characteristics	−0.39 (.006)	−0.45 (<.001)	−0.47 (<.001)	−0.34 (.02)	−0.35 (.02)	−0.26 (.08)
Neutral body characteristics	−0.21 (.16)	−0.27 (.07)	−0.15 (.32)	−0.28 (.06)	−0.26 (.08)	−0.16 (.28)
Psychological functioning						
Global functioning (CGAS)	0.60 (<.001)	0.52 (.002)	0.52 (.002)	0.27 (.14)	0.58 (<.001)	0.50 (.004)
Depression (BDI)	−0.76 (<.001)	−0.72 (<.001)	−0.51 (.002)	−0.49 (.003)	−0.61 (<.001)	−0.77 (<.001)
Trait anger (TPI)	−0.37 (.03)	−0.18 (.31)	−0.22 (.20)	−0.29 (.09)	−0.33 (.07)	−0.35 (.05)
Trait anxiety (STAI)	−0.58 (<.001)	−0.64 (<.001)	−0.38 (.03)	−0.44 (.01)	−0.49 (.004)	−0.57 (<.001)
CBCL–ABCL						
Total *T* score	−0.20 (.20)	−0.12 (.45)	−0.07 (.65)	−0.14 (.35)	−0.32 (.03)	−0.16 (.29)
Internalizing *T* score	−0.29 (.06)	−0.29 (.06)	−0.23 (.14)	−0.12 (.44)	−0.48 (<.001)	−0.36 (.02)
Externalizing *T* score	−0.13 (.40)	−0.05 (.75)	0.16 (.29)	−0.20 (.19)	−0.15 (.36)	0.00 (.99)
Youth Self Report (YSR–ASR)						
Total *T* score	−0.53 (<.001)	−0.45 (.002)	−0.33 (.03)	−0.42 (.005)	−0.52 (<.001)	−0.55 (<.001)
Internalizing *T* score	−0.62 (<.001)	−0.61 (<.001)	−0.47 (<.001)	−0.40 (.007)	−0.66 (<.001)	−0.60 (<.001)
Externalizing *T* score	−0.23 (.13)	−0.10 (.53)	−0.07 (.67)	−0.37 (.02)	−0.22 (.15)	−0.35 (.02)

P values are in parentheses.

a desire for improved surgery techniques. This finding warrants further study of the specific concerns of young transmen.

Despite promising findings, there were various limitations. First, the study sample was small and came from only 1 clinic. Second, this study did not focus on physical side effects of treatment. Publications on physical parameters of the same cohort of adolescents are submitted or in preparation. A concurring finding exists in the 22-year follow-up of the well-functioning first case now at age 35 years who has no clinical signs of a negative impact of earlier puberty suppression on brain development, metabolic and endocrine parameters, or bone mineral density.[43] Third, despite the absence of pretreatment differences on measured indicators, a selection bias could exist between adolescents of the original cohort that participated in this study compared with nonparticipants.

Age criteria for puberty suppression and CSH are under debate, although they worked well for adolescents in the current study. Especially in natal females, puberty will often start before the age of 12 years. Despite the fact that developing evidence suggests that cognitive and affective cross-gender identification, social role transition, and age at assessment are related to persistence of childhood GD into adolescence, predicting individual persistence at a young age will always remain difficult.[44] The age criterion of 16 years for the start of CSH may be problematic especially for transwomen, as growth in height continues as long as cross-sex steroids are not provided (causing the growth plates to close). Therefore, psychological maturity and the capacity to give full informed consent may surface as the required criteria for puberty suppression and CSH[45] in cases that meet other eligibility criteria.

CONCLUSIONS

Results of this study provide first evidence that, after CSH and GRS, a treatment protocol including puberty suppression leads to improved psychological functioning of transgender adolescents. While enabling them to make important age-appropriate developmental transitions, it contributes to a satisfactory objective and subjective well-being in young adulthood. Clinicians should realize that it is not only early medical intervention that determines this success, but also a comprehensive multidisciplinary approach that attends to the adolescents' GD as well as their further well-being and a supportive environment.

ACKNOWLEDGMENTS

The authors thank the young adults and their parents for their repeated participation in this study over the years.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013
2. 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(4):246–248
3. Nakatsuka M. [Adolescents with gender identity disorder: reconsideration of the age limits for endocrine treatment and surgery.] *Seishin Shinkeigaku Zasshi*. 2012;114(6):647–653
4. Zucker KJ, Bradley SJ, Owen-Anderson A, Singh D, Blanchard R, Bain J. Puberty-blocking hormonal therapy for adolescents with gender identity disorder: a descriptive clinical study. *J Gay Lesbian Ment Health*. 2010;15(1):58–82
5. 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):578–581
6. Olson J, Forbes C, Belzer M. Management of the transgender adolescent. *Arch Pediatr Adolesc Med*. 2011;165(2):171–176
7. 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(3):418–425
8. Byne W, Bradley SJ, Coleman E, et al. Treatment of gender identity disorder. *Am J Psychiatry*. 2012;169(8):875–876
9. Adelson SL. Practice parameter on gay, lesbian, or bisexual sexual orientation, gender nonconformity, and gender discordance in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 2012;51(9):957–974
10. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2009;94(9):3132–3154
11. Coleman E, Bockting W, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. *Int J Transgenderism*. 2012;13(4):165–232
12. Cohen-Kettenis PT, Steensma TD, de Vries AL. Treatment of adolescents with gender dysphoria in the Netherlands. *Child Adolesc Psychiatr Clin N Am*. 2011;20(4):689–700
13. Thornton P, Silverman LA, Geffner ME, Neely EK, Gould E, Danoff TM. Review of outcomes after cessation of gonadotropin-releasing hormone agonist treatment of girls with precocious puberty. *Pediatr Endocrinol Rev Mar*. 2014;11(3):306–317
14. 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(suppl 1):S131–S137
15. Steensma TD, Biemond R, Boer FD, Cohen-Kettenis PT. Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. *Clin Child Psychol Psychiatry*. 2011;16(4):499–516
16. 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):2276–2283
17. Skevington SM, Lotfy M, O'Connell KA. The World Health Organization's WHOQOL-BREF

quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Qual Life Res.* 2004;13(2):299–310

18. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction With Life Scale. *J Pers Assess.* 1985;49(1):71–75
19. Lyubomirsky S, Lepper HS. A measure of subjective happiness: preliminary reliability and construct validation. *Soc Indic Res.* 1999;46(2):137–155
20. Koot HM. The study of quality of life: concepts and methods. In: Koot HM, Wallander JL, eds. *Quality of Life in Child and Adolescent Illness: Concepts, Methods and Findings.* London, UK: Harwood Academic Publishers; 2001:3–20
21. Carver PR, Yunger JL, Perry DG. Gender identity and adjustment in middle childhood. *Sex Roles.* 2003;49(3–4):95–109
22. Grossman AH, D'Augelli AR. Transgender youth: invisible and vulnerable. *J Homosex.* 2006;51(1):111–128
23. Steensma TD, Kreukels BP, Jurgensen M, Thyen U, De Vries AL, Cohen-Kettenis PT. The Urecht Gender Dysphoria Scale: a validation study. *Arch Sex Behav.* provisionally accepted
24. Lindgren TW, Pauly IB. A body image scale for evaluating transsexuals. *Arch Sex Behav.* 1975;4:639–656
25. Shaffer D, Gould MS, Brasic J, et al. A children's global assessment scale (CGAS). *Arch Gen Psychiatry.* 1983;40(11):1228–1231
26. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II.* San Antonio, TX: Psychological Corporation; 1996
27. Spielberger CD. *Manual for the State-Trait Anger Expression Inventory (STAXI).* Odessa, FL: Psychological Assessment Resources; 1988
28. Spielberger CD, Gorssuch RL, Lushene PR, Vagg PR, Jacobs GA. *Manual for the State-Trait Anxiety Inventory.* Palo Alto, CA: Consulting Psychologists Press, Inc; 1983
29. Achenbach TM. *Manual for the Youth Self-Report.* Burlington, VT: University of Vermont, Department of Psychiatry; 1991
30. Achenbach TM, Rescorla LA. Manual for the ASEBA Adult Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2003
31. Achenbach TM, Edelbrock CS. *Manual for the Child Behavior Checklist and Revised Child Behavior Profile.* Burlington, VT: University of Vermont, Department of Psychiatry; 1983
32. Cohen-Kettenis PT, Owen A, Kaijser VG, Bradley SJ, Zucker KJ. Demographic characteristics, social competence, and behavior problems in children with gender identity disorder: a cross-national, cross-clinic comparative analysis. *J Abnorm Child Psychol.* 2003;31(1):41–53
33. Statistics Netherlands. Landelijke Jeugdmonitor. In: Ministerie van Volksgezondheid, Wetenschap en Sport, ed. Den Haag, Heerlen: Tuijtel, Hardinxveld-Giessendam; 2012
34. Arrindell WA, Heesink J, Feij JA. The Satisfaction With Life Scale (SWLS): appraisal with 1700 healthy young adults in The Netherlands. *Pers Individ Dif.* 1999;26(5):815–826
35. Murad MH, Elamin MB, Garcia MZ, et al. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin Endocrinol (Oxf).* 2010;72(2):214–231
36. Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol Med.* 2005;35(1):89–99
37. Ross MW, Need JA. Effects of adequacy of gender reassignment surgery on psychological adjustment: a follow-up of fourteen male-to-female patients. *Arch Sex Behav.* 1989;18(2):145–153
38. Lawrence AA. Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. *Arch Sex Behav.* 2003;32(4):299–315
39. Grossman AH, D'Augelli AR. Transgender youth and life-threatening behaviors. *Suicide Life Threat Behav.* 2007;37(5):527–537
40. Garofalo R, Deleon J, Osmer E, Doll M, Harper GW. Overlooked, misunderstood and at-risk: exploring the lives and HIV risk of ethnic minority male-to-female transgender youth. *J Adolesc Health.* 2006;38(3):230–236
41. Toomey RB, Ryan C, Diaz RM, Card NA, Russell ST. Gender-nonconforming lesbian, gay, bisexual, and transgender youth: school victimization and young adult psychosocial adjustment. *Dev Psychol.* 2010;46(6):1580–1589
42. McGuire JK, Anderson CR, Toomey RB, Russell ST. School climate for transgender youth: a mixed method investigation of student experiences and school responses. *J Youth Adolesc.* 2010;39(10):1175–1188
43. 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):843–847
44. 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):582–590
45. Kreukels BP, Cohen-Kettenis PT. Puberty suppression in gender identity disorder: the Amsterdam experience. *Nat Rev Endocrinol.* 2011;7(8):466–472
46. Wechsler D. *Wechsler Intelligence Scale for Children: Manual.* 3rd ed. San Antonio, TX: The Psychological Corporation; 1997
47. Wechsler D. *Wechsler Adult Intelligence Scale (WAIS-III).* 3rd ed. Dutch version. Lisse, Netherlands: Swets and Zetlinger; 1997
48. Wechsler D, Kort W, Compaan EL, Bleichrodt N, Resing WCM, Schittkatte M. *Wechsler Intelligence Scale for Children (WISC-III).* 3rd ed. Lisse, Netherlands: Swets and Zettlinger; 2002

(Continued from first page)

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by a personal grant awarded to the first author by the Netherlands Organization for Health Research and Development (ZonMw 100002028).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

An Analysis of All Applications for Sex Reassignment Surgery in Sweden, 1960–2010: Prevalence, Incidence, and Regrets

Article *in* Archives of Sexual Behavior · May 2014

DOI: 10.1007/s10508-014-0300-8 · Source: PubMed

CITATIONS
158

READS
39,310

4 authors:

Cecilia Dhejne
Karolinska Institutet
54 PUBLICATIONS 2,337 CITATIONS
SEE PROFILE

Katarina Oberg
51 PUBLICATIONS 1,105 CITATIONS
SEE PROFILE

Stefan Arver
Karolinska Institutet
207 PUBLICATIONS 7,754 CITATIONS
SEE PROFILE

Mikael Landén
University of Gothenburg
421 PUBLICATIONS 25,018 CITATIONS
SEE PROFILE

Arch Sex Behav
DOI 10.1007/s10508-014-0300-8

ORIGINAL PAPER

An Analysis of All Applications for Sex Reassignment Surgery in Sweden, 1960–2010: Prevalence, Incidence, and Regrets

Cecilia Dhejne · Katarina Öberg · Stefan Arver · Mikael Landén

Received: 8 October 2013 / Revised: 11 December 2013 / Accepted: 14 December 2013

Abstract Incidence and prevalence of applications in Sweden for legal and surgical sex reassignment were examined over a 50-year period (1960–2010), including the legal and surgical reversal applications. A total of 767 people (289 natal females and 478 natal males) applied for legal and surgical sex reassignment. Out of these, 89 % (252 female-to-males [FM] and 429 male-to-females [MF]) received a new legal gender and underwent sex reassignment surgery (SRS). A total of 25 individuals (7 natal females and 18 natal males), equaling 3.3 %, were denied a new legal gender and SRS. The remaining withdrew their application, were on a waiting list for surgery, or were granted partial treatment. The incidence of applications was calculated and stratified over four periods between 1972 and 2010. The incidence increased significantly from 0.16 to 0.42/100,000/year (FM) and from 0.23 to 0.73/100,000/year (MF). The most pronounced increase occurred after 2000. The proportion of FM individuals 30 years or older at the time of application remained stable around 30 %. In contrast, the proportion of MF individuals 30 years or older increased from 37 % in the first decade to 60 % in the latter three decades. The point prevalence at December 2010 for individuals who applied for a new legal gender was for FM 1:13,120 and for MF 1:7,750. The FM:MF sex ratio fluctuated but was 1:1.66 for the whole study period. There were 15 (5 MF and 10 MF) regret applications corresponding to a 2.2 % regret rate for both sexes. There was a significant decline of regrets over the time period.

Keywords Transsexualism · Gender identity disorder · Gender dysphoria · Incidence · Prevalence · Sex ratio

Introduction

Gender identity denotes the personal sense of being a female or male. Gender dysphoria denotes the distress caused by a discrepancy between the gender identity and a person's sex assigned at birth. For some people, the level of distress meets criteria for a formal diagnosis of Transsexualism according to ICD-10, Transsexualism according to DSM-III and DSM-III-R, Gender Identity Disorder according to the DSM-IV and DSM-IV-TR, or Gender Dysphoria according to the DSM-5 (American Psychiatric Association, 1980, 1987, 1994, 2000, 2013; World Health Organization, 1992). The clinical presentation generally includes discomfort with natal sex characteristics and a request for medical help to alter the phenotypic expression of the body. Requests may include treatment with contrary sex hormones, hair removal in natal males, surgery to aid changes of primary and secondary sex characteristics, and a new legal gender.

C. Dhejne
Center for Psychiatric Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

C. Dhejne (✉) · K. Öberg · S. Arver
Center for Andrology and Sexual Medicine, C2:84, Karolinska University Hospital, 141 86 Stockholm, Sweden
e-mail: cecilia.dhejne@karolinska.se

K. Öberg · S. Arver
Department of Medicine/Huddinge, Karolinska Institutet, Stockholm, Sweden

M. Landén
Institute of Neuroscience and Physiology, Sahlgrenska University Hospital, Gothenburg, Sweden

M. Landén
Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Published online: 29 May 2014

Epidemiological studies on incidence, prevalence, and sex ratio of transsexualism are usually based on indirect calculations, for example the number of individuals in a specified catchment area (a whole country or part of a country) who apply for sex reassignment at gender clinics, who receive a diagnosis of transsexualism, who start sex reassignment treatment, and/or apply for legal gender recognition (Zucker & Lawrence, 2009). Most but not all incidence and prevalence estimates have been based on the population over 15 years of age. Legal sex reassignment is in most countries not allowed before the legal age, which is 18 years in most countries. Germany is an exception with no lower age limit.

Table 1 summarizes the reported prevalence, incidence, and sex ratio in different regions. Prevalence figures range from 1:8,300–1:400,000 for female-to-males (FM) and 1:2,900–1:100,000 for male-to-females (MF). Incidence figures for diagnosed transsexualism are available from Australia, Catalonia, Denmark, England and Wales, Germany, and Sweden and vary from 0.15 to 0.73 per 100,000 per year for both genders (Gómez-Gil et al., 2006; Hoenig & Kenna, 1974; Landén, Wålinder, & Lundström, 1996; Meyer zu Hoberge, 2009; Olsson & Möller, 2003; Ross, Wålinder, Lundström, & Thuwe, 1981; Sørensen & Hertoft, 1980; Wålinder, 1971; Weitze & Osburg, 1996). There is a dearth of studies assessing incidence rates over time in adults. In Sweden, the incidence rate of applications for sex reassignment surgery (SRS) increased from 0.17/100,000/year between 1972 and 1992 to 0.24/100,000/year between 1992 and 2002 (Landén et al., 1996; Olsson & Möller, 2003). Anecdotal evidence suggests that this trend has accelerated after 2002. In Canada, a sharp increase was reported in referrals of adolescents with gender dysphoria between the periods 2000–2003 and 2008–2011 (Wood et al., 2013). Similar data for adolescents have been reported from Amsterdam's clinic for adolescents (de Vries & Cohen-Kettenis, 2012).

As can be seen in Table 1, the sex ratio (here reported as FM:MF ratio) differs across studies, clinics, and countries. Some have found an excess of MF, for example 1:6 in New Zeeland (Veale, 2008), 1:6.1 in Australia (Ross et al., 1981), 1:3 in Singapore (Tsoi, 1988), and 1:2.6 in Catalonia (Gómez-Gil et al., 2006). Other have showed a more equal sex ratio such as 1.3:1 in Hamburg, Germany, 1.1:1 in Oslo, Norway (Kreukels et al., 2010), and 1:1 in Finland (Pimenoff, 2006) whereas Japan and Poland have reported an excess of FM, 2:1 and 3.4:1, respectively (Baba et al., 2011; Dulko & Imielinski, 2004). A trend towards a more equal sex distribution over time has been demonstrated in Germany, from 1:2.3 (1981–1990) to 1:1.5 (1991–2000) (Meyer zu Hoberge, 2009; Weitze & Osburg, 1996). Likewise, the sex ratio in Serbia has gone from 1:2 in 1987 to 1:1 in 2007 (Vujovic, Popovic, Sbutega-Milosevic, Djordjevic, & Gooren, 2008). Sweden went in the opposite direction from 1:1.4 in 1972 to 1:1.8 in 2002 (Olsson & Möller, 2003).

Sweden is uniquely positioned to assess trends in applications for gender reassignment/confirmation at a national level as every person requesting a legal sex change and a genital surgical procedure must apply to the Legal Board of the National Board of Health and Welfare. The aims of this study were to investigate incidence trends and prevalence for persons applying for a new legal gender and SRS, as well as the number of applications for reversal to the original sex. We also examined changes over time with respect to sex ratio, applicants' age, average time elapsed from first visit to being granted a new legal gender, reasons for application rejection, and numbers of individuals choosing surgical treatment abroad.

Method

The Swedish Procedure for Sex Reassignment

A law regulating surgical and legal sex reassignment in Sweden came into force in 1972. The law was updated on January 1, 2013. During the period examined, the law stated that if the person since youth had felt that she/he belongs to a sex other than that recorded on the birth certificate, had lived for a considerable time in accordance with this new gender role, and is anticipated to continue to live in such a gender role, the person could obtain permission for surgical and legal sex reassignment. Gradual changes in praxis have for the last 30 years enable late onset gender dysphoric individuals to be included. The person must be at least 18 years old, a Swedish citizen, unmarried, and sterile. As of January 1, 2013, the prerequisite of being unmarried was removed and it is now sufficient to have permanent residency in Sweden. As of July 1, 2013, the prerequisite of being sterile was removed.

Figure 1 illustrates the flow described below. Individuals presenting with gender dysphoria in Sweden are referred to one of six specialized gender teams that adhere to a national consensus program regulating evaluation and treatment. This national consensus program includes approximately 1 year of evaluation. Individuals diagnosed with transsexualism then start gender confirmation treatment, including cross-sex hormones along with real life experience. FMs also may undergo bilateral mastectomy with chest contouring. MFs receive hair removal, and speech therapy. Adolescents are treated as adults although they cannot receive permission for genital surgery and a new legal gender before 18 years of age.

After a minimum of 2 years of evaluation and treatment, the person can apply to the Legal Board of the National Board of Health and Welfare in order to receive permission for SRS and a change of legal sex status. A medical certificate based on the evaluation describing the gender dysphoria, the diagnosis of transsexualism, and other potential health problems accompanies the application. Until 1990, it was common with a two-step procedure where the initial application was for name change and sterilization. The second application was for final permission to undergo surgical and legal gender reassignment. All application

Table 1 Incidence, prevalence, and sex ratio of transsexualism in different countries

Author	Country	Year or time period	Incidence/ 100,000/year	Prevalence FM	Prevalence MF	Sex ratio FM:MF	Population	Prevalence and incidence calculations based on
Sørensen and Hertoft (1982)	Denmark	1951–1981	x	x	x	1:3.6	Surgical and legal sex reassigned individuals	15 years and older
Hoenig and Kenna (1974)	England and Wales	1958–1968	0.17–0.26 total	1:108,000	1:34,000	1:2.9	Referral to a clinic and diagnosed, according to Wålinder (1968)	15 years and older
Wålinder (1968)	Sweden	1965–1967	x	1:103,000	1:37,000	1:2.5	Application to a clinic and diagnosed according to Wålinder (1968)	15 years and older
Wålinder (1971)	Sweden	1967–1970	0.15 total	x	x	1:1	Application to a clinic and diagnosed according to Wålinder (1968)	15 years and older
Dixen, Maddever, Van Maasdam, and Edwards (1984)	USA	ca. 1967–1979	x	x	x	1:1.7	Applicants for sex reassignment	15 years and older
Pauly (1968)	USA	1968	x	1:400,000	1:100,000	1:4	Applying for treatment and diagnosed with transsexualism	Total population
O'Gorman (1982)	Northern-Ireland	ca. 1968–1981	x	1:100,000	1:35,000	1:3	Diagnosed with transsexualism	Total population
Sørensen and Hertoft (1980)	Denmark	1970–1977	0.21 total 0.11 FM 0.31 MF	x	x	1:2.8	Applicants for sex reassignment	15 years and older
Garrels et al. (2000)	Germany	1970–1998	x	x	x	1:1.9	Diagnosed with transsexualism at clinics	Not stated
Landén, Wålinder, and Lundström, (1996)	Sweden	1972–1992	0.17 total	x	x	1:1.4	Applications to court for legal and surgical sex reassignment	15 years and older
Godlewski (1988)	Cracow, Poland	1974–1980	x	x	x	5.5:1	Diagnosed with transsexualism (DSM-III)	Not stated
van Kesteren, Gooren, and Megens (1996)	The Netherlands	1975–1992		1:30,400	1:11,900	1:3	Presented at the clinic with gender dysphoria	Total population
Ross, Wålinder, Lundström, and Thuwe (1981)	Australia	1976–1978	0.58 total	1:150,000	1:24,000	1:6.1	Referrals to a clinic and diagnosed according to Wålinder (1968)	15 years and older
Eklund, Gooren, and Bezemer (1988)	The Netherlands	1976–1986	x	1:54,000	1:18,000	1:3	Started hormone therapy and diagnosed according to Wålinder (1968)	15 years and older
Blanchard, Clemmensen, and Steiner (1987)	Canada	1980–1984	x	x	x	1:1.7	Referred to own clinic due to gender dysphoria	16 years and older
Weitze and Osburg (1996)	West Germany	1981–1990	0.24 total	1:94,000	1:36,000	1:2.3	Applications for legal sex reassignment to court	Total population
De Cuypere et al. (2007)	Belgium	1985–2003	x	1:33,800	1:12,900	1:2.43	Individuals who had underwent SRS	15 years and older
Tsoi (1988)	Singapore	1986	x	1:8,300	1:2900	1:3	Applied for SRS and diagnosed, with transsexualism (DSM-III)	15 years and older
Bakker, van Kesteren, Gooren, and Bezemer (1993)	The Netherlands	1986–1990	x	1:30,400	1:11,900	1:2.5	Started hormone therapy and diagnosed according to Wålinder (1968)	15 years and older
De Cuypere, Janes, and Rubens (1995)	Belgium	1986–1994	x	x	x	1:1.7	Diagnosis of transsexualism	15 years and older

Table 1 continued

Author	Country	Year or time period	Incidence/ 100,000/year	Prevalence FM	Prevalence MF	Sex ratio FM:MF	Population	Prevalence and incidence calculations based on
Meyer zu Hoberge (2009)	Germany	1991–2000 incidence 1981–2000 prevalence	0.34 total 0.26 FM 0.41 MF	1:32,050	1:18,250	1:1.5	Applications for legal sex reassignment to court	Total population
Olsson and Möller (2003)	Sweden	1992–2002	0.24 total	x	x	1:1.9	Applications to court for legal and surgical sex reassignment	15 years and older
Pimenoff 2006)	Finland	1993–2002	x	x	x	1:1	Application for castration due to transsexualism	Not stated
Veale (2008)	New Zealand	1995–2008	x	1:22,700	1:3600	1:6	Gender change in passport	15 years and older
Gómez-Gil et al. (2006)	Catalonia	1996–2004 prevalence 2000–2004 incidence	0.73 total	1:48,100	1:21,000	1:2.6	Diagnosed transsexualism (ICD-10)	15–65
Wilson, Sharp, and Carr (1999)	Scotland	ca. 1998	x	1:31,200	1:7400	1:4	Patients with gender dysphoria with or without treatment known by GP:	15 years and older
Wilson, Sharp, and Carr (1999)	Scotland	ca. 1998	x	1:52,100	1:12,800	1:3.8	Receiving hormone therapy or post-surgery	15 years or older
Gómez-Gil, Trilla, Salamero, Godás, and Valdés (2009)	Barcelona, Spain	2000–2006	x	x	x	1:2.24	Diagnosed with transsexualism (ICD-10)	Not stated
Smith, van Goosen, Kuiper, and Cohen-Kettenis (2005)	The Netherlands	Before 2003	x	x	x	1:1.5	Completed sex reassignment	15 years of old
Baba et al. (2011)	Japanese region Hokkaido	2003–2010	x	1:12,200	1:25,200	2:1	Applying for treatment at a clinic and diagnosed with GID (DSM-IV)	Total population
Kreukels et al. (2010)	Amsterdam, Netherlands	2009	x	x	x	1:2.34	Applicants with gender dysphoria data from own clinic	17 years and older
Kreukels et al. (2010)	Ghent, Belgium	2009	x	x	x	1:2.5	Applicants with gender dysphoria data from own clinic	16 years and older
Kreukels et al. (2010)	Hamburg, Germany	2009	x	x	x	1.33:1	Applicants with gender dysphoria data from own clinic clinic	16 years and older
Kreukels et al. (2010)	Oslo, Norway	2009	x	x	x	1.12:1	Applicants with gender dysphoria from own clinic clinic	16 years and older
Dulko and Imielinski (2004)	Poland	Not stated	x	x	x	3.4:1	Diagnosis of transsexualism	Not stated

records are classified as secret and kept on file. If the application is approved, a new national registration number signifying the new gender is assigned after SRS. The time lapse between application and permission for surgery and finally a new legal gender is currently no more than 1 year. Persons who have undergone SRS abroad can present the Board with a certificate that they have had surgical sex reassignment and receive legal gender reassignment without evaluation and real life experience. The National Board of Health and Welfare also handles applications for reversal to the original sex in cases of regrets (regret applications). Regret applications are also accompanied by a medical certificate. To date, all regret applications have been approved, which gives the person the right to treatment to reverse the body as much as possible. All costs for medical care and pharmacological treatment, except facial surgery, are covered by the national health insurance.

Subjects and Procedure

All application files from 1960 to 2010 were reviewed with permission from the Ethical review board, Stockholm, and the National Board of Health and Welfare. Files from January 1, 2011 to June 30, 2011 were also analyzed in order to determine if applications were approved or not. We extracted data on assigned sex at birth, date of birth, date of first visit to a healthcare provider with a documentation of gender dysphoria, date of application for legal and surgical sex reassignment or name change and sterilization if it was a two-step procedure. Furthermore, date and outcome of the decision (if refused, the reasons for this), date of new legal gender, whether the person had undergone sex reassignment abroad, and regret applications were extracted. Age of the applicants was calculated based on the date of the first application. Data were missing for 26 cases and, for these cases, age at first application was estimated to have occurred two months before the date of decision if that was available, or otherwise 12 months before the date of the second application, or if that was also missing, 24 months before the date of the new legal gender.

Incidence for the first application per individual was calculated and stratified for four periods between 1972 and 2010 (the time the law has been in force). The means of the total Swedish population over 17 years of age for the first and the last year of the 10-year intervals were used for incidence calculations (Sweden Statistics, 2012). We had no data on the number of sex reassigned individuals alive and residing in Sweden at each given time point, which precluded exact point prevalence figures (total number of cases in the population divided by the number of individuals in the population) or lifetime prevalence. However, several previous studies have reported transsexualism prevalence rates without taking into account the number of living cases (Baba et al., 2011; De Cuypere et al., 2007; Tsoi, 1988; Veale, 2008). For comparison reasons, we therefore decided to calculate prevalence numbers based on all persons who ever applied for a new legal gender as if they were all alive during the study period. This will slightly overestimate the point prevalence. The regret rate is defined as the number of sex reassigned individuals at the time period when they did their first application that will later apply for reversal to the original sex, compared to the total number of individuals who did their first application at that time period and received a new legal gender. The data were stratified in 10 years' time periods. The study was conducted in the same way as earlier Swedish incidence studies (Landén et al., 1996; Olsson & Möller, 2003; Wålinder, 1971), with the exception that we calculated incidence rates for the population over 17 instead of over 14 years of age, since a new legal gender cannot be granted before 18.

Statistics

All tables and statistical analyses were generated in the software package R: A Language and Environment for Statistical Computing (R Core Team, 2013). For dichotomous data, cross tabulation with χ^2 or Fisher's exact test were used where appropriate. Results were defined statistically significant if the p value was <0.0001.

Results

Number of Applications, Granted Applications, and Time to New Legal Gender

A total of 767 people (289 natal females and 478 natal males) applied for legal and surgical sex reassignment in Sweden due to transsexualism/gender dysphoria during the period 1960–2010. Figure 2 shows the number of natal females and natal males applying for a new legal gender stratified per year. Of these 767 applicants, 89 % or 681 persons (FM: 252/289, 87 %; MF: 429/478, 90 %) were granted a new legal gender and had undergone sex confirmation surgery by the end of June 2011. Eight individuals (4 FM and 4 MF) of 681 were assigned a new legal gender before the law came in force 1972. A total of 25 persons (3.3 %, 7 natal females and 18 natal males) were denied a new legal gender due to reasons listed in Table 2. The mean time between the first visit at any clinic for gender dysphoria and a new legal gender for the 681 individuals who underwent sex reassignment declined from a mean of 87 (SD = 70) months between 1972 and 1980, to 46 (SD = 31) months between 2001 and 2010.

Incidence

Table 3 shows stratified incidence of applications for a new legal gender for the four periods for each gender. The overall incidence of applications for a new legal sex increased from

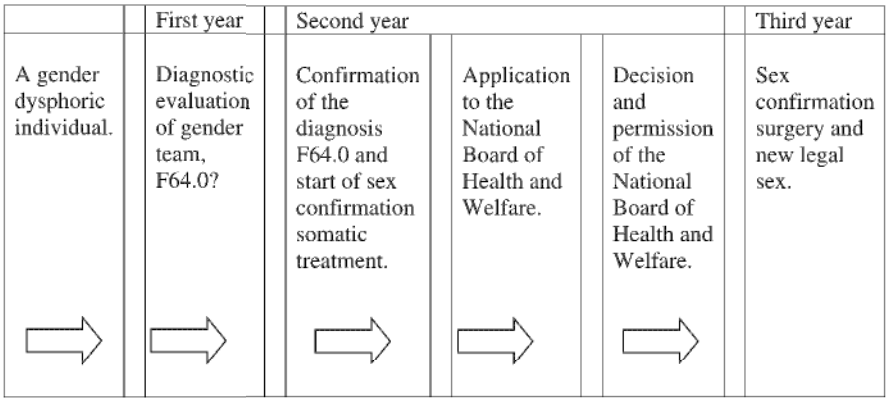


Fig. 1 Procedural flow for individuals applying for sex confirmation genital surgery and new legal sex

0.20/100,000/year (1972–1980) to 0.57/100,000/year (2001–2010). For FMs, there was a 2.5 fold increase from 0.16 to 0.42/100,000/year from the first decade to the last; and for MFs, there was a threefold increase from 0.23 to 0.73/100,000/year. The incidence differed significantly between the time periods for both genders combined, $\chi^2(3) = 308$, $p < .0001$, as well as for FM, $\chi^2(3) = 107$, $p < .0001$, and MF, $\chi^2(3)$, $p < .0001$. Likewise, the incidence rates for people who actually received a new sex tripled for both sexes from 0.16 to 0.51/100,000/year (FM: 0.13–0.37/100,000/year, MF: 0.20–0.66/100,000/year).

Prevalence

At the end of December 2010, there were 3,791,791 females and 3,704,685 males over 17 years of age alive and living in Sweden. This gives a point prevalence for persons who had applied for a new legal gender of 1:13,120 for FM and 1:7,750 for MF. As of the same date, the point prevalence for persons who had undergone legal and surgical sex reassignment in Sweden during 2010 was 1:15,047 for FM and 1:8,636 for MF.

Sex Ratio

The FM:MF sex ratio for those who applied was 1:1.66 for the whole study period, but fluctuated between 1:1.42 and 1:1.93 as presented in Table 3. The fluctuation of the sex ratio was not significant over time, $\chi^2(3) = 2.76$. The sex ratio for those who received a new legal gender was 1:1.53 (1972–1980), 1:1.45 (1981–1990), 1:1.89 (1991–2000), 1:1.73 (2001–2010), and was 1:1.70 for the whole study period 1960–2010.

Age of Applicants

The median (min–max) age at application for the whole period was 27 years (16–65) for FMs and 32 years (18–75) for MFs. The proportion of FMs who were 30 years of age or older at the time of application remained stable at around 30 %. By contrast, MFs 30 years of age or older increased from 37 % in the first decade to around 60 % over the last three decades (see Table 3).

Regrets

A total of 15 individuals (5 FM and 10 MF) out of 681 who received a new legal gender between 1960 and 2010 applied for reversal to the original sex (regret applications). This corresponds to a regret rate of 2.2 % for both sexes (2.0 % FM and 2.3 % MF). As showed in Table 4, the regret rate decreased significantly over the whole study period, Fisher's exact test, $p < .0001$. The median (min–max) age at which this group first applied for a new legal sex was 22 (18–52) years in FM and 35 (27–49) years in MF. The median (range) time elapsed from attaining a new legal gender to the regret application was

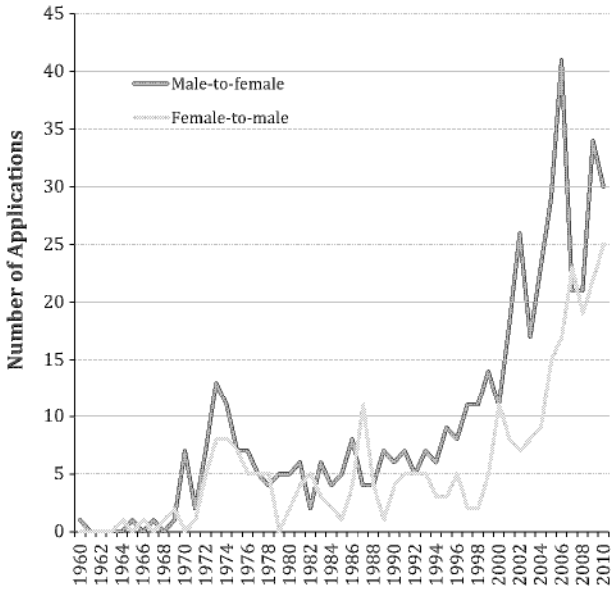


Fig. 2 New applicants for a new legal sex and permission for sex confirmation surgery to the National Board of Health and Welfare in Sweden, 1960–2010, per year, males and females as assigned at birth

Table 2 Applications and outcomes for new legal and surgical sex reassignment submitted to the National Board of Health and Welfare in a Swedish sample, male or female as assigned at birth, between January 1960 and June 2011

Applications for new legal sex January 1960–December 2010 (% of all applications)	Assigned female $N = 289$ (37.7 %)	Assigned male $N = 478$ (62.3 %)	Total $N = 767$ (100 %)
Granted new legal sex between January 1960 and 30 June 2011, out of the applications made January 1960–December 2010 (% of all applications)	252 (87.2 %)	429 (89.7 %)	681 (88.8 %)
Permission not granted for new legal sex (% of all applications)	37 (12.8 %)	49 (10.3 %)	86 (11.2 %)
Reasons for not granting new legal sex			
Application withdrawn by applicant (% of all applications)	3 (1.0 %)	6 (1.3 %)[a]	9 (1.2 %)
Pending new legal sex; chosen by applicant (% of all applications)	17 (5.9 %)	11 (2.3 %)	28 (3.7 %)
Waiting-list for operation (% of all applications)	8 (2.8 %)	9 (1.9 %)	17 (2.2 %)
Partly granted; name-change (% of all applications)	2 (0.7 %)	5 (1.0 %)	7 (0.9 %)
Dismissal of the application (% of all applications)	7 (2.4 %)	18 (3.8 %)	25 (3.3 %)
Reasons for dismissal			
Did not meet diagnosis criteria (% of all applications)	2 (0.7 %)	6 (1.3 %)	8 (1.0 %)
Application incomplete (% of all applications)	3 (1.0 %)	9 (1.9 %)	12 (1.6 %)
Co-morbidity (% of all applications)	2 (0.7 %)	0	2 (0.3 %)
Not sterile (% of all applications)	0	1 (0.2 %)	1 (0.1 %)
Missing data (% of all applications)	0	2 (0.4 %)	2 (0.3 %)

[a] One male applicant died during the time period after application and before permission granted and legally accounted as withdrawn

7.5 years (90 months, range 75–137) for FM, and 8.5 years (102 months, range 22–177) for MF.

SRS Abroad

A total of 41 persons had surgical sex reassignment abroad: 2 females aged 29 and 42, and 39 males with median (min–max) age 36 (18–59). Most sex reassignments abroad occurred after 1991 (36/41). The surgery was conducted mainly in Thailand and the US (36/41) while the remainder took place in the UK, the Baltic States, or Norway. One of these 41 individuals had been denied sex reassignment in Sweden prior to surgery abroad. The rest had not applied for legal and surgical sex reassignment in Sweden before they underwent their surgery abroad. Up to 2010, there had been no regret applications from this group.

Discussion

We studied the applications for sex reassignment in the total population of Sweden during 50 years. There was a pronounced increase of applications from the year 2000. Approximately 2.5 times more FMs and three times more MFs applied between 2001 and 2010 compared to the three previous decades. This accords with reports from Toronto and the Netherlands where the number of adolescents who seek help for gender dysphoria has increased (de Vries & Cohen-Kettenis, 2012; Wood et al., 2013). The same has also been reported from Catalonia (Gómez-Gil et al., 2006).

There are several possible explanations for the increase in gender reassignment applications. First, a drift in diagnostic criteria has occurred in that the Legal Board in Sweden has been increasingly more likely to sanction late onset MF (Olsson & Möller, 2003). As a consequence, the proportion of MF

Table 3 Incidence of FM and MF applications/100,000/year stratified in 10-year periods, 1972–2010, with median age and percentage over 30 years of age at time for application and sex ratio

Year of application	FM number/female population >17 years/	FM incidence/100,000/year	FM age median (min–max)	FM % above 30 years old (%)	MF number/male population >17 years	MF incidence/100,000/year	MF age median (min–max)	MF % above 30 years old (%)	Sex ratio FM:MF
1972–1980	45/3,166,037	0.16	29 (16–51)	36	64/3,062,456	0.23	27 (18–55)	37	1:1.42
1981–1990	39/3,340,105	0.12	26 (18–45)	33	52/3,198,147	0.16	33 (18–56)	62	1:1.33
1991–2000	46/3,497,821	0.13	26 (18–65)	28	89/3,347,178	0.27	36 (19–55)	61	1:1.93
2001–2010	153/3,674,613	0.42	27 (17–53)	31	260/3,559,056	0.73	33 (18–75)	59	1:1.70

in general and late onset MF in particular increased during the study period. But this occurred back in the 1980s and 1990s and cannot explain the surge after the turn of the century. Second, it has been suggested that homophobia in countries like Australia and Singapore may cause gay males to undergo SRS (Ross et al., 1981; Tsoi, 1988). A recent report from Toronto suggests that the increased number of applications from adolescents may be because it is perceived easier to be transsexual than homosexual, but it is unknown whether this applies to adults (Wood et al., 2013). A Swedish survey found more tolerant attitudes toward transsexual than homosexual persons (Landén & Innala, 2000, 2002). Homophobia is nevertheless an unlikely explanation to an increase in MF:s in Sweden, which rates low on homophobia; same-sex marriage has for example been allowed for 10 years (ILGA-Europe, 2013). A third potential explanation could be easier access to care and better care for transsexualism. Reports from Singapore and the Netherlands suggest that good care of gender dysphoric people and especially good surgical techniques for MFs facilitates sex reassignment (Bakker, van Kesteren, Gooren, & Bezemer, 1993; Tsoi, 1988). Since 1999, evaluation of those who request gender change has been centralized in Stockholm County (which comprises 20 % of the Swedish population). Prior to that, care of transsexual individuals was more random and the level of expertise and experience varied considerably between care providers. Fourth, increased public awareness, easier access to information, and increasing societal acceptance of individuals with gender dysphoria may have contributed to the increased incidence. Internet access in Swedish households increased from 47 % in 2003 to 91 % in 2010 (Sweden Statistics, 2013) and people with gender dysphoria may have become aware of their condition and learned to seek help via the internet, which also gives the possibility for easy connections with support groups.

We estimated the point prevalence for individuals who have been granted a new legal gender and who have undergone a complete sex reassignment to be 1:15,047 in FM and 1:8,636 in MF. These figures should be compared with the prevalence among Belgian-born people who had undergone complete SRS 2003, as estimated by data retrieved from all surgical departments in the country, which were 1:33,800 in FM and 1:12,900 in MF (De Cuypere et al., 2007). The Swedish figures slightly overestimate the prevalence as we were not able to exclude those who deceased after sex reassignment and those who were born outside Sweden (see "Method"). But this is unlikely to explain the more than double prevalence for FM compared to Belgium.

The FM:MF sex ratio in Sweden was rather stable between 1972 and 2010. There was a trend towards more male applicants during 1991 and 2000 (1:1.93) that abated during the following decade to 1:1.73. Presumably, several structural and other factors influence the sex ratio and also the frequency of applications. Such factors, which may differ across countries, include access to healthcare and insurance coverage, trust in healthcare providers, diagnostic traditions, legal possibilities for being granted a new legal gender, and societal prejudice (Nieder et al., 2011; Okabe et al., 2008).

The average age at application was stable over the time period for both genders. FMs were younger (median 27 years old) than MFs (median 32 years old). These figures are in line with those from the European Network of the Investigation on Gender Incongruence (ENIGI) consortium (the clinics in Amsterdam, Gent, Hamburg, and Oslo) (Nieder et al., 2011). By contrast, in Singapore and Spain, the mean age was 24–25 years in both groups (Gómez-Gil et al., 2009; Tsoi, 1988). This is in line with the suggestion that applicants for gender reassignment tend to be older in individualistic countries (Sweden is an individualistic country according to Hofstede's index that divides cultures and countries into either individualistic or collectivistic) compared to collectivistic countries like Spain and Singapore (Lawrence, 2010). The proportion of FMs over 30 years old was stable at 30 %. By contrast, the percentage of MFs over 30 years of age increased from 37 to 60 % during the study period. This is most likely related to the change in the interpretation of the law and diagnostic criteria that occurred ca. 1985, when also late onset gender dysphoria was accepted for legal and surgical sex reassignment.

The time from the first appointment for gender dysphoria until being granted a new legal gender decreased from 7.3 years

Table 4 Individuals who will subsequently apply for reversal to the original sex

Time period	Number of sex reassigned individuals at the time period when they did their first application that will later apply for reversal to the original sex/total number of individuals who did their first applications at this time period who received a new legal sex (%)	Number of regret applications, during that time period
1960–1971	4/15 (27 %)	0
1972–1980	6/103 (5.8 %)	5
1981–1990	1/76 (1.3 %)	3
1991–2000	3/127 (2.4 %)	3
2001–2010	1/360 (0.3 %)	4
1960–2010	15/681 (2.2 %)	15

in the first decade (1972–1981) to 3.8 years in the last (2001–2011). This represents an improvement in care, even though 3.8 years may still seem unnecessarily long to complete the entire process. Only 3.3 % of applicants were denied a new legal gender by the Legal Board of the National Board of Health and Welfare. This implies good diagnostic precision and selection of individuals who can proceed to a complete legal sex change. An alternative interpretation would be that the gender teams adjusted well to the demands of the legal prerequisites and, because of this, act as gatekeepers. The 3.3 % (2.4 % FM and 3.8 % MF) denial rate was slightly higher than has been reported from Germany: 1 % for FM and 3 % for MF (Meyer zu Hoberge, 2009).

In June 2011, 30 applicants who had been granted permission to undergo surgery and subsequently obtain a new legal gender status (17 females and 13 males) had postponed surgery more than 12 months (Table 1). It is assumed that these people were waiting for a change in the Swedish law in order to escape the requirement to be sterile to be eligible for sex change operation. By rule of court and EC regulation, this requirement has since been revoked and the Swedish law changed.

The regret rate defined as application for reversal of the legal gender status among those who were sex reassigned was 2.2 % for the whole period 1960–2010 with no significant sex difference. The risk of regretting the procedure was higher if one had been granted a new legal gender before 1990 (11/15). For the two last decades, the regret rate was 2.4 % (1991–2000) and 0.3 % (2001–2010), respectively. The decline in the regret rate for the whole period 1960–2010 was significant. However, the last period is still undecided since the median time lag until applying for a reversal was 8 years. If excluding 2001–2010 the p value is .002. The Swedish regret rate is slightly higher compared to previous reports: 1 % for FM and 1–1.5 % for MF (Pfäfflin, 1992), 0.4 % for both genders (Weitze & Osburg, 1996), and 0.6 % for both genders (Meyer zu Hoberge, 2009). This might be explained by the extensive follow-up time in the present study and by the fact that virtually all cases of regrets are captured in the Swedish registry system. The FMs who applied for reversal were younger at application than those who did not (median 22 years compared to 27 years for the whole FM group). Conversely, the MFs who later applied for reversal were older when they applied for sex reassignment than those who did not (median 35 years vs. 32 years for the whole MF group). Since the group is small, these data must, however, be interpreted cautiously. A previous Swedish study identified lack of family support and transsexualism secondary to transvestism (today late onset gender dysphoria) as risk factors for regret (Landén, Wålinder, Hambert, & Lundström, 1998). Since then, all gender teams in Sweden include support to next-of-kin, which hence might have contributed to the decreased rate of regret. A Canadian study with 84.1 % follow-up rate of at least one year post SRS identified heterosexual MF as significant factor for regret (Blanchard, Steiner, Clemmensen, & Dickey, 1989). We had no data on sexual orientation in the present study and can neither confirm nor refute this finding. A German study identified poor differential diagnosis, failure to carry out the social transition, and poor surgical result and lack of proper care in treating the patients as risk-factors for regrets (Pfäfflin, 1992). Another study identified dissatisfaction with the physical and functional result of the SRS as a factor for regret to the treatment (Lawrence, 2003). One could speculate that workup procedures and surgical treatment have improved since 1990 contributing to a declined regret rate. It was beyond the scope of this study to survey details about the regret process and we can neither confirm nor refute previous predictors of regret.

About 6 %, more MF than FM, underwent surgical procedures abroad at their own expense, mostly in the U.S. and Thailand. This began ca. 1991 and has gradually become more common. In some instances, it reflects a wish to speed up the process or avoid the evaluation process.

Although all applications for legal gender reassignment were included, it is important to emphasize that this study does not represent all people with transsexualism or gender dysphoria; there may still be those who do not need or want a medical transition or have been denied early in the process by health care providers. The incidence of gender dysphoria/incongruence in a population, disregarding requests for treatment, is not known in Sweden but there is some information from the U.S., The Netherlands, Finland, and Taiwan. In a household probability sample of adults in Massachusetts, 0.5 % labeled themselves as transgender (Conron, Scott, Stowell, & Landers, 2012). In a recent Dutch study, 0.6 % of males and 0.2 % of females were gender dysphoric (Kuyper & Wijsen, 2014). In a population-based Finnish sample (222 men and 349 women 18–44 years), 6 % reported that they had felt like the opposite sex and/or wished they had the body of the opposite gender (Ålgars, Santtila, & Sandnabba, 2010). In a college student sample (2,588 men and 2,463 women) from Taiwan, 7.3 % females and 1.9 % males reported that they often or very often wished to be the opposite sex (Lai, Chiu, Gadow, Gau, & Hwu, 2010). These data must be interpreted cautiously due to differences in methodology and different definitions of gender dysphoria and importantly, these figures do not reflect the proportion of people who need or request medical help to ease their gender dysphoria. Nevertheless, these studies suggest that some degree of gender dysphoria is more common than the number of persons who actually decide to proceed with a gender reassignment. If societal changes result in increased awareness and acceptance of gender change, a further increase in incidence cannot be excluded.

Strengths and Limitations

This study was unique as it represents a complete national cohort of individuals who have applied for legal gender change in Sweden over the past 40 years. The quality of the data was

assured by access to all the original files and applications since 1960 and by the legal framework regulating legal sex change in Sweden. This contrasts with many studies from other countries that only pertain to one or a few clinics in a country and therefore cannot provide reliable prevalence estimates (Baba et al., 2011; Gómez-Gil et al., 2006). Moreover, this study covered 50 years which allows for observation of secular trends over the years. The methodology was similar to previous Swedish studies, which allows for comparisons (Landén et al., 1996; Olsson & Möller, 2003; Wålinder, 1971). A limitation was that the point prevalence was slightly overestimated (see "Method"). We had no data about sexual orientation and could therefore not test this factor in relation to changes in sex ratio or regrets.

Acknowledgments The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Financial support was provided through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and the Karolinska Institutet, through grants from the Royal Swedish Academy of Sciences (Torsten Amundson's Foundation) and from the Clinical Department of Psychiatry Stockholm Health Care Services. We thank Linda Almqvist, at the time for data collection legal adviser at The National Board of Health and Welfare, Stockholm, Sweden for valuable assistance with data collection and administrative support. We also thank Dr. Gail Knudson, who generously commented on the article.

References

Ålgars, M., Santtila, P., & Sandnabba, N. K. (2010). Conflicted gender identity, body dissatisfaction, and disordered eating in adult men and women. *Sex Roles, 63*, 118–125. doi:10.1007/s11199-010-9758-6.

American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington, DC: Author.

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed., rev.). Washington, DC: Author.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.

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

Baba, T., Endo, T., Ikeda, K., Shimizu, A., Honnma, H., Ikeda, H., et al. (2011). Distinctive features of female-to-male transsexualism and prevalence of gender identity disorder in Japan. *Journal of Sexual Medicine, 8*, 1686–1693. doi:10.1111/j.1743-6109.2011.02252.x.

Bakker, A., van Kesteren, P. J., Gooren, L. J., & Bezemer, P. D. (1993). The prevalence of transsexualism in the Netherlands. *Acta Psychiatrica Scandinavica, 87*, 237–238.

Blanchard, R., Clemmensen, L. H., & Steiner, B. W. (1987). Heterosexual and homosexual gender dysphoria. *Archive of Sexual Behavior, 16*, 139–152.

Blanchard, R., Steiner, B. W., Clemmensen, L., & Dickey, R. (1989). Prediction of regrets in postoperative transsexuals. *Canadian Journal of Psychiatry, 34*, 43–45.

Conron, K. J., Scott, G., Stowell, G. S., & Landers, S. J. (2012). Transgender health in Massachusetts: Results from a household probability sample of adults. *American Journal of Public Health, 102*, 118–122. doi:10.2105/AJPH.2011.300315.

De Cuypere, G., Janes, C., & Rubens, R. (1995). Psychosocial functioning of transsexuals in Belgium. *Acta Psychiatria Scandinavia, 91*, 180–184.

De Cuypere, G., Van Hemelrijck, M., Michel, A., Carael, B., Heylens, G., Rubens, R., et al. (2007). Prevalence and demography of transsexualism in Belgium. *European Psychiatry, 22*, 137–141. doi:10.1016/j.eurpsy.2006.10.002.

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*, 301–320. doi:10.1080/00918369.2012.653300.

Dixen, J. M., Maddever, M., Van Maasdam, J., & Edwards, P. W. (1984). Psychosocial characteristics of applicants evaluated for surgical gender reassignment. *Archive of Sexual Behavior, 13*, 269–276.

Dulko, S., & Imielinski, C. (2004). The epidemiology of transsexualism in Poland. *Journal of Psychosomatic Research, 56*, 637.

Eklund, P. L., Gooren, L. J., & Bezemer, P. D. (1988). Prevalence of transsexualism in the Netherlands. *British Journal of Psychiatry, 152*, 638–640.

Garrels, L., Kockott, G., Michael, N., Preuss, W., Renter, K., Schmidt, G., et al. (2000). Sex ratio of transsexuals in Germany: The development over three decades. *Acta Psychiatria Scandinavia, 102*, 445–448.

Godlewski, J. (1988). Transsexualism and anatomic sex ratio reversal in Poland. *Archives of Sexual Behavior, 17*, 547–548.

Gómez-Gil, E., Trilla García, A., Godás Sieso, T., Halperin Rabinovich, I., Puig Domingo, M., Vidal Hagemeijer, A., et al. (2006). Estimación de la prevalencia, incidencia y razón de sexos del transexualismo en Cataluña según la demanda asistencial [Estimation of prevalence, incidence and sex ratio of transsexualism in Catalonia according to health care demand]. *Actas Españolas de Psiquiatría, 34*, 295–302.

Gómez-Gil, E., Trilla, A., Salamero, M., Godás, T., & Valdés, M. (2009). Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. *Archives of Sexual Behavior, 38*, 378–392. doi:10.1007/s10508-007-9307-8.

Hoenig, J., & Kenna, J. C. (1974). The prevalence of transsexualism in England and Wales. *British Journal of Psychiatry, 124*, 181–190.

ILGA-Europe, the European Region of the International Lesbian, Gay, Bisexual, Trans and Intersex Association. (2013). *The rainbow map and index*. Retrieved from http://www.ilga-europe.org/home/publications/reports_and_other_materials/rainbow_europe_map_and_index_may_2012.

Kreukels, B. P., Haraldsen, I. R., De Cuypere, G., Richter-Appelt, H., Gijs, L., & Cohen-Kettenis, P. T. (2010). A European network for the investigation of gender incongruence: The ENIGI initiative. *European Psychiatry, 27*, 445–450. doi:10.1016/j.eurpsy.2010.04.009.

Kuyper, L., & Wijsen, C. (2014). Gender identities and gender dysphoria in the Netherlands. *Archives of Sexual Behavior, 43*, 377–385. doi:10.1007/s10508-013-0140-y.

Lai, M. C., Chiu, Y. N., Gadow, K. D., Gau, S. S., & Hwu, H. G. (2010). Correlates of gender dysphoria in Taiwanese university students. *Archives of Sexual Behavior, 39*, 1415–1428. doi:10.1007/s10508-009-9570-y.

Landén, M., & Innala, S. (2000). Attitudes toward transsexualism in a Swedish national survey. *Archives of Sexual Behavior, 29*, 375–388.

Landén, M., & Innala, S. (2002). The effect of a biological explanation on attitudes towards homosexual persons. A Swedish national sample study. *Nordic Journal of Psychiatry, 56*, 181–186. doi:10.1080/08039480231760715 6.

Landén, M., Wålinder, J., Hambert, G., & Lundström, B. (1998). Factors predictive of regret in sex reassignment. *Acta Psychiatrica Scandinavica, 97*, 284–289.

Landén, M., Wålinder, J., & Lundström, B. (1996). Prevalence, incidence and sex ratio of transsexualism. *Acta Psychiatrica Scandinavica, 93*, 221–223.

Lawrence, A. A. (2003). Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. *Archives of Sexual Behavior, 32*, 299–315.

Lawrence, A. A. (2010). Societal individualism predicts prevalence of nonhomosexual orientation in male-to-female transsexualism. *Archives of Sexual Behavior, 39*, 573–583. doi:10.1007/s10508-008-9420-3.

Meyer zu Hoberge, S. (2009). *Prevalence, incidence and sex ratio of transsexualism in Germany established by counting applications of the German Transsexual Act during the period 1991 until 2000.* Unpublished doctoral thesis, Medical Faculty Christian-Albrechts-Universität zu Kiel, Kiel, Germany.

Nieder, T. O., Herff, M., Cerwenka, S., Preuss, W. F., Cohen-Kettenis, P. T., De Cuypere, G., et al. (2011). Age of onset and sexual orientation in transsexual males and females. *Journal of Sexual Medicine, 8*, 783–791.

O'Gorman, E. C. (1982). A retrospective study of epidemiological and clinical aspects of 28 transsexual patients. *Archives of Sexual Behavior, 11*, 231–236.

Okabe, N., Sato, T., Matsumoto, Y., Ido, Y., Terada, S., & Kuroda, S. (2008). Clinical characteristics of patients with gender identity disorder at a Japanese gender identity disorder clinic. *Psychiatry Research, 157*, 315–318. doi:10.1016/j.psychres.2007.07.022.

Olsson, S. E., & Möller, A. R. (2003). On the incidence and sex ratio of transsexualism in Sweden, 1972–2002. *Archives of Sexual Behavior, 32*, 381–386.

Pauly, I. (1968). The current status of change of sex operation. *Journal of Nervous and Mental Disease, 147*, 460–471.

Pfäfflin, F. (1992). Regrets after sex reassignment surgery. *Journal of Psychology and Human Sexuality, 5*, 69–85.

Pimenoff, V. (2006). On the care of transsexuals in Finland. *International Journal of Transgenderism, 9*, 23–33.

R Foundation for Statistical Computing. (2013). R: A Language and Environment for Statistical Computing, Vienna, Austria. Retrieved from http://www.r-project.org/.

Ross, M. W., Wålinder, J., Lundström, B., & Thuwe, I. (1981). Cross-cultural approaches to transsexualism. A comparison between Sweden and Australia. *Acta Psychiatrica Scandinavica, 63*, 75–82.

Smith, Y. L., van Goozen, S. H., Kuiper, A. J., & Cohen-Kettenis, P. T. (2005). Transsexual subtypes: Clinical and theoretical significance. *Psychiatry Research, 137*, 151–160.

Sørensen, T., & Hertoft, P. (1980). Sexmodifying operations on transsexuals in Denmark in the period 1950–1977. *Acta Psychiatrica Scandinavica, 61*, 56–66.

Sørensen, T., & Hertoft, P. (1982). Male and female transsexualism: The Danish experience with 37 patients. *Archives of Sexual Behavior, 11*, 133–155.

Sweden Statistics. (2012). *Befolkningsstatistik*. Retrieved from http://www.scb.se/Pages/SSD/SSD_SelectVariables_340507.aspx?px_tableid=ssd_extern%3aBefolkningNy&rxid=0b3f5d00-ca4f-4813-9c77-5803f5fff6da.

Sweden Statistics. (2013). *Tillgång till it-utrustning och internet i hemmet för personer i åldern 16-74 år. År 2003–2012*. Retrieved from http://www.scb.se/Pages/SSD/SSD_TablePresentation_340486.aspx?layout=tableViewLayout1&rxid=f3be8994-75f3-4f4c-b0d6-e17cf3d08019.

Tsoi, W. F. (1988). The prevalence of transsexualism in Singapore. *Acta Psychiatrica Scandinavica, 78*, 501–504.

van Kesteren, P. J., Gooren, L. J., & Megens, J. A. (1996). An epidemiological and demographic study of transsexuals in the Netherlands. *Archives of Sexual Behavior, 25*, 589–600.

Veale, J. F. (2008). Prevalence of transsexualism among New Zealand passport holders. *Australian and New Zealand Journal of Psychiatry, 42*, 887–889.

Vujovic, S., Popovic, S., Sbutega-Milosevic, G., Djordjevic, M., & Gooren, L. (2008). Transsexualism in Serbia: A twenty-year follow-up study. *Journal of Sexual Medicine, 6*, 1018–1023. doi:10.1111/j.1743-6109.2008.00799.x.

Wålinder, J. (1968). Transsexualism: definition, prevalence, and sex distribution. *Acta Psychiatrica Scandinavica, 203*(Suppl.), 255–258.

Wålinder, J. (1971). Incidence and sex ratio of transsexualism in Sweden. *British Journal of Psychiatry, 119*, 195–196.

Weitze, C., & Osburg, S. (1996). Transsexualism in Germany: Empirical data on epidemiology and application of the German Transsexuals' Act during its first ten years. *Archives of Sexual Behavior, 25*, 409–425.

Wilson, P., Sharp, C., & Carr, S. (1999). The prevalence of gender dysphoria in Scotland: A primary care study. *British Journal of General Practice, 49*, 991–992.

Wood, H., Sasaki, S., Bradley, S. J., Singh, D., Fantus, S., Owen-Anderson, A., … Zucker, K. J. (2013). Patterns of referral to a gender identity service for children and adolescents (1976–2011): Age, sex ratio, and sexual orientation [Letter to the Editor]. *Journal of Sex and Marital Therapy, 39*, 1–6. doi:10.1080/0092623X.2012.675022.

World Health Organization. (1992). *The international statistical classification of diseases, and related health problems* (10th ed.). Geneva: Author.

Zucker, K. J., & Lawrence, A. A. (2009). Epidemiology of Gender Identity Disorder: Recommendations for the Standards of Care of the World Professional Association for Transgender Health. *International Journal of Transgenderism, 11*, 8–18.

Adolescent Health, Medicine and Therapeutics

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Gender nonconforming youth: current perspectives

This article was published in the following Dove Press journal:
Adolescent Health, Medicine and Therapeutics
25 May 2017
Number of times this article has been viewed

Diane Ehrensaft

Department of Pediatrics, University of California, San Francisco, CA, USA

Abstract: Beginning with a case vignette, a discussion follows of the reformulation of theories of gender development taking into consideration the recent upsurge of gender nonconforming and transgender youth presenting for gender services and also in the culture at large. The three predominant models of pediatric gender care are reviewed and critiqued, along with a presentation of the recently developed interdisciplinary model of gender care optimal in the treatment of gender nonconforming youth seeking either puberty blockers or cross-sex hormones.

Keywords: gender nonconforming, transgender, pediatric gender care, puberty blockers, cross-sex hormones

Introduction

The field of interdisciplinary treatment for gender nonconforming children and youth has not just expanded at an astronomically fast rate; to switch metaphors, it has rather been such as a tsunami, with a swell of children and families seeking support and services and stretching existing gender clinics and programs at their seams. This cohort of young people includes those who do not accept the sex assignment given to them at birth, those who do not accept their culture's expectations and rules about gender roles and gender behaviors, and those who present with a combination of both.

The case of Daniel is presented to launch this review of current perspectives on gender nonconforming youth. Daniel was 19 years old and in his first year of college (note: all identifying information has been changed to preserve confidentiality. In addition, the patient in the case vignette has provided written informed consent for the publication of the anonymized case details). Just a few months earlier he had announced to each of his parents, who were divorced, that he was transgender. For some years before that, he had been living as a girl, assuming that he was either a "butch dyke" or a masculine identified bisexual young woman. His father and stepmother's response was, "Yes, of course, it makes perfect sense. We'll support you in whatever you need". His mother's response was quite different, "God gave you a body, why would you want to go against God's will? I am so ashamed. What will I ever tell my family? I've always supported you, but I can't do this".

Taking a history, Daniel reported that by the end of his sophomore year in high school he discovered that he was transgender. Before that, he never had the language for who he was. Up until second grade, he, then she with the name Daisy, truly believed that when she reached puberty she would simply switch gears, grow a penis, get a beard,

Correspondence: Diane Ehrensaft
Department of Pediatrics, University of California, 445 Bellevue Avenue Suite 302 Oakland, CA 94610, USA
Email dehrensaft@earthlink.net

and become a man. From early childhood she dressed like a boy, insisted on wearing her hair short, and was perceived by all as the neighborhood tomboy. When she learned about the physical changes that accompanied female–menstruating, growing breasts, she responded, by her own report: "Whew, I'm so glad I'll never have to go through that". When an older youth disabused her of her misconception, informing her that she would receive no exemption and she would never grow to be a man because she was born a girl, she was temporarily devastated, coming to the realization that she was now doomed to walk the plank of female development. For her, this was a horrible thought. When she actually got her period in the sixth grade, she experienced, with trepidation, that her fate had been sealed – "I'm cooked, there's no turning back now".

In middle school, Daisy had her first girlfriend; she confided in her older brother about her new romance, and he promptly issued her a label, "You're a dyke". Except Daisy kept protesting, "I like boys, too". For high school, Daisy chose to go to a boarding school, the prime reason being that she was tired of going back and forth between two houses in her postdivorce family, and just wanted one place to settle into. It was a Catholic all-girls school and she got in trouble for having a romantic relationship with another girl at school. She persisted in dating girls, just not ones from her school, and through her peer connections first learned about the concept of transgender. She surfed the internet, joined chat rooms, and came to discover that "transgender would be me". Her then girlfriend, beginning to recognize who her partner really was, began referring to Daisy as D. and using male pronouns for D. D. never felt happier. But D. kept it a secret for 2 years, waiting out the end of high school and the opportunity to start a new life in college before affirming a male identity publicly. D. chose a liberal arts college far away from home and within weeks came out at school as Daniel. By Thanksgiving break, Daniel was ready to disclose to his parents, and that circles back to the beginning of the story.

After disclosing to his parents, Daniel then wanted hormones to align his body with his male identity, envisioning surgeries, including top and genital surgery, in his future, but not right then. Daniel's story is presented as an opener to highlight the two questions, "What is your gender?" and "What is to be done once discovered?" that underlie all existent adolescent gender care.

Daniel's case is not a unique one. One might even say that it is emblematic of the increasing number of youth who are seeking professional services, along with their parents, to sort out their authentic gender and discover ways to affirm that authenticity. In most Western cultures gender has historically been considered bedrock: one is assigned a sex at birth, either male or female, typically based on external appearance of genitalia, and this assignment determines one's gender for the duration of that individual's life. Upon entrance into the 21st century, that paradigm of gender bedrock has been hit with a sledge hammer; in its stead, we now have gender as moving boulders, with a sensibility of gender not coming in two boxes, but in infinite varieties, and not necessarily stable over the course of one's lifetime. As this has occurred, providers struggle to keep up with newly emerging theories of gender development and standards of care for the proper care of these youth. Just as an example, the World Professional Association for Transgender Health 7th Edition of the Standards of Care,[1] released in 2011, is already outdated and in the process of being revamped, with the section on children and adolescents in particular need of an update. The needed changes come most significantly in the area of social gender transitions for prepubertal youth, minimum ages for medical interventions, particularly puberty blockers and cross-sex hormones, but also surgeries for individuals before reaching the age of majority. Regarding numbers, the cohort of gender nonconforming youth seems to have expanded exponentially in the most recent decade, as reported by gender programs serving these children throughout North America and beyond.[2,3] In negotiating these phenomenal changes in the gender terrain, four major areas have needed to be addressed: the necessity of relearning gender so that health professionals can retool themselves to best serve this group of youth; the tensions between the three models of care; the importance of interdisciplinary collaboration in care; the introduction of medical interventions in the care of the youth.

Reformulate theories of gender development in light of gender nonconforming youth

Most professionals in the field of gender care have had to unlearn everything taught in training about gender and relearn a new model of gender development. To review the traditional model, children at birth are assigned a sex, male or female, typically based on appearance of external genitalia. If the genitalia were ambiguous in appearance, genital surgical procedures to establish a stable singular sex assignment with matching gender were to be performed as soon as possible, and no later than 18 months. The reasoning behind this, as propounded by Dr John Money and his associates,[4] was that after 18–24 months a child is firm in a core gender identity – I am male, I am female, and thereafter it becomes very difficult to change that identity as it is

already cognitively fixed. Once knowing one's gender label, which is both facilitated and mediated by parents' conscious and unconscious messages and reflections, a child's next developmental task is to learn how to "do" gender. Known as gender role socialization, this process is done in close relationship to one's mother and father, with the underlying assumption that all children will have both.[5,6] Within the psychoanalytic paradigm, during this same period a tumultuous drama unfolds, the Oedipal phase – children have intense erotic fantasies about their parents: boys will want to marry their mothers, girls their fathers. Through successful negotiation of these fantasies, facilitated by parents' empathy and boundary setting, children will emerge from the Oedipal phase relinquishing those infantile incestuous desires, firming their own heterosexual identities as they forestall gratification and await an opposite sex partner of their own when they reach adulthood.[7] Within that process they will establish a firm gender identity with a new understanding that one is and always will remain the sex listed on one's birth certificate or assigned early in life (for intersex children).[8] Throughout middle childhood youth will continue to internalize the gender norms of their culture, and learn to conform to them. With the advent of puberty and the entrance into adolescence, a new phase of gender consolidation occurs as youth awaken to their adult sexual urges and prepare for their gender-divided roles as men or women.

Within the traditional model of gender development, if this developmental trajectory takes a course other than that described above, there is cause for concern for the child, along with scrutiny of the parents, as parents are held accountable for the child's anomalies. To quote Robert Stoller, a pioneer in the treatment of gender disorders in youth in the 20th century,[9] speaking of "primary transsexual" boys (those nonintersex boys who have been feminine from the first year of life): "As an infant, such a boy usually has an excessively intimate, blissful, skin-to-skin closeness with his mother. This, unfortunately, is not interrupted by his father, a passive distant man who plays no significant part in bringing up his son" (p. 16). In family situations like the one inscribed above by Stoller, professional help was recommended to cure the youth's gender anomalies and to treat the parents so they cease veering their child's gender development in wrong directions because of their own internal conflicts.

For a theory of development to be robust, it should be evident in empirical observation or investigation. The traditional theory of gender development and disordered gender, which is still in use by many, fails that test, for the following reasons:[10]

- Many individuals continue renegotiating their gender throughout childhood or adulthood, with no observable detriment to their mental health;
- Youth may establish a gender identity in concordance with their assigned sex, be firm in that identity, yet not embrace a heterosexual identity, with no aspersion on their emotional well-being. Gender development and sexual identity development are two separate developmental tracks, albeit crossing at certain points.
- Whereas core gender identity is typically concordant with assigned sex based on observable external genitalia, for a minority of people this is not the case, with increasing evidence that gender identity lies not between our legs, in our genitalia and primary sex characteristics, but in our brains and minds.[11]
- Therefore, one's assigned sex at birth may differ from one's core gender identity, not because of poor parental handling or infantile confusions, but because of brain and mind gender messages overriding signals from genitalia, chromosomes, or parental expectations. Recently, this phenomenon of mind over matter has been referred to as "neurological sex", defined as a uniform standard of legal sex based on gender identity, in which brain messages are privileged over anatomy and chromosomes in determining an individual's authentic gender.[12]

In contemporary versions of gender development theory that take into account gender variations as a normal part of the human condition, the understanding is that the sex assigned at birth may match the gender a youth will eventually know themselves to be, but it might not. Each child is presented with a developmental task of weaving together threads of nature, nurture, and culture to establish their individual and unique authentic gender self. This self will be composed of both gender identity – who I know myself to be as male, female, or other, and gender expressions – how I choose to perform my gender, including clothing choices, activity preferences, friendship choices, and so forth. Recently, this transactional relationship between nature, nurture, and culture in gender development has been referred to as the gender web,[13] broken up into components that consist of the items in Table 1.

In this contemporary model of gender development, added to the three dimensions of nature, nurture, and culture is the fourth dimension: time. Each child alters their gender web as they weave together nature, nurture, and culture, "over time". In other words, gender is neither fixed by age 6, as in the traditional model, nor static throughout all stages of child and adult development, thus explaining how an individual

Table 1 Gender development: elements of the gender web

- Chromosomes
- Hormones
- Hormone receptors
- Gonads/primary sex characteristics
- Secondary sex characteristics
- Brain
- Mind
- Socialization: family, school, religious institutions, community
- Culture: values, ethics, laws, theories, and practices

at age 40 or 50 could come to the realization that the gender they had identified as being is no longer a good fit. It is also recognized that gender development is a discrete and separate track from development of one's sexual identity, and typically proceeds it in a youth's development.

In this model the role of parents and socialization agents is not to shape or reinforce a child's gender identity or expressions, but rather to facilitate it, mirroring back to the child the messages that the child communicates about their preferred gender expressions and articulated gender identity, which may or may not be in concordance with the sex assigned to the child at birth. With the advent of adolescence, it is recognized that some youth's gender trajectories may benefit from medical interventions, including puberty blockers (gonadotropin-releasing hormone [GnRh] agonist) and cross-sex hormones to bring the youth's body in better alignment with their affirmed gender identity.[14] To that end, the model of care that extends from this contemporary theory of gender development is one that strongly relies on interdisciplinary care, especially between mental health and medical providers as they address the holistic medical and psychosocial needs of the emergent cohort of gender nonconforming youth from the perspective of both their psychological and physical development.

Major mental health treatment models for gender nonconforming children and youth

As of the second decade of the 21st century, three major treatment models are available for addressing the needs of gender nonconforming children and their families, with overlapping premises based on the contemporary model of gender development outlined above but with distinct differences between them. The first model, represented in the work of Drs Susan Bradley and Ken Zucker, assumes that young children have malleable gender brains, so to speak, and that treatment goals can include helping a young child accept the gender that matches the sex assigned to them at birth. The second model, represented in the work of practitioners in the Netherlands, allows that a child may have knowledge of their gender identity at a young age, but should wait until the advent of adolescence before engaging in any full transition from one gender to another. The third model, represented in the work of an international consortium of gender affirmative theoreticians and practitioners, allows that a child of any age may be cognizant of their authentic identity and will benefit from a social transition at any stage of development. To situate and compare each of the three models, a typical referral that may come the way of a gender specialist, regardless of their orientation, is presented, with the assumption that this potential patient may be in need of services from a young age through adolescence:

> Hi Dr, I came across your information while I was researching for my son.
>
> He recently just turned 4 and wants to be a girl and is only drawn to girl toys/clothes for the past 2 years.
>
> We have not spoken with a professional doctor. But wanted to reach out early and find ways we as parents can support him.
>
> Please let me know if you could help.
>
> Thank you!

Dialing back a generation, if this child's name was Kyle and the same query came to a mental health professional participating in, for example, Dr Richard Green's clinic at the University of California Los Angeles, the treatment recommended and then implemented could very well have looked like this:

> When he was five, Kyle entered a behavior modification program. [...] Kyle received blue tokens for "desirable" behaviors […] red ones for "undesirable" behaviors […]. Blue tokens were redeemable for treats […]. Red tokens resulted in a loss of blue tokens, periods of isolation, or spanking by father.[15]

Setting a precedent for other clinicians of the time treating children who presented as gender nonconforming, Kyle's treatment at the UCLA program is emblematic of the model implemented during this era, with the goal of helping children accept the sex assigned to them at birth and adopt the culturally defined appropriate gender behaviors that would match that sex assignment, in alignment with the traditional model of gender development. Underlying the treatment was the intent of warding off a homosexual outcome for young effeminate boys. It should be mentioned

that this model is still practiced today, referred to by some as the reparative model.

Focusing now on contemporary approaches that stand in contrast to the above mode, all of which are to be differentiated from the UCLA program, the three major models, outlined earlier, are typically referred to, in order of presentation, as the following:

- The "live in your own skin" model
- The watchful waiting model
- The gender affirmative model

Below is a review of the manner in which each of these models would approach the treatment of a child or youth who is presenting as gender nonconforming, in their gender identity, gender expressions, or both.

The "live in your own skin" model

As mentioned earlier, this model was developed by Drs Susan Bradley and Ken Zucker at the Center for Alcoholism and Mental Health gender clinic in Toronto.[16] The treatment goal of facilitating a young child accepting the gender identity matching the sex assigned to that child at birth, based on the supposition that younger children, in contrast to older youth, have a malleable gender brain, is tied to a medical–social rationale. Specifically, being transgender is a harder way to live one's life, both because of social stigma and potential requested hormonal treatments and surgeries to align a youth's body with their transgender identity. Given the perceived plasticity of the young child's gender brain, best practice would be to introduce interventions to help a child accept the sex assigned to them at birth as their gender identity, with no harm done and indeed added benefit to their psychological and social well-being. As explained by Dr Zucker, employing this strategy results in lowering the odds that "as such a kid gets older, he or she will move into adolescence feeling so uncomfortable about their gender identity that they think that it would be better to live as the other gender and require treatment with hormones and sex reassignment surgery".[17] In addition to presuming gender identity malleability in young children, the model also assumes that parents' own conflicts or issues about gender likely contribute to a young child's gender dysphoria. With the parents' consent, the "live in your own skin" model employs a combination of behavior modification, ecological interventions, and family system restructuring to facilitate the child arriving at a place of accepting the gender matching their sex assigned at birth. Practices could include taking away cross-gender toys at home and replacing them with "gender-appropriate" toys, altering children's playmate choices to include more same-sex contacts, enrolling the children in "gender-appropriate" activities, encouraging the like-sex parent to become more actively involved and the opposite-sex parent to step back in relationship to the child, and offering psychotherapy to both the child and parents. The aim of treatment of the child is to explore the child's gender and solidify a "live in your own skin" outcome, and the treatment with the parents is aimed at investigating conflicts or psychological issues stemming from or contributing to the child's gender dysphoria. If by the arrival of puberty a child is still exhibiting cross-gender identifications and expressing a cross-gender identity, that child should be supported in transitioning to the affirmed gender, including receiving puberty blockers and hormones, once it is assessed through clinical interviews and psychometric testing that the affirmed gender identity is authentic. The reasoning behind this shift in adolescence is as follows: 1) by adolescence it is too late to intervene in facilitating a child living in their own skin, as the sensitive period of malleable brain development of gender has closed; 2) this individual can now be reliably identified as one of the small minority of youth who persist with a cross-gender identity from early childhood into adolescence, an indicator that this identification will most likely remain stable into adulthood. In the live in your own skin model, the parent reaching out for support of her 4-year-old son might be encouraged to engage in the treatment program outlined above, with the goal of helping her child accept that he is a boy, not a girl and with the intent of warding off a transgender outcome.

The watchful waiting model

The "watchful waiting" model was designed by the members of the interdisciplinary team at the Amsterdam Center of Expertise on Gender Dysphoria, VU University Medical Center, under the leadership of Dr Peggy Cohen-Kettenis. Borrowing from the medical use of GnRH agonists for children exhibiting precocious puberty, the Netherlands team is responsible for introducing the use of puberty blockers for gender purposes, to put a pause on pubertal growth and allow more time for a youth to explore their gender and consolidate their adolescent gender identity, with the future possibility of cross-sex hormone therapy to align their bodies with their affirmed gender identity. In contrast to the live in your own skin approach, a young child's demonstration of gender nonconformity, be it in identity, expressions, or both, is not to be manipulated in

any way, but observed over time. If a child's cross-gender identifications and affirmations are persistent over time, interventions are made available for a child to consolidate a transgender identity, once it is assessed, through therapeutic intervention and psychometric assessment, as in the best interests of the child. These interventions include social transitions (the shift from one gender to another, including possible name change, gender marker change, and gender pronoun changes), puberty blockers, and later hormones and possible gender-affirming surgeries. No attempts are made to alter a child's gender identity or expressions; yet it is postulated in this model that it would be better to hold off until puberty on any social transitions of a child from one gender to another, and instead give them safe spaces to fully express their gender as they prefer before facilitating any full gender transitions.[18,19] The rationale for holding off on any social transitions until adolescence is not to ward off a transgender identity but rather that 1) it would be advantageous that a child experiences the first stages of physical puberty for that child to best make a determination of the gender that feels most authentic to him/her; 2) given developmental stages of childhood, facilitating a social transition from one gender to another at a young age may create a form of cognitive constriction – the child may be prematurely blocked from considering any other possibilities once moved into a cross-gender status and socially constricted from further childhood gender exploration because now they know the cross-gender identity is what everyone has come to expect from them; 3) socially transitioning a child at a very young age may preclude the child from maintaining a realistic understanding of their body and historical status – as a penis-bodied (once a boy) or a vagina-bodied (once a girl) person. In informing their practices, this model, like the live in your own skin model, relies on the data gathered about "persisters" and "desisters", both at their own clinic in the Netherlands and in other international studies, particularly those conducted at the Centre for Addiction and Mental Health (CAMH) gender program in Toronto. In the most recent review of these studies, it was found that 63% of the children seeking services at a gender clinic at a young age, and diagnosed with gender dysphoria, no longer had that diagnosis at puberty, while 37% did have the diagnosis consistently from early childhood to adolescence.[20] Since a large majority of gender nonconforming young children seeking services at gender clinics desist in their gender dysphoria by adolescence, best practices would be to wait and see if the child persists into adolescence before making any significant changes in a child's gender identity.

During the preadolescent waiting period, the children are followed carefully by the clinical team in the watchful waiting model, with the support of outside therapists in the community (which is required before a child can receive medical services), to assure that the children are growing well and getting their emotional needs met, and in preparation for later transitioning and medical interventions if the child proves to be a good candidate. Like in the live in your own skin model, the children going through the program also receive a full battery of psychological tests, documenting not only their gender status but also their cognitive–social–emotional functioning. Some of these instruments are delivered to the children directly, some to their parents or teachers.

If the mother asking for help with her 4-year-old were to attend the Amsterdam clinic with her child, the team might do an assessment and advise that the 4-year-old be followed over time, with the understanding that if her son's declarations of wanting to be a girl persisted over time and if he continued to be drawn only to "girl" toys and activities, consideration of puberty blockers to buy more time to explore gender could certainly happen later, but for now it would be best to let her son continue to be a son free to explore whatever activities he enjoyed, with no corrections on his expressed desire to be a girl.

The gender affirmative model

The third model of care, the gender affirmative model, is closely aligned with the watchful waiting model but in opposition to the live in your own skin model. Where the gender affirmative model parts ways with the watchful waiting model is in the waiting part.

The gender affirmative model is defined as a method of therapeutic care that includes allowing children to speak for themselves about their self-experienced gender identity and expressions and providing support for them to evolve into their authentic gender selves, no matter at what age. Interventions include social transition from one gender to another and/or evolving gender nonconforming expressions and presentations, as well as later gender-affirming medical interventions (puberty blockers, cross-sex hormones, surgeries). A particular set of premises informs the model, as listed in Table 2.

The model is informed by the contemporary theory of gender development outlined above, with a recognition that although gender evolves over the course of a lifetime, gender identity appears to be a relatively more stable and consistent construct compared to gender expressions. Gender health is defined as a youth's opportunity to live in the gender that feels most real and/or comfortable, or, alternatively, a youth's

Table 2 Basic premises of the gender affirmative model

- Gender variations are not disorders.
- Gender presentations are diverse and varied across cultures, requiring cultural sensitivity.
- Gender involves an interweaving, over time, of biology; development and socialization; and culture and context.
- Gender may be fluid; it is not always binary.
- If present, individual psychological/psychiatric problems are more often than not secondary to negative interpersonal and cultural reactions to a child.
- Gender pathology lies more in the culture than in the child.

ability to express gender with freedom from restriction, aspersion, or rejection.[21] When considering a child's gender status, attention is paid to both gender identity and gender expressions, with the understanding that a child's gender identity may communicate something very different about the child than a child's gender expressions might.

Therapeutic goals in the gender affirmative model include:

- Facilitating an authentic gender self
- Alleviating gender stress or distress
- Building gender resilience
- Securing social supports

In contrast to the first two models, no assumption is made that every child exhibiting a gender nonconforming presentation is in need of mental health treatment. Because of the emphasis on social factors affecting the youth, interventions may be targeted at the surrounding environment, rather than the child's individual psyche. This might include interfacing with schools, social and religious institutions, and policy-making bodies to remove the "social" pathology impinging on the child, such as transphobic attitudes and responses, gender policing, or bullying and harassment. Relatedly, parent consultations often take precedence over individual treatment of the child,[22–24] with provision of services to help a parent make sense of their child's gender nonconformity, work through any extant conflicts and anxieties about their child's gender, and move toward acceptance of their child.

Individual treatment for the child is indicated for one of five reasons: 1) to assess a child's gender status; 2) to afford the child a "room of their own" to explore their gender; 3) to identify and attend to any co-occurring psychological issues; 4) to address and ameliorate a child's gender stress or distress; 5) to provide sustenance in the face of a nonaccepting or rejecting social milieu, which might include family, school, religious institution, or community. Some professionals working in this model will call on psychometric or projective measures to gather information about the child; others will rely on observation, play, interviewing, and dialog. If assessment instruments are employed, every effort is made to use protocols that do not rely on binary measures of gender (e.g., Are you a boy or a girl?) and are not pathology oriented, but instead assess strengths as well as weaknesses and differentiate between gender expressions and gender identity.

The basic therapeutic tenet of the gender affirmative model is quite simple: When it comes to knowing a child's gender, it is not for us to tell, but for the children to say. In contrast to the watchful waiting model, once information is gathered to assess a child's gender status, action is taken to allow that child to exercise that gender. Therefore, if after careful consideration, it becomes clear that a young child is affirmed in their gender, demonstrating that the gender they know themselves is different than or opposite to the gender that would match the sex assigned to them at birth, the gender affirmative model supports a social transition to allow that child to fully live in that gender, whether that child is 3, 7, or 17 years old. Such decision-making is governed by stages, rather than ages, both for social transitions and later for medical interventions. Once the child's gender comes into clear focus, which is posited as happening with a child of any age, no need is seen to hold off until adolescence to affirm that gender. This viewpoint is informed by data indicating the psychological harm that can be done, including heightened risk for generalized anxiety, social anxiety, oppositional behaviors, depression, compromised school performance, if a youth experiences themselves living in a gender that is inauthentic to them.[25]

In the gender affirmative model, the mother of the 4-year-old querying about her son's cross-gender interests would be invited in to the consultation room, along with any other parenting figure involved, to report more about what she had been observing in her child's behaviors from infancy to the present; to determine whether her son is showing any signs of stress or distress about his interest in all things girly things; to explore whether her child is indicating cross-gender expressions vs identity. If there was evidence of stress or distress, by parents' report, or if the parents desired to get a clearer picture of their child's gender status, the family would be invited to bring their son in for observation and play sessions. There would then be the opportunity to reflect, in collaboration with the parents or caregivers, on any evidence that this child was consistent in cross-gender declarations, as in "I'm a girl, not a boy", and that these declarations were persistent over time and not attributable to any other problems in life. If that evidence made clear that this child was communicating about a cross-gender identity rather than desired cross-

gender expressions, and if the parents were supportive of their child's gender identity affirmations, it would not be found necessary to recommend to this mother that she wait until puberty to take action regarding her child's gender identity. Instead, a present social transition to the gender that was more authentic for this child, in this case, female, would be considered. If, on the other hand, the child was happy as he was, if given the latitude to play with whatever he wanted and wear whatever he desired, as a boy, the recommendation to the mother might be to give her son the opportunity to express his gender freely, with the opportunity to return for services as requested. Along with this recommendation would be a reminder that all that can be known is the cross section of this child's gender as he presents it at age 4, a gender that may evolve into another configuration later in childhood, at which point a new assessment may be in order.

Critique of the three models

In brief, the live in your own skin model has been challenged as causing potential harm to gender nonconforming youth. A Canadian study conducted by Wallace and Russell assessed that in the living-in-your-own-skin model "there appears to be an enhanced risk of fostering proneness to shame, a shame-based identity and vulnerability to depression."[26] Major health organizations, including the World Professional Association for Transgender Health, the American Psychological Association, and the American Psychiatric Association, have issued statements stipulating that mental health professionals are not to engage in practices that attempt to alter the gender expressions or identity of an individual, including children and adolescents. The watchful waiting model is a highly respected model of care worldwide, offering careful and cautious procedures; but it has run into a snag: many contemporary families in the Netherlands are not content to hold their children back from social transitions until puberty, and have, through both local and international support networks of parents and professionals, proceeded to facilitate their children's social transitions without awaiting clinical approval or waiting until puberty arrives. Parents do this not because they dismiss professional care, but because evidence is accruing that young children thrive when given permission to live in the gender that is most authentic,[27,28] and are at risk for symptomatic behaviors if prevented from doing so. At the same time, the watchful waiting model is effective in its thorough attention and assessment of the child over time, integrating the services of mental health and medical professionals.

The gender affirmative model is questioned by some on the basis of the lack of evidence-based data that indicates that young children can reliably communicate and have self-knowledge of a transgender identity or benefit from a social transition. There is also concern that the model of listening to the children puts too much weight on a child's self-report. This is a valid concern, and to address it the self-report is embedded within a collaborative model with the child as subject and the collaborative team including the child, parents, and professionals. Together, the team will be making informed determinations about the most appropriate gender pathways to promote a child's gender health, be it a gender social transition, expanded opportunity to express gender in ways that feel authentic to the child, or deeper exploration of underlying issues that may be presenting as gender stress or distress. Such determinations typically involve extensive consultation and observation, but with no requirement for ongoing psychotherapy or psychometric testing, in comparison to the other two models.

Integration of medical and mental health care in adolescence

All of the three models of care referenced earlier share in common the administration of hormonal treatment in adolescence. The first category would be consideration of GnRH agonists (puberty blockers) to put a temporary pause on puberty, providing a youth with additional time to explore gender or, alternatively, warding off an unwanted puberty. The latter is particularly true for youth who socially transitioned early in life, living consistently in their affirmed gender from a young age; in those instances administration of puberty blockers could be considered a form of continuity of care, from social transitions to hormonal intervention. The second category includes feminizing or masculinizing hormones to bring a youth's body in better alignment with their affirmed gender identity. The minimal age for being eligible for such treatments may vary among approaches and indeed among clinics adopting the same approach, but there is common agreement that these treatments are in the best interests of the child who has a documented transgender identity.[29] It should be noted that there is probably no other aspect of adolescent care in which the medical and mental health professionals are so vitally interdependent in both assessment and treatment of the youth.[30] The reason for this is that each of the interventions has vital interconnected psychological and medical components, requiring an integration of medical evaluation and mental health assessment both to determine appropriateness, assess any medical or psychological impediments to treatment, and monitor follow-up, in terms of effects and supports over time as the youth is administered either the puberty blockers or hormones.

The role of the medical professional is first to assess the youth's level of puberty development, with an assessment of physical readiness for considerations for puberty blockers, which can be administered as soon as the youth enters Tanner Stage 2 of puberty. The medical professional will be responsible for ordering the lab work and bone density scans necessary to monitor a youth's progress and also to screen for any medical counter-indications to administering the blockers. As RnGH agonists are a completely reversible procedure regarding development of secondary sex characteristics, the medical provider will not need to worry about untoward permanent effects in that regard if the youth decides to go off blockers and return to the unfolding of a physical puberty in concordance with the sex assigned at birth. It should be noted, however, that the provider will need to alert the child and family about any side- or long-term effects of RnGH agonists, including effects on bone mineral density and overall bone health. If, on the other hand, the youth decides to proceed with cross-sex hormones to affirm a gender identity not in concordance with the sex assigned at birth, the medical provider will then be faced with the task of determining if the youth is a good candidate for this next step of treatment. Some youth will have already gone through full puberty before discovering or communicating to others a transgender identity, and the medical provider will be faced with the same task with these youth, with the added feature of explaining to the youth that certain of the developed features of the puberty they have already gone through will not disappear as they go through a second puberty on cross-sex hormones. In either case, cross-sex hormones involve a weightier decision than puberty blockers, as these interventions are only partially reversible in terms of secondary sex characteristics, so the provider will want to be cautious and judicious in determining if cross-sex hormones are appropriate for a particular youth.

This is where the mental health professional enters. In all of the models of gender care, the mental health professional is asked to weigh in as to 1) the authentic gender identity of the youth or level of gender dysphoria exhibited by the youth; 2) the youth's level of maturity and ability to assent to and follow through on the recommended hormonal treatment; 3) the evidence of any coexisting psychological conditions that might interfere with the hormone treatment or that alternatively might bear no weight on the requested treatments or even be alleviated by the hormonal interventions; and 4) the level of family support and willingness to consent to the treatment. In consultation with the medical professional, a decision will be made as to whether a youth is a good candidate for either puberty blockers or cross-sex hormones.

Another critical task for the medical-mental health team is the necessary discussion of fertility implications for each of these interventions. Although advances are being made in reproductive medicine to preserve immature gametes or reproductive tissues for later reproduction, at this point in history a child who begins puberty blockers at Tanner Stage 2 and proceeds directly to cross-sex hormones will be rendered infertile. Administration of testosterone or estrogen to a postpubertal adolescent may compromise a youth's later fertility, or might require going off the hormones for a period of time if a transgender youth who has not had gonad or genital surgeries later in life desires to have a genetically related child. Alternatively, a youth can bank gametes for the future before going on a course of cross-sex hormones, which is a medical possibility but also a psychological challenge for many transgender youth who find this antithetical to their affirmed gender status, requiring a transgender female to attend a fertility clinic and masturbate or a transgender male to undergo a gynecological vaginal ultrasound. Exploring fertility issues before making decisions about blockers or hormones are necessary but sensitive discussions to be had with both the youth and parents, and are best done with the presence of both a medical and a mental health professional who together can provide medical and psychological counsel to the family in this decision affecting later family-building.[31]

Not only is there no other aspect of adolescent care where the teamwork between medical and mental health provider is critical; there is no other domain of youth services in which a mental health provider is so actively involved in medical decision making. Where this has surfaced most recently is in the recent emergence of youth in gender clinics who present as neither male nor female, but rather gender nonbinary or "in the middle", adopting the platform of the multiplicity of gender. The challenge is when these youth ask for a particular medical intervention that achieves that goal of a middle ground – perhaps a touch of testosterone, or chest surgery with no other intervention and a chosen pronoun of "they" rather than "he" or "she". These are new horizons for both medical and mental health professionals today, and there is a mutuality, therefore, in the medical professional training the mental health professional while the mental health professional is in turn training the medical professional in order to integrate the biopsychosocial aspects of care to include the gamut of all the gender nonconforming youth presenting for care.[32]

With that said, it has proved to be critical that mental health professionals involved in this team work be trained gender specialists, with a basic understanding of the medical interventions involved in transgender care, expertise in

assessing gender dysphoria and identifying a youth's gender identity, and recognition of psychological issues other than gender that might drive a youth's request for a hormonal treatment. For example, a nurse practitioner on a gender team had administered a puberty blocker implant, Supprelin, which could stay in place for a year, after receiving a letter of support from a trained mental health expert recommending such treatment for this youth who presented as gender dysphoric and in need of further exploration of his gender before going forward with puberty. Over the course of the following year, he failed to return for follow up visits. A year had gone by and it was now time to replace the implant, which the nurse practitioner was prepared to do. The mental health member of the team first did a follow-up evaluation of the youth and discovered that he had made no efforts to explore his gender any further, with his motivation to continue on blockers driven by a desire to remain prepubertal for as long as possible. With the psychologist's guidance, the medical provider was able to recognize that the medical intervention as it stood was inappropriate for this youth. The interdisciplinary team informed the youth that he would be able to receive a new implant only if he was simultaneously working with a mental health gender specialist to further explore his gender identity. If that condition was met, once the twelve additional months on the puberty blockers was completed, the youth would then have to make a determination of which puberty path he would take – cross-sex hormones or the unfolding of his male, testosterone-producing puberty.

Conclusion

In the course of only two decades, sophisticated models for the care of gender nonconforming and transgender youth have evolved. There is an urgent need to provide more research data documenting the efficacy of these different programs, but the recent findings of the Amsterdam group provide hope that the care, particularly within the watchful waiting and gender affirmative models, is promoting gender health. In the Dutch authors' words, the treatment, including puberty suppression, cross-sex hormones, and then in adulthood gender affirmation surgery, "leads to improved psychological functioning of transgender adolescents. While enabling them to make important age-appropriate developmental transitions, it contributes to a satisfactory objective and subjective well-being in young adulthood".[33] The authors propose that not only early medical intervention, but also a comprehensive multidisciplinary approach contributes to the youth's gender health. Reflecting back on Daniel, the youth introduced at the opening of this review, the ability of professionals to aid youth such as Daniel in getting his authentic gender into focus and providing the appropriate treatments to bring that gender in alignment with his body is the key to overall well-being for all youth seeking professional gender care.

Disclosure

The author reports no conflicts of interest in this work.

References

1. World Professional Association for Transgender Health. *Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People*. WPATH; 2011.
2. Hidalgo MA, Ehrensaft D, Tishelman AC, et al. The Gender affirmative model: what we know and what we aim to learn. *Hum Dev*. 2013;56:285–290.
3. Zucker KJ, Wood H, VanderLaan, DP. Models of psycho-pathology in children and adolescents with gender dysphoria. In: Kreukels BPC, T. Steensma TD, de Vries ALC, editors. *Gender Dysphoria and Disorders of Sex Development: Progress in Care and Knowledge*. New York, NY: Springer; 2014:171–192.
4. Money J, Ehrhardt A. *Man & Woman, Boy & Girl: Gender Identity from Conception to Maturity*. Northvale, NJ: Jason Aronson; 1996.
5. Diamond M. Sex, gender, and identity over the years: a changing perspective. *Child Adolesc Psychiatr Clin N Am*. 2004;13(3):591–607.
6. Tyson P. A Developmental line of gender identity, gender role, and choice of love object. *J Am Psychoanal Assoc*. 1982;30(1):61–86.
7. Freud S. *Three Contributions to the Theory of Sex*. New York, NY: E.P. Dutton; 1962.
8. Fast I. Aspects of core gender identity. *Psychoanal Dial*. 1999;9(5):633–661.
9. Stoller R. *Presentations of Gender*. New Haven, CT: Yale University Press; 1985.
10. Ehrensaft D. *Gender Born, Gender Made*. New York, NY: The Experiment Press; 2011.
11. Diamond M. Sex and gender: same or different? *Feminism Psychol*. 2000;10(1):46–54.
12. Vanderhorst B. Whither lies the self: intersex and transgender individuals and a proposal for brain-based legal sex. *Harvard Law & Policy Review*. 2015;9:241–274.
13. Ehrensaft D. From gender identity disorder to gender identity creativity: true gender self child therapy. *J Homosex*. 2012;59(3):337–356.
14. Sherer I, Rosenthal S, Ehrensaft D, Baum J. Child and adolescent gender center: a multidisciplinary collaboration to improve the lives of gender nonconforming children and teens. *Pediatr Rev*. 2012;33(6):273–276.
15. Green R. *The 'Sissy boy' Syndrome and the Development of Homosexuality*. New Haven, CT: Yale University Press; 1987:295.
16. Zucker K, Bradley S. *Gender Identity Disorder and Psychosexual Problems in Children and Adolescents*. New York, NY: The Guilford Press; 1995.
17. Cross JM. Outcry prompts CAMH to review its controversial treatment of trans youth. *Metro News*, Toronto; 2015, March 18; online. Available from: http://metronews.ca/news/toronto/1315743/outcry-prompts-camh-to-review-its-controversial-treatment-of-trans-youth
18. Cohen-Kettenis PT, Pfäfflin F. *Transgenderism and Intersexuality in Childhood and Adolescence*. Thousand Oaks, CA: Sage Publications; 2003.
19. Steensma TD, McGuire J, 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):582–590.

20. 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(4):499–516.
21. Ehrensaft D. *The Gender Creative Child.* New York, NY: The Experiment; 2016.
22. Ehrensaft D. Boys will be girls, girls will be boys. *Psychoanalytic Psychol.* 2011;28(4):528–548.
23. Ehrensaft D. From gender Identity disorder to gender identity creativity: true gender self child therapy. *J Homosex.* 2012;59(3):337–356.
24. Malpas J. Between pink and blue: a multi-dimensional family approach to gender non-conforming children and their families. *Fam Process.* 2011;50(4):453–470.
25. Roberts L, Rosario M, Corliss HL, et al. Childhood gender nonconformity: a risk indicator for childhood abuse and post-traumatic stress in youth. *Pediatrics.* 2012;129:410–417.
26. Wallace R, Russell H. Attachment and shame in gender-nonconforming children and their families: toward a theoretical framework for evaluating clinical interventions. *Int J Transgenderism.* 2013;14(3):113–126.
27. Olson KR, Key AC, Eaton NR. Gender cognition in transgender children. *Psychol Sci.* 2015;26(4):467–474.
28. Durwood L, McLaughlin KA, Olson KR. Mental health and self-worth in socially transitioned transgender youth. *J Am Acad Child Adolesc Psychiatry.* 2017;56(2):116–123.
29. Rosenthal SM. Approach to the patient: transgender youth: endocrine considerations. *J Clin Endocrinol Metab.* 2014;99(12):4379–4389.
30. Vance SR, Ehrensaft D, Rosenthal SM. Psychological and medical care of gender nonconforming youth. *Pediatrics.* 2014;134(6):1184–1192.
31. Ehrensaft D, Hastings J, Hsaio K. Ferility issues for youth: puberty blockers, hormones. Decision-making through the lens of family building options. World Professional Association for Transgender Health Symposia. Amsterdam, June 20, 2016.
32. Harris A. *Gender as Soft Assembly.* New York, NY: The Analytic Press; 2005.
33. deVries ALC, McGuire JK, Steensma TD, Wagenaar EC, Doreleijers TA, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics.* 2014;134(4):696–704.