COSMETIC
Outcomes Article

Male-to-Female Sex Reassignment Surgery Using the Combined Technique Leads to Increased Quality of Life in a Prospective Study

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Background: The authors' previous research showed that various plastic surgical procedures can increase a patient's quality of life in its different aspects. In a prospective setting, they evaluated whether sex reassignment surgery has similar effects for male-to-female transgender patients compared to baseline data before sex reassignment surgery.
Methods: All 39 patients who underwent their first-stage male-to-female sex reassignment surgery between October of 2012 and January of 2014 received one set of questionnaires preoperatively (time 0) and approximately 6 months after their final operation (time 1). Each set contained self-developed, indication-specific questions combined with the standardized validated Questions on Life Satisfaction, Modules (German version) questionnaire, the Freiburg Personality Inventory, the Rosenberg Self-Esteem Scale, and the Patient Health Questionnaire, which were compared to available norm data.
Results: The mean patient age was 38.6 years. The majority of the patients were highly educated, childless, and single. Significant improvements were found in the Questions on Life Satisfaction, Modules (German version), especially for the items "partnership," "ability to relax," "energy," "freedom from anxiety," "hair," "breast," and "penis/vagina" ($p < 0.01$). Furthermore, the patients appeared more emotionally stable ($p = 0.03$), showed higher self-esteem ($p = 0.01$), and showed much lower depression/anxiety ($p < 0.01$).
Conclusions: The positive study findings were confirmed with the results from prior retrospective studies. However, medical literature focuses largely on surgical and functional satisfaction and not overall quality of life. In addition, standardized questionnaires are used rarely and solely retrospectively, with the risk of recall bias. The increased quality of life of transgender women postoperatively endorses sex reassignment surgery as a valuable option for these patients. (*Plast. Reconstr. Surg.* 140: 286, 2017.)
CLINICAL QUESTON/LEVEL OF EVIDENCE: Therapeutic, IV.

Any literature search will show that quality of life is a crucial part of modern day medicine. It is a well-established instrument and goal criterion to evaluate success rates of operations from a patient's point of view, especially after elective procedures. Opposite to the primary beliefs

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Received for publication November 1, 2016; accepted December 28, 2016.
The first two authors contributed equally to the article as a first author.
Presented in part at the 26th Annual Meeting of the European Association of Plastic Surgeons, in Edinburgh, United Kingdom, May 28 through May 30, 2015.

The work described in this article was approved by the authors' university's ethics committee (approval number 252/14 TUM).

DOI: 10.1097/PRS.0000000000003529

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. No external funding was received for the work presented in this article.*

A Video Discussion by Alexes Hazen, M.D., accompanies this article. Go to PRSJournal.com and click on "Video Discussions" in the "Digital Media" tab to watch.

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in the 1970s when examiners would evaluate a person's well-being by objective measurements, it is in fact only the patients who can truly judge the results after plastic surgery and thus assess their quality of life.[1] Health is naturally an integral component of this multidimensional concept. The World Health Organization defines health not only as an "absence of disease" but as a "state of complete … well-being."[2] Other aspects of quality of life include social, psychological, emotional, and spiritual components to assess a patient's state of happiness.[3,4] The desire to improve one's well-being is often the major indication for interventions in plastic surgery rather than the patient's interest for perfect physical appearance. Of course, quality of life can also be assessed preoperatively as baseline data to measure the effects of plastic surgery after a procedure.

The authors' previous studies and countless other international reports show that interventions in plastic surgery yield many improvements in different aspects of life. These studies also reveal lower levels of psychological distress in patients after surgery compared with preoperative or general norm data.[5,6]

The desire for a higher quality of life is naturally one of the many aspects of why people with gender dysphoria undergo sex reassignment surgery. According to the latest *Diagnostic and Statistical Manual of Mental Disorders: DSM-5* catalogue, gender dysphoria is defined as the distress that someone experiences who suffers from an extreme urge to belong to the opposite sex and would prefer to be addressed as such by others.[7] Occurrence figures do exist reporting a prevalence of one in 2900 to one in 100,000 for male-to-female transgender individuals in several Western countries, as a recent study showed.[8] However, we must consider the estimated number of unreported cases to be high because patients with gender dysphoria face the perils of financial, social, and occupational disadvantages along with discrimination if they decide to come out as transgender.[9]

Medical professionals have different possibilities to help these patients over their course of life, such as psychotherapy, hormone replacement therapy, and sex reassignment surgery, a term that includes a number of diverse procedures and techniques. No strict guidelines on how to combine these treatments exist yet and they can vary internationally. However, there is a broad agreement that patients who decide to undergo sex reassignment surgery need to have had successful psychotherapy and hormone replacement therapy in their past.[10,11] This article concentrates on the effects of sex reassignment surgery being the most invasive and for many patients the last hope for an increase in quality of life. The aim of this prospective study was to find out whether there are any measurable significant changes in various attributes of quality of life after male-to-female sex reassignment surgery using our combined two-stage surgical vaginoplasty technique.[12]

PATIENTS AND METHODS

With a set of questionnaires, we designed a prospective observational cohort study at our division of plastic surgery. We personally contacted all male-to-female transgender individuals to join our study who were about to undergo their first stage of sex reassignment surgery involving orchiectomy, penectomy, and vaginoplasty. Patients who had previously operated genitals or did not agree to enter the study were excluded. Between October of 2012 and January of 2014, 49 patients met our inclusion criteria and 47 consented to participate in our study before sex reassignment surgery.

The study participants received the first set of questionnaires in person at admission to the hospital, 1 day before their first stage of sex reassignment surgery (time 0). Next, the second stage of sex reassignment surgery was performed approximately 6 months later to address any cosmetic concerns, such as scar revisions or the removal of dog-ears. The second set was sent out by mail 6 months after the second stage (time 1) (Fig. 1). This follow-up period ensured enough time had passed for the patients to get accustomed to their final surgical results but also guaranteed high response rates postoperatively. Patients who did not send back the second questionnaire within 4 weeks were encouraged to do so by phone. On average, the questionings were separated by 11.3 ± 3.2 months. In this article, we present the results of the 39 patients who, ultimately, filled out both sets of questionnaires (return rate, 83 percent).

Thirty-four patients (87 percent) had two or more operations during the course of this study. The most common procedure besides the main genital surgery was breast augmentation, with 18 cases (46 percent). All operations were performed by the same board-certified plastic surgeon, who has decades of experience in both male-to-female and female-to-male, genital and nongenital, sex reassignment surgery. The patients were not reimbursed financially for joining this study, and their surgical treatment was unaffected by our research. The work described in this article was approved by

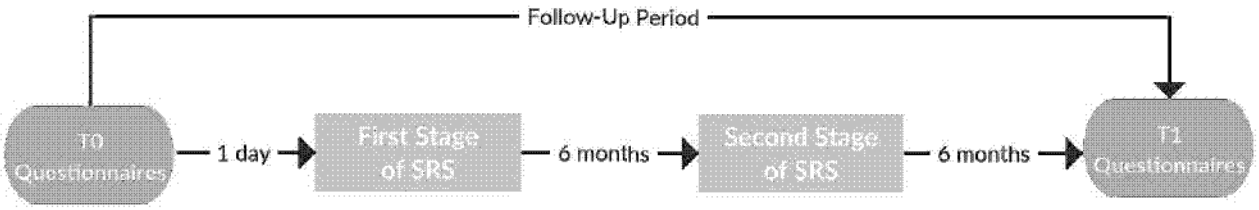

Fig. 1. Graphic illustration of patient questioning and surgery timing. *T0*, admission to the hospital, 1 day before the first stage of sex reassignment surgery; *SRS*, sex reassignment surgery; *T1*, 6 months after the second stage.

our university's ethics committee (approval number 252/14 TUM). The authors adhered to the Declaration of Helsinki at all times.

Operative Technique

First, orchiectomy, penectomy, and separation of the urethra from the penile skin and neurovascular bundle and its glans penis is performed. The spatulated urethra and a scrotal skin graft then join the penile skin flap to form the neovagina within the previously dissected cavity between the prostate and the rectum. This procedure is therefore referred to as a combined technique because we use all tissue available in our reconstructive process. It achieves favorable vaginal depth and width, leads to pleasing lubrication, and guarantees a cosmetic mons pubis by decreasing tension to the lower abdomen, in contrast to the penile invagination technique. For a detailed operative description, we refer to our separate report.[12]

Questionnaires

Both the preoperative and postoperative questionnaires included a number of self-developed indication-specific questions about the socioeconomic and demographic characteristics of our participants, and the Questions on Life Satisfaction, Modules (German version) developed by two consulting colleagues in our Department of Psychosomatic Medicine.[13] Additional questionnaires were the Freiburg Personality Inventory,[14] the Rosenberg Self-Esteem Scale,[15] and the Patient Health Questionnaire.[16] Patient data from all these standardized and validated tests can be compared to norm data collected during large surveys of a general population.

The Questions on Life Satisfaction, Modules (German version) is a standardized instrument for German-speaking countries to measure a patient's weighted quality of life subjectively. It consists of three modules: General Satisfaction, Health Satisfaction, and Satisfaction with Outer Appearance (also known as Body Image). In every module, the patient evaluates each subitem for its subjective importance and degree of satisfaction, resulting in a total score between −12 and 20 for any item. Furthermore, each module comes with a sum score representing the total of all its items. Numerous research groups use this questionnaire in the medical literature because it allows them to compare patient data to those of existing norm populations (general, $n = 2562$; health, $n = 2226$).[13]

Another popular instrument used in quality-of-life research is the Freiburg Personality Inventory. It consists of 12 modules yielding to a total of 138 statements that the participants are to mark as "correct" or "incorrect." In our study, we chose only the module Emotionality with its 14 items to get a closer look at our patients' emotional situation, stress management abilities, anxiety, and character. German norm data ($n = 2035$) are available in the medical literature,[14] and study results can be interpreted as very emotionally stable (score of 0 to 4), stable without behavioral issues (5 to 7), and problematically unstable (8 to 14).

The Rosenberg Self-Esteem Scale is a short, standardized questionnaire used internationally to analyze the self-esteem of study participants. Its most common version applied in research consists of 10 items and awards 1 ("strongly disagree") to 4 ("strongly agree") points, each leading to a total score between 10 and 40. The authors do not provide assistance for interpretation, yet one can derive some information from a study that collected norm data for 53 different countries (Germany, $n = 782$; total, $n = 16{,}998$).[17] Values higher than 30 are usually regarded as indicating high self-esteem.

Depressive symptoms were assessed using the German version of the four-item Patient Health Questionnaire-4, which is a construct of the Generalized Anxiety Disorder scale and the Patient Health Questionnaire-2. The Patient Health Questionnaire-4 is a self-report measure that provides both a diagnosis of a major depressive syndrome and a continuous severity score, and is based on the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Diseases, Fourth*

Edition, criteria for depressive episodes.[18] Participants rate each item based on how often they have experienced depressive feelings or thoughts in the past 2 weeks. The scale ranges from 0 ("not at all") to 3 ("nearly every day"). Total scores of 0 to 2 are considered unremarkable, whereas scores of 3 to 5, 6 to 8, and 9 to 12 indicate a mild, moderate, and severe depression, respectively.[16] This short and simple test allows us to compare our patient data before and after sex reassignment surgery and to the German population, as norm data are available ($n = 5003$).[19]

Statistical Analysis

For the statistical analysis of the data, we used IBM SPSS Version 21 (IBM Corp., Armonk, N.Y.). For all tests, the statistical level of significance was set at 5 percent or less using the (un)paired sample t test. Histograms of our data were analyzed visually to ensure normal distribution.

RESULTS

Self-Developed Questionnaire

The mean age of our patients at the time of the first stage of surgery was 38.6 ± 12.8 years (range, 19 to 66 years). We noticed two peaks in the graphic analysis of the age distribution: midtwenties and late forties (Fig. 2). According to our preoperative questionnaire, the average time our patients lived with a female identity before the first operation was 3.0 ± 1.5 years. The majority of our patients were single by civil law (62 percent), lived alone or with a partner (69 percent), and did not have children (64 percent). The majority (59 percent) had an education of either a high school or a university degree.

All of the study participants had sessions of psychotherapy preoperatively, as it is mandatory according to German law and is required by German health insurance providers for receipt of financial coverage for services rendered.[20] The average period of psychotherapy was 28.7 months, and 76 percent of the patients agreed that those sessions were "helpful." However, only 24 percent attended therapy after their second operation.

Questions on Life Satisfaction Questionnaire

In the module General Satisfaction, our patients had significantly higher scores for the items "hobbies" ($p = 0.03$), "health" ($p = 0.01$), and "partner relationship" ($p < 0.01$), and a significantly higher sum score ($p < 0.01$) after sex reassignment surgery. Regarding the provided norm data, four of the time-0 scores were significantly lower and two time-1 scores were significantly higher. Point values for "income" and "family life" remained below the German population even after surgery (Table 1).

Considering the results of the second module, Health Satisfaction, we discovered significant postoperative improvements for the items "ability to relax" ($p < 0.01$), "energy" ($p < 0.01$), "mobility" ($p = 0.04$), and "freedom from anxiety" ($p < 0.01$), in addition to a higher sum score ($p < 0.01$). Four

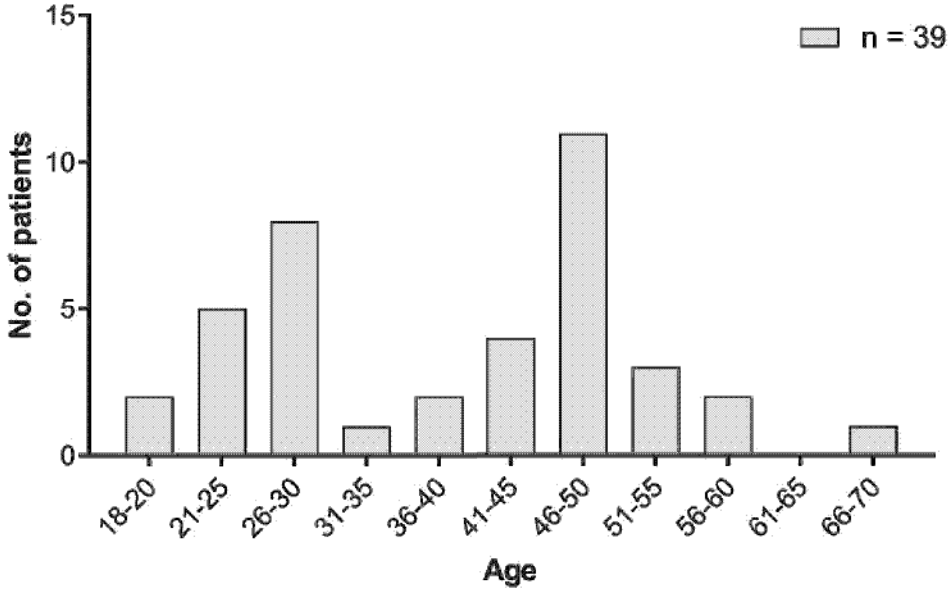

Fig. 2. Age distribution of the study group at the time of the first stage of sex reassignment surgery.

Table 1. Weighted Results for the Questions on Life Satisfaction, Modules: General Satisfaction*

	Study Group T0			Study Group T1		Norm Data 1994†			p (t Test)		
	No.	Mean	SD	Mean	SD	No.	Mean	SD	T0 vs. T1	T0 vs. Norm	T1 vs. Norm
Friends	39	9.26	6.94	10.41	6.11	2536	8.08	6.33	0.26	0.25	0.02‡
Hobbies	39	4.54	6.26	7.18	6.64	2531	6.31	6.36	0.03†	0.08	0.40
Health	39	8.23	7.86	11.41	7.14	2541	8.06	7.51	0.01†	0.89	0.01‡
Income	39	2.97	7.08	3.44	6.87	2537	6.49	7.27	0.66	<0.01‡	0.01‡
Work	39	4.26	7.12	5.46	7.56	2462	5.45	7.3	0.41	0.31	0.99
Living conditions	39	7.87	6.20	8.41	7.68	2533	8.33	6.4	0.68	0.66	0.94
Family life	39	5.18	8.00	7.15	9.30	2519	9.84	6.94	0.20	<0.01‡	0.02‡
Partner relationship	39	−2.26	6.29	6.18	10.31	2509	7.90	7.69	<0.01†	<0.01‡	0.17
Sum score	39	40.05	26.70	59.64	30.09	2534	60.49	37.13	<0.01†	<0.01‡	0.89

T0, time 0; T1, time 1.
*Data from Henrich G, Herschbach P. Questions on Life Satisfaction (FLZM): A short questionnaire for assessing subjective quality of life. *Eur J Psychol Assess.* 2000;16:150–159.
†Statistically significant difference with $p < 0.05$ (paired t test).
‡Statistically significant difference with $p < 0.05$ (unpaired t test).

items were significantly worse at baseline compared with norm values. However, these time-0 findings could not be reproduced during the time-1 interviews after surgery (Table 2).

Regarding the third module, Body Image, seven of 22 items and the sum score delivered significantly increased results after surgery, with the highest improvements for "hair" ($p < 0.01$), "breasts" ($p < 0.01$), and "penis/vagina" ($p < 0.01$) (Table 3).

Freiburg Personality Inventory

The results from the time-1 questionnaire demonstrated a very high emotional stability of our study patients at an average test value of 4.72. Compared with both our preoperative ($p = 0.03$) and the German norm data ($p = 0.01$), this score was significantly improved after surgery (Table 4).

Rosenberg Self-Esteem Scale

The Rosenberg Self-Esteem Scale questionnaire revealed strongly increased self-esteem after surgery ($p = 0.01$), with an average score of 35.03 being significantly higher than even the one of a general German population ($p < 0.01$). The baseline score was not statistically different from norm values, with a mean score of 32.54 being a strong indicator for high self-esteem (Table 5).

Patient Health Questionnaire

Before surgery, the results of the Patient Health Questionnaire-4 in our study group illustrated an elevated value of 3.95, which was significantly higher compared with norm data ($p < 0.01$) and suggested a mild depression and anxiety disorder. However, the following time-1 value of 1.79 was significantly lower ($p < 0.01$) and not statistically different from the same norm population (Table 6).

DISCUSSION

In our constant efforts to improve health care, a patient's quality of life is increasing in

Table 2. Weighted Results for the Questions on Life Satisfaction, Modules: Health Satisfaction*

	Study Group T0			Study Group T1		Norm Data 1995†			p (t Test)		
	No.	Mean	SD	Mean	SD	No.	Mean	SD	T0 vs. T1	T0 vs. Norm	T1 vs. Norm
Fitness	39	5.36	7.25	6.72	6.30	2220	8.09	7.01	0.18	0.02‡	0.23
Ability to relax	39	4.90	9.06	9.31	6.82	2214	7.40	6.50	<0.01†	0.02‡	0.07
Energy	39	5.51	7.28	10.46	6.59	2215	9.14	6.53	<0.01†	<0.00‡	0.21
Mobility	39	11.18	6.90	13.49	6.39	2210	9.07	6.96	0.04†	0.06	<0.01‡
Vision/hearing	39	10.05	7.09	10.72	7.40	2217	11.03	7.03	0.48	0.39	0.79
Freedom from anxiety	39	3.59	8.13	7.69	7.33	2204	8.10	6.71	<0.01†	<0.00‡	0.71
Freedom from pain	39	8.31	7.15	9.85	8.06	2217	9.10	7.39	0.25	0.51	0.53
Independence from help	39	12.85	7.44	12.23	7.95	2215	12.45	6.72	0.65	0.71	0.84
Sum score	39	61.74	40.33	80.46	37.62	2218	74.39	41.54	<0.01†	0.06	0.37

T0, time 0; T1, time 1.
*Data from Henrich G, Herschbach P. Questions on Life Satisfaction (FLZM): A short questionnaire for assessing subjective quality of life. *Eur J Psychol Assess.* 2000;16:150–159.
†Statistically significant difference with $p < 0.05$ (paired t test).
‡Statistically significant difference with $p < 0.05$ (unpaired t test).

Table 3. Weighted Results for the Questions on Life Satisfaction, Module: Body Image

		Study Group T0		Study Group T1		
	No.	Mean	SD	Mean	SD	*p* (*t* Test, T0 vs. T1)
Hair	39	5.59	10.1	9.21	9.50	<0.01*
Ears	39	7.31	5.83	9.26	7.06	0.06
Eyes	39	9.69	5.91	10.72	6.94	0.39
Nose	39	6.03	7.00	7.56	7.79	0.09
Mouth	39	7.28	6.97	9.28	7.18	0.05*
Teeth	39	6.38	5.46	7.38	7.28	0.32
Facial hair	39	−0.64	8.68	3.62	9.61	0.01*
Chin/neck	39	5.05	6.84	6.67	6.92	0.10
Shoulders	39	3.31	5.88	5.18	6.00	0.03*
Breasts/bosom	39	−0.49	8.53	8.92	9.01	<0.01*
Abdomen	39	0.00	6.04	3.51	7.58	0.01*
Waist	39	3.92	7.85	4.74	7.99	0.55
Hips	39	5.51	7.52	5.97	7.36	0.72
Penis/vagina	39	−10.03	3.05	14.36	6.30	<0.01*
Bottom	39	5.82	6.20	6.97	6.60	0.32
Thighs	39	4.97	5.45	6.46	6.41	0.21
Feet	39	4.41	6.22	5.44	6.60	0.29
Hands	39	5.03	7.06	6.62	6.72	0.07
Skin	39	5.87	7.42	8.49	7.29	0.06
Body hair	39	1.90	7.75	4.15	8.14	0.15
Size	39	5.74	6.75	6.33	6.69	0.60
Weight	39	3.82	7.73	4.26	8.32	0.75
Sum score	39	86.49	79.2	155.10	99.12	<0.01*

T0, time 0; T1, time 1.
*Statistically significant difference with $p < 0.05$ (paired *t* test).

Table 4. Results of the Freiburg Personality Inventory*

	No.	Mean	SD	*p* (*t* Test)
Study group				
T0	39	6.54	3.95	
T1	39	4.72	3.22	
Literature norm data†	2035	6.20	3.60	
T0 vs. T1				0.03†
T0 vs. norm				0.56
T1 vs. norm				0.01‡

T0, time 0; T1, time 1.
*Data from Fahrenberg J, Hampel R, Selg H. *Das Freiburger Persönlichkeits-inventar FPI. Revidierte Fassung FPI-R und teilweise geänderte Fassung FPI-A1*. Göttingen: Hogrefe-Verlag; 1994.
†Statistically significant difference with $p < 0.05$ (paired *t* test).
‡Statistically significant difference with $p < 0.05$ (unpaired *t* test).

Table 5. Results of the Rosenberg Self-Esteem Scale*

	No.	Mean	SD	*p* (*t* Test)
Study group				
T0	39	32.54	5.86	
T1	39	35.03	5.05	
German norm data†	782	31.73	4.71	
T0 vs. T1				0.01†
T0 vs. norm				0.30
T1 vs. norm				<0.01‡

T0, time 0; T1, time 1.
*Data from Schmitt DP, Allik J. Simultaneous administration of the Rosenberg Self-Esteem Scale in 53 nations: Exploring the universal and culture-specific features of global self-esteem. *J Pers Soc Psychol.* 2005;89:623–642.
†Statistically significant difference with $p < 0.05$ (paired *t* test).
‡Statistically significant difference with $p < 0.05$ (unpaired *t* test).

Table 6. Results of the Four-Item Patient Health Questionnaire*

	No.	Mean	SD	*p* (*t* Test)
Study group				
T0	39	3.95	2.54	
T1	39	1.79	2.00	
Norm data†	5003	1.76	2.06	
T0 vs. T1				<0.01†
T0 vs. norm				<0.01‡
T1 vs. norm				0.93

T0, time 0; T1, time 1.
*Data from Lowe B, Wahl I, Rose M, et al. A 4-item measure of depression and anxiety: Validation and standardization of the Patient Health Questionnaire-4 (PHQ-4) in the general population. *J Affect Disord.* 2010;122:86–95.
†Statistically significant difference with $p < 0.05$ (paired *t* test).
‡Statistically significant difference with $p < 0.05$ (unpaired *t* test).

importance compared with objective clinical parameters. Especially in plastic surgery, success depends greatly on the patient's subjective satisfaction.[21] In earlier studies, our research group was able to report that various plastic procedures are able to improve many aspects of quality of life after elective operations.[5,6,22–26] However, transgender male-to-female patients are primarily interested in a female appearance rather than a perfect appearing body. They must meet high diagnostic criteria to be eligible for sex reassignment surgery and usually require multiple operations to achieve their goals. In addition, they face many bureaucratic obstacles regardless of the fact

that gender dysphoria is a recognized disease in the *International Classification of Diseases, 10th Revision* (F64.0),[27] whose costs are covered by German health insurers once the diagnosis is established. Even though it is hard to draw a line where medical necessity ends and aesthetic desires begin, transgender surgery ought not to be confused with purely cosmetic procedures performed during one appointment. The basis for sex reassignment surgery is a definite psychiatric diagnosis. The questions remain the same: Does sex reassignment surgery improve the general quality of life? Are there any effects on the patient's emotional status, self-esteem, and depression? With our experience in quality-of-life research, we aimed to test our hypotheses as statistically accurately as possible, thus using standardized validated questionnaires with access to the norm data from German control populations and designing the study in a prospective setting.

The demographic data we gathered of our patients were similar to those of other retrospective studies.[28,29] The age distribution most likely relates to the fact that patients usually choose to undergo sex reassignment surgery before starting a professional career or after establishing themselves in a working field.[30]

Patient satisfaction was high overall, and several items improved significantly after sex reassignment surgery in all three Questions on Life Satisfaction (German version) modules (Tables 1 through 3). Moreover, each one of three time-1 sum scores showed significantly higher results compared with baseline data. The highest improvement in the General Satisfaction module was the item "partner relationship" ($p < 0.01$) because having satisfactory genital organs is a key factor in the majority of intimate relations. Its time-1 score ended up being even higher than German norm values. Interestingly, in the Body Image module, some items showed improvements even though no interventions on these body parts took place in our clinic, for example, "mouth" ($p = 0.05$) or "shoulders" ($p = 0.03$). Most likely, the impact of sex reassignment surgery on the overall body image satisfaction, which is represented by the increased sum score ($p < 0.01$), was so massive that it even affected other anatomical regions. In a retrospective study with both male-to-female and female-to-male patients, however, our research group showed that, 3.2 years after sex reassignment surgery, the sum scores of the General and Health modules were significantly lower than norm values. In that report, we eventually concluded that our results would require further testing, separately for transgender men and women.[31] In addition, we were able to demonstrate that, postoperatively, our patients had significantly increased emotional stability ($p = 0.03$), stronger self-esteem ($p = 0.01$), and lower depression or anxiety ($p < 0.01$) while still maintaining a high response rate.

World literature about quality of life and sex reassignment surgery has increased in recent years, as more patients tend to decide in favor of transgender surgery. Numerous studies do show positive results for patients after male-to-female sex reassignment surgery,[32] yet they rarely use standardized tools and therefore do not provide objective data comparable to norm populations. Their major focus is usually patient satisfaction with surgical and functional results. In our opinion, these studies fail to demonstrate the detailed evaluation of the operation's outcome and the patient's everyday life. Satisfaction with the operative results does not necessarily correlate with overall patient satisfaction.[31] Others examine only physical aspects after surgery,[33] design retrospective studies to gather data after many years and risk recall bias, or even include patients who underwent sex reassignment surgery performed by different surgeons.[29,34] These factors may lead to data that are more inconclusive and result in poor return rates of questionnaires. A personal communication between the examining study physician and the patient is important to achieve a high postoperative response rate as in our report (83 percent) and to avoid a loss-to–follow-up bias.

The single available prospective study about male-to-female transgender patients using standardized questionnaires included only breast augmentation procedures. It showed psychological improvements correlating to our patients who reported significantly higher satisfaction with their breasts ($p < 0.01$) (Table 3).[35]

CONCLUSIONS

Sex reassignment surgery absolutely affects the quality of life of transgender women positively. Using various standardized measuring tools, such as the Questions on Life Satisfaction, Modules (German version), the Freiburg Personality Inventory, the Rosenberg Self-Esteem Scale, and the Patient Health Questionnaire-4, we were able to meet the two vital components in assessing quality of life: multidimensionality and subjectivity.[36] This study showed overall favorable results of sex reassignment surgery in each one of the four standardized questionnaires.

After a thorough MEDLINE search of international literature, no other prospective study has been identified that assessed quality of life after transgender surgery. There is also a paucity of data resulting from standardized validated questionnaires in retrospective reviews. In addition, more research will be necessary to compare our findings to those of different surgical techniques. A study designed with a control group of transgender patients who decided not to undergo sex reassignment surgery is definitely desirable too, because sex reassignment surgery is not free of risks. Kockott and Fahrner already stated that, over time, only sex reassignment surgery leads to significant improvements for male-to-female patients. Unfortunately, their study was retrospective and did not include standardized questionnaires.[37] Long-term prospective results (>5 years postoperatively) would be a further valuable contribution to evaluate our findings.

The results of this study might even be helpful for various governmental lawmakers, health care systems, medical societies developing guidelines, and health insurance companies that are sometimes hesitant to cover the costs of these procedures by classifying them as purely "aesthetic."[38] Therefore, our research group already presented parts of these results at the 26th Annual Meeting of the European Association of Plastic Surgeons, in Edinburgh, United Kingdom.[39]

Ultimately, medicine is on the right track to support patients who suffer from gender dysphoria, although we do not fully understand its etiopathogenesis.[40] Regarding the low procedure risk and the highly improved quality of life, male-to-female sex reassignment surgery continues to be a worthy consideration for affected patients who wish to adjust their sex operatively toward their desired phenotype. Nevertheless, secondary procedures are common, and patients must be informed that these are often necessary to achieve the best possible outcome.

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ACKNOWLEDGMENTS

The authors would like to acknowledge with appreciation Aariane Abdollahi, Pharm.D., Auburn University Harrison School of Pharmacy, for advice on language and writing.

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Friedemann Pfäfflin, Astrid Junge

Sex Reassignment. Thirty Years of International Follow-up Studies After Sex Reassignment Surgery: A Comprehensive Review, 1961-1991(Translated from German into American English by Roberta B. Jacobson and Alf B. Meier)

Published by
Symposion publishing

Introduction

Quick Orientation

The volume reviews thirty years of international follow-up studies of approximately two thousand persons who have undergone sex reassignment surgery.

Usually, surgery was performed due to a condition which, in medical terms, is called transsexualism. The volume includes more than seventy individual studies and eigth previously published reviews from many countries and four continents. It describes the history of sex reassignment, the development of the various treatments applied, the procedures of documentation and evaluation, and the results.

The individual studies and reviews are annotated by the authors, and are discussed within the frame of the development of the field. Sex reassignment, properly indicated and performed, has proven to be a valuable tool in the treatment of individuals with transgenderism.

It is, however, not the only powerful change agent in sex reassignment. Real Life experience, hormone treatment, counseling, psychotherapy, legal name and sex change, and other factors play major roles in contributing toward favorable outcomes.

The quick reader finds an overview of all studies included in the chapter "Table of Overview" and a summary of all results in the chapter "Results and Discussion". This reader is encouraged, however, to start with the paragraphs on terminology in the chapter "Introduction" to become acquainted with the abbreviations "FMT" and "MFT" and the usage of the words "male" and "female" in the book.

The authors wish to express their appreciation to Symposion Publishers for their support and for offering the book as a supplementary volume of The International Journal of Transgenderism (IJT). The International Journal of Transgenderism will include full-text versions of the most important original follow-up studies and reviews discussed in the book in its section "Historic Papers" in forthcoming issues. Readers of The International Journal of Transgenderism will thus have direct access to these papers by links and will be able to review the evaluations of the authors.

Since publication of the German version of this book by Schatt
Stuttgart and New York, in 1992, a number of further follow-u
been published which confirm our conclusions.

Pl. Trial Ex. 202

Still needed are more follow-up studies of attempts to create male genitalia. Techniques are constantly improving in this field, perhaps not as rapidly as one might wish. Instead of studies from individual centers only, multi-site studies would be much preferable. The International Journal of Transgenderism will put all its endeavor into presenting progress in this field.

Intent

This contribution provides an overview of follow-ups of patients with transsexual symptoms who have undergone surgical procedures to adjust their physical appearances to images these men or women had of themselves.

There are three main reasons that prompted us to present this. The first is the major need for information about the various groups as well as our immediate clinical activities. Primarily, the patients want to know what the results of the treatments are. They want to know it for themselves and want to be able to give their family members information. However, the referring general practitioners, specialists and psychologists need -- in order to counsel adequately -- information that is as broad as possible. Finally, the medical insurances and other liable parties, as well as courts that in cases of dispute have to decide liability, need to be able to access reliable data.

The second reason is that in the maintained discussion about whether or not these procedures are justifiable, the claim that there are not sufficient post-surgical examinations is repeated almost ritually. Not seldom this claim is also made in scientific literature (e.g., Docter, 1988); this mainly has the function either to evade the efforts that it signifies to collect widely spread literature and to evaluate it, or to suggest that one's work is a new area. There is, as we will show in the following, ample international literature about follow-ups, more vast than with other illnesses and many other routinely used treatment methods. The literature is frequently not very accessible because it was published in reviews and books not available in most medical or university libraries. Not everybody who has worked on this topic has had the time to order (by way of distance lending) and review all this literature. What has been missing until now is a sufficiently vast overview of the topic. The latest overview (Green & Fleming, 1990) regards only 11 single works and three previously published (incomplete) reviews.

The third reason is that we deem it necessary to include content or methodical remarks and, in addition, state out of which contexts follow-up studies originated and what goals the respective authors were pursuing. The attitudes of the authors have been made evident independently if they refer to them directly or if they write about them in the sense of speech, "between the lines." The attitudes are evident in the selection of words and statements about the patients in which the authors and caregivers express their big ambivalence about what they are doing, mostly without really reflecting on it. Frequently this leads to characterizations of patients that they (the patients) must experience as demeaning or else make them appear in an unpleasant light. It is best to illustrate what we mean with a few examples. If a work has the title *Course of Treatments and Katamnesis of Operated Female Transsexuals* (Junge, 1987) and describes previous patients who now live as males and have legally completed a name change and legal sex change, then this title reflects less that what the previous patients actually have achieved. Most of them do not view themselves as transsexuals -- and definitely not as female transsexuals -- but as males. To us it seems just as problematic if an author who provided psychiatric care to patients for years referred them for operations and then post-examined them, declares that the desires of the patients

to be recognized legally as a member of the other sex is "...an untenable request in my view, for I do not subscribe to the opinion that a phenotypic male can have a female psyche. Those who profess to have such mental orientations are in fact anatomical males with obsessional beliefs or over-valued ideas that they are females; and therefore psychiatrically abnormal." (Randell, 1969, p. 367) "Only a minority accept it for what it really is - that is, a neutering procedure or, perhaps more correctly, a castrating process. It is difficult to persuade transsexuals who have had their genitals removed that they are, in fact, nothing more than castrated males...Following operation, there was a tendency to further self-deception over sexual status, and at least nineteen regarded themselves as having achieved the female sexual status." (Randell, 1969, p p. 375-376)

Because of the reasons mentioned, we will first give a complete as possible summary of the follow-ups published until now. Because of the vast number of publications on the topic of transsexuality, we shall limit the selection to such works in which the treatment results of at least five operated patients are documented. We do not include single case reports or katamnesis of smaller samples because we do not consider them post-surgical examinations in the proper sense. In some cases they are more informative than the descriptions of larger samples, but because they are geared toward description of the particulars of individual development, they are not suited to be used comparatively and to reach generally applicable conclusions. We realize that completeness can only be reached approximately. This is why we ask of authors whose works we missed for forbearance and ask them for leads to their works. We must also mention our limit, that we could only view English and German-language professional literature and cannot judge if follow-up studies have been published in other languages, or how many. Disregarding this limitation, we arrived at 70 follow-up studies and eight reviews from the years 1961 - 1991, far more than have ever been examined in other single works or collective reviews. Of particular note, we have compiled a series of German-language post-surgical examinations not mentioned in the almost exclusively English-language overview works, probably because the publications in which they were published are not included in American Index Data Bases.

Because as we refer to every single work or collective paper in chronological order, we give an overview in the genealogy of the study of post-surgical examinations to transsexuality. We deem it important to examine the critique that is sometimes made (Springer, 1981) that transsexuality as an illness whose treatment is an invention of a small circle of so-called sex researchers who constantly quote one another. This criticism was repeated without proof by the medical insurances or expert witnesses for the insurances in social court cases during the 1970s and 80s in Germany, by which the medical insurances have tried -- without success -- to avoid liability for the costs of treatment.

The inclusion of every individual work is not solely for the purpose of compiling the main treatment data of the described patients, but also to illuminate the peculiarities, position and opinion of the examiner. If one would, as it is usual in collected works, just present the results of post-surgical examinations as tables, we could have saved much space. We would, however, either have a false impression of objectivity or could retire, as it frequently happens, to a generalized methodology critique. Many follow-up studies are hardly comparable to each other, even though their results condensed into extracts may appear quite similar. Most authors have worked hard and should therefore be heard. The

reader is invited to fathom, by means of the ample material about follow-up studies, the development, stagnation, evolution of new questions.

Terminology

In the terminology, we diverge from other follow-up studies and reviews fundamentally in that we avoid the standard terminology "he" and "she" regarding transsexuals wherever possible. We think that the frequently used clinical abbreviations the *Transi*, the *Transe*, the *Transen* are even more unpleasant. It all reminds us too much of expressions such as "the appendix in room six," "the apoplexy," "the alcoholic," "the gall." Also the words "biological male or female" or "male-to-female" or "female-to-male transsexuals" that we used in previous publications are considered unsatisfactory by us. In the American-English language, these terms are common. German authors who are not familiar with the professional discussions but like to publish in English even use "man-to-woman" and "woman-to-man transsexuals." (Täschner & Wiesbeck, 1988a) We prefer to talk about people, persons or patients with transsexual symptoms. It is true that transsexuality is about (gender) identity, so that substantiveness is more called for than in other cases and that some patients identify themselves with these terms, but they consider them titles of honor which they do not wish to renounce. Others deny such terms from the beginning and declare that they always view themselves as male or female. On the other hand, other patients may accept them -- as long as they are not operated -- but insist after the operation they are not transsexuals. We will not be able to satisfy everybody, no matter what the wording. As important as the transsexual topic is to the individual, we are opposed to reducing anybody to *it*. After completed surgical treatment, we speak only of "females" and "males" oriented on which gender the subject considers one's self. Because most of them have completed a name change and legal sex change, this mostly corresponds to one's experience and also to the legal position as a female or male.

Naturally, this evaluation elected by us is not without problems because it makes the surgical procedure the turning point that does not represent the individual transsexual development. Under the aspect of treatment we highlight, to the contrary, the mostly relative significance of the surgical procedure for the managing as male or female. Here we do not discuss the treatment instructions, but rather treatment results. While before surgery, and as such without surgery, a legal sex change is possible in Sweden, this is not true for all other countries. The legal change of the gender is conditioned to a sex reasignment surgery. Most follow-up studies do not mention this legal step, which does not correspond immediately but is part of this treatment. The exact time at which a patient is defined as male or female is not important to us, but rather the time at which the new status is accepted and that one is not stuck with a particular diagnosis until the end of one's days that may have been important in a certain segment in life, but does not define one's whole life.

For the following representation, the problem is complicated by a population of patients where samples and partial samples have to be compared constantly with one another, in which males and females have to be described before, during and after treatment. We can hardly do without abbreviations, especially in the tables, if the overview is not to be totally lost. To solve this problem, we have elected abbreviations or codifications that we not only used in the tables but in the text and we did not write out fully on purpose. For patient population which includes operated and non-operated without distinguishing by gender, we use the code *T*. For samples in which there are males who have been operated on and those who

have not been operated on, we use the code *females (MFT)*. For samples of females who have been operated on and females who have not been operated on, we use the code *males (FMT)*. The corresponding figures for mixed population of that kind -- unless there are other corresponding indications in the original text -- are put in parentheses. For males who are still in treatment and have not been operated on, we use the code *MFT*. For females who are still in treatment and have not been operated on, we use the code *FMT*. In the rare cases in which a patient has been operated on and the code *T* should be deleted, it is kept if the patient returns to the original gender role in spite of the operation. Simplified, we can summarize that until the operation, and in case of a so-called role-return, the code *T* is valid; after the operation females or males are described by their present classification. We want to make clear that these classifications are to be understood as codes and not as descriptive categories. This sounds much more complicated than it is in reality and readers will easily find their way through the text; as *females (MFT)* in principle are compiled in the left column and *males (FMT)* in principle are compiled in the right column; with all post-surgical results, the new classifications as female or male is applied.

Terminological problems are caused by the term used in the examinations of the operation results. In letters from doctors and expert attests -- including our own, but also in literature -- you find expressions such as "plastic surgical construction of the neo-vagina," resp., "neo-phallus," "mammary reduction" or "augmentation." The *neo-vagina* is also called *vaginoid* or *artificial vagina*; the *neo-phallus*, *artificial penis*, *substitute penis* or *penoid* and if it is a clitoral augmentation, it's called *clitoris-penoid*. As a rule, this all sounds much more artificial than it looks and, more importantly, as it is experienced by the patient. This is why we use the simple terms "vagina" or "vaginoplasty," "penis" or "phalloplasty," "clitoris augmentation" and "surgical breast augmentation" or "reduction." The other medical terms such as hysterectomy, ovarectomy, mastectomy, penectomy and orchidectomy, we were not in the same way consequent because the medical terms -- especially within the small space of a tabular representation -- were allocated easier.

We use the terms "transsexualism," "transsexuality" or "transsexual" as sparingly as possible and rather talk about, as explained above, transsexual development, transsexual symptoms, etc. In some older follow-ups, the terms transvestitism and transvestites are still used. Until the mid-1960s it was not usual to talk in German literature about transsexualism. The corresponding phenomena were summarized under the term transvestitism, termed by Hirschfeld (1910), to separate and define properties of certain clinical developments summarized until the end of the last century under the term homosexuality. Hirschfeld (1923) first mentioned "psychic transsexualism" in passing, but it was not accepted. Even though transsexualism literature mentions it until today, with the exception of Seidel (1969), Eicher (1984) and recently Sigusch (1991a, b), it is not true that the originator of this term is Cauldwell (1949), but Hirschfeld (1923). With the works of Benjamin (1953; 1964 a, b, c; 1966; 1967; 1969) as well as the popularization of the clinical history of the former American soldier Christine Jorgensen (Hamburger, et al., 1953; Jorgensen, 1967), the term transsexualism was established in everyday language as well as in professional literature. At the same time there was a separation from the transvestitism or so-called compulsive cross-dressing mania. What is called temporary in transvestitism -- the playful or compulsive changing into the other sex role -- is a permanent characteristic of transsexualism. The classic description in the medical literature and the key diagnosis is that, to the contrary of physical appearances, individuals experience

themselves as belonging to the "other" gender and do everything so that their experiences take form and are acknowledged by others.

Finally a word from us for the term used in the title and continuously used throughout this text - "sex change." It is controversial when we are referring to the evaluation of the treatment whose results are broadly represented here. Persons who experience themselves as transsexuals will, as a rule, try to get hormonal, surgical and legal sex changes. Some say simply that they don't have to be changed, but only adapted physically to their own gender. In American-English, the short definition "sex reassignment surgery" (SRS) has been established by which the assignment process is best defined. At the beginning the term "Geschlechtsumwandlung" (sex change) was transposed from German to American English. Benjamin (1966), who was from Berlin and later moved to the United States of America, prepared the way for sex reassignment treatment (Pfäfflin, 1997) and defined in his publications the processes as "sex change operation, conversion operation, change of sex, conversion, transformation." All these terms are used by other authors, but the one used mostly, as said above, is "sex reassignment surgery." It should be noted that occasionally the terms "gender transmutation" (Kubie & Mackie, 1968; comp. Lothstein, 1980) and "gender reassignment" (Mate-Kole, et al., 1990) are used -- even though in the professional discussion about transsexualism it is always specifically mentioned that in American-English (to the contrary of German, which only has just one word for "gender") there is a distinct difference between sex and gender (Stoller, 1968, 1975) -- and that surgical sex change is the equalization of the corporal sexual characteristics (sex) to the sexual identity (gender).

Many authors have raised objections to the use of the term *sex change*. Randell (1969) already mentioned concerns about it. Eicher, who presented the first German-language monography about transsexualism, considers this term as "incorrect, because *only* an equalization to the psychological gender is realized. The possibility of a gender-specific reproduction can never be achieved " (Eicher, 1984, p. 1; italics F.P. and A.J.). More important, it seems to us, are the objections raised by Hertoft and Sörensen (1979), who stress that the term suggests that a sex change is possible, in reality being impossible. Further, that it contains a seductive promise that cannot be fulfilled. They regard surgical procedures as a desperate attempt to solve a deep conflict in which the solution is frequently poor or is no solution at all. According to their opinion, one should not suppose that through such a surgical procedure a human being can be changed. The number of those for whom an operation has been recommended as an emergency measure and who have profited by it is small and all others know deep in their psyche that they have not changed their gender.

This critique for the use of the term *sex change* in connection to sex reassignment surgery stems from the concern about the patient, to take the patient seriously. The term *change* raises hopes, possibly nourishes illusions and reminds one of the magic word "mutabor" in the tale 1001 Arabian Nights. We have chosen it despite all of this and justify our decision by the same argument - out of concern for the patient. If psychology, medicine and the law agree to the desires of patients, regardless of their reservations, and support the patients to live in accordance to their self-image as a member of the opposite sex, then they contribute -- however limited -- to a changing process that results in a human being who was born as a boy or a girl to live as an adult as a female or a male. As a rule, this is a difficult process full of conflicts that burden the patient enough. It is our task to make this destiny as bearable as possible. The surgical operations

are -- if done appropriately -- just a few of many steps in a changing process requiring and containing many interior or exterior changes. The patients will adapt to the results of the treatment better the more their intents to face this conflict find support. Under retrospective biographical aspects, it may be true that a human does not fundamentally change - regardless of any operations. Even though a new human being has not been created, there has been change, along with many new experiences. To treat patients first psychiatrically, hormonally and then surgically and then to inform them, as Randell did, that they are only castrated males and females, is considered by us inappropriate and hardly conducive. Due to psychological reasons and because a legal sex change is a real change, we consider it legitimate and proper to talk about gender change and/ or sex change.

Advancing Methods for U.S. Transgender Health Research

Article *in* Current Opinion in Endocrinology, Diabetes, and Obesity · February 2016
DOI: 10.1097/MED.0000000000000229

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Advancing methods for US transgender health research

Sari L. Reisner[a,b,c], *Madeline B. Deutsch*[d], *Shalender Bhasin*[e], *Walter Bockting*[f], *George R. Brown*[g], *Jamie Feldman*[h], *Rob Garofalo*[i], *Baudewijntje Kreukels*[j], *Asa Radix*[k], *Joshua D. Safer*[l], *Vin Tangpricha*[m,n], *Guy T'Sjoen*[o], *and Michael Goodman*[p]

Purpose of review
This article describes methodological challenges, gaps, and opportunities in US transgender health research.

Recent findings
Lack of large prospective observational studies and intervention trials, limited data on risks and benefits of sex affirmation (e.g., hormones and surgical interventions), and inconsistent use of definitions across studies hinder evidence-based care for transgender people. Systematic high-quality observational and intervention-testing studies may be carried out using several approaches, including general population-based, health systems-based, clinic-based, venue-based, and hybrid designs. Each of these approaches has its strength and limitations; however, harmonization of research efforts is needed. Ongoing development of evidence-based clinical recommendations will benefit from a series of observational and intervention studies aimed at identification, recruitment, and follow-up of transgender people of different ages, from different racial, ethnic, and socioeconomic backgrounds and with diverse gender identities.

Summary
Transgender health research faces challenges that include standardization of lexicon, agreed upon population definitions, study design, sampling, measurement, outcome ascertainment, and sample size. Application of existing and new methods is needed to fill existing gaps, increase the scientific rigor and reach of transgender health research, and inform evidence-based prevention and care for this underserved population.

Keywords
health disparity, research methods, transgender

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Curr Opin Endocrinol Diabetes Obes 2015, 22:000–000

DOI:10.1097/MED.0000000000000229

KEY POINTS

- Challenges in transgender health research include standardization of lexicon, agreed-upon population definitions, study design, sampling, measurement, outcome ascertainment, and sample size.
- Ongoing development and refinement of clinical recommendations will benefit from a series of evidence-based observational and intervention studies aimed at identifying, recruiting, and following diverse cohorts of transgender people.
- Applying existing and new methodologies will increase the scientific rigor and reach of transgender health research, and inform evidence-based prevention and care for this underserved patient population.

INTRODUCTION

Expansion of the evidence base to inform transgender clinical care requires rich systematically collected data that at present are scarce or lacking in the USA [1]. The available data pertaining to transgender health are often based on convenience samples and the majority of published studies in the USA are cross-sectional [2,3,4▪,5–7] or retrospective [8,9,10▪]. The few published prospective follow-up studies are small and have examined a limited number of outcomes [11,12]. Most US studies evaluating transgender health focus on substance use and abuse, sexual health, and mental health issues (Fig. 1). Relatively little emphasis has been placed on other relevant issues such as healthcare access and utilization patterns over time, determinants of hormonal and surgical treatment complications, and rates of chronic age-related conditions thought to be affected by hormone exposures [13,14▪].

An important methodological issue specific to transgender health research is identification, measurement, and operationalization of 'transgender' [15]. Additional challenges facing transgender health research include heterogeneity of settings, limited numbers of trained physicians and researchers with a specific focus in transgender medicine, lack of uniform data collection, and potential problems of nonparticipation, retention, and dropout.

Important unanswered questions in transgender health research may be placed into two broad categories: those that deal with estimating population parameters and those concerned with evaluating causal effects of exposures on health outcomes [16]. Both categories of research are needed in transgender health. An essential methodological requirement of studies aimed at answering questions in the first category is a representative sample of the population of interest. By contrast, for the second category, representativeness is of a lesser concern [17]; the main issue is whether a particular sample allows testing a causal hypothesis through comparability of exposed and nonexposed groups [18]. Studies that most often meet this criterion are randomized placebo-controlled clinical trials; however, in transgender clinical research individual randomized controlled trials may not always be feasible or ethically acceptable [19,20]. For example, randomizing transgender people to receive or not receive hormone therapy would violate the principle of equipoise, given guidelines recommending hormonal treatment to alleviate gender dysphoria [21,22]. In those circumstances, observational comparative effectiveness research is needed. Other research questions do lend themselves to

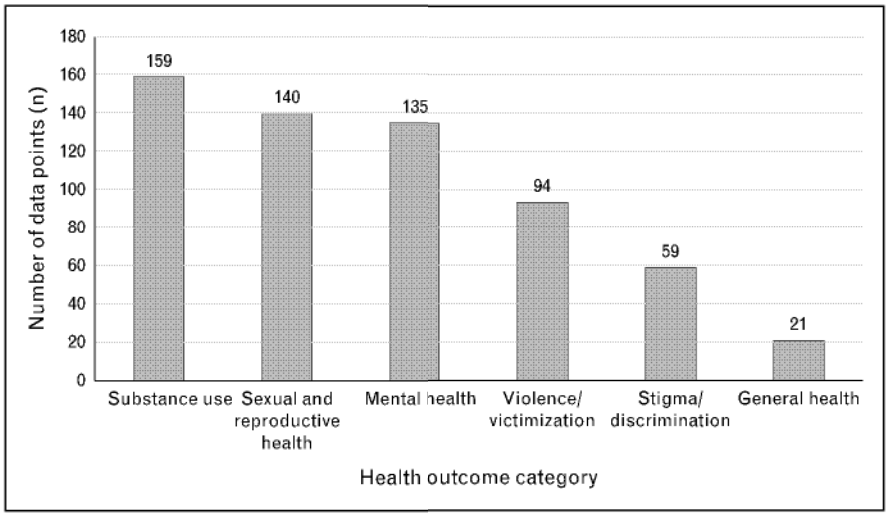

FIGURE 1. Distribution of health outcomes in US Transgender Research, 2008–2014.

randomized controlled trials; for example, comparing different hormone regimens, or giving some transgender women aspirin and some placebo to see if rates of deep vein thrombosis or coronary artery disease differ.

The acquisition of high-quality study samples to examine transgender health may be carried out via four main systematic approaches: general population based, health systems based, clinic based, and venue based. Although in some circumstances other approaches such as respondent-driven sampling or Internet-based recruitment may offer useful alternatives, those are considered a form of convenience sampling [23] and remain beyond the scope of this review.

In the next sections of this communication, we describe each of the four main sampling approaches, discuss their advantages and disadvantages, and provide illustrative examples of completed or ongoing studies. We then address additional methodological challenges facing transgender health research and propose paths forward toward the goal of identifying and filling current methods' gaps through various observational and interventional studies.

GENERAL POPULATION-BASED APPROACH

A population-based study is feasible if the members of a given population can be enumerated to enable drawing of random samples or even inclusion of the entire population of interest [24]. Common sources of data for population-based studies include the Department of Motor Vehicles records, voter registration lists, and various commercial population directories [25]. For population-based transgender health research, these data sources would only be useable if they systematically collected information on gender beyond binary natal 'sex' categories [26,27]. A number of recent publications urge expansion of existing data capture to identify transgender individuals in a systematic fashion, including use of the two-step method [28▪,29,30]; however, to date these efforts have not translated into standard practice in population-level research.

TransPOP is an example of an ongoing federally funded population-based study [31]. Conducted at the Williams Institute in collaboration with Gallup, Inc., the study's primary goal is to collect a national probability-based sample to examine sociodemographic characteristics and health status of the US transgender population.

A well designed and executed population-based study maximizes external validity and offers accurate estimation of frequency and distribution of various health-related measures, such as incidence of disease or prevalence of risks [32]. On the other hand, this approach may be inefficient, if the goal is to assemble a cohort of sufficient power to examine relatively rare events, or to assess clinically relevant exposure–outcome associations.

HEALTH SYSTEMS-BASED APPROACH

Electronic medical records offer a number of research opportunities, especially in integrated healthcare systems. The most notable examples of integrated systems are the Veterans Health Administration (VHA) and health maintenance organizations (HMOs).

Several studies examined transgender health within the VHA using International Classification of Diseases Ninth edition (ICD-9) codes. Kauth and colleagues examined all VHA encounters 2006–2013 for the following three ICD-9 codes: 302.85 (gender identity disorder in adolescent or adult), 302.6 (gender identity disorder not otherwise specified), and 302.5 (transsexualism) [33]. Additional VHA-based studies examined incidence of breast cancer [10▪] and lifetime prevalence of various health conditions [9,33] among veterans with and without transgender-related diagnoses.

Another possible source of integrated health systems data are HMOs, which often collaborate via the Healthcare Systems Research Network [34]. HMO data make it possible to construct historical and prospective multicenter cohorts, and track the enrollment and healthcare utilization histories over extended periods of time [35].

The research infrastructure available through HMOs is used in the ongoing federally funded study 'Comparative risk and benefits of gender confirmation therapies' [35]. The study is designed as a mixed historic/prospective cohort of transgender people enrolled in Kaiser Permanente plans at three sites (Atlanta Georgia, Northern California, and the Greater Los Angeles area) (Fig. 2). Cohort candidates are identified based on relevant ICD-9 codes or presence of free-text keywords in the medical notes [36].

The advantages of a health systems-based approach include its relative efficiency in identifying eligible study participants, availability of cisgender (nontransgender) controls who can be matched to transgender participants, and ability to involve multiple sites. On the other hand, this approach may miss key hard-to-reach (e.g., uninsured or not engaged in healthcare) transgender population subgroups. Additionally, if data collection procedures are limited to electronic medical records, the resulting information may lack detail.

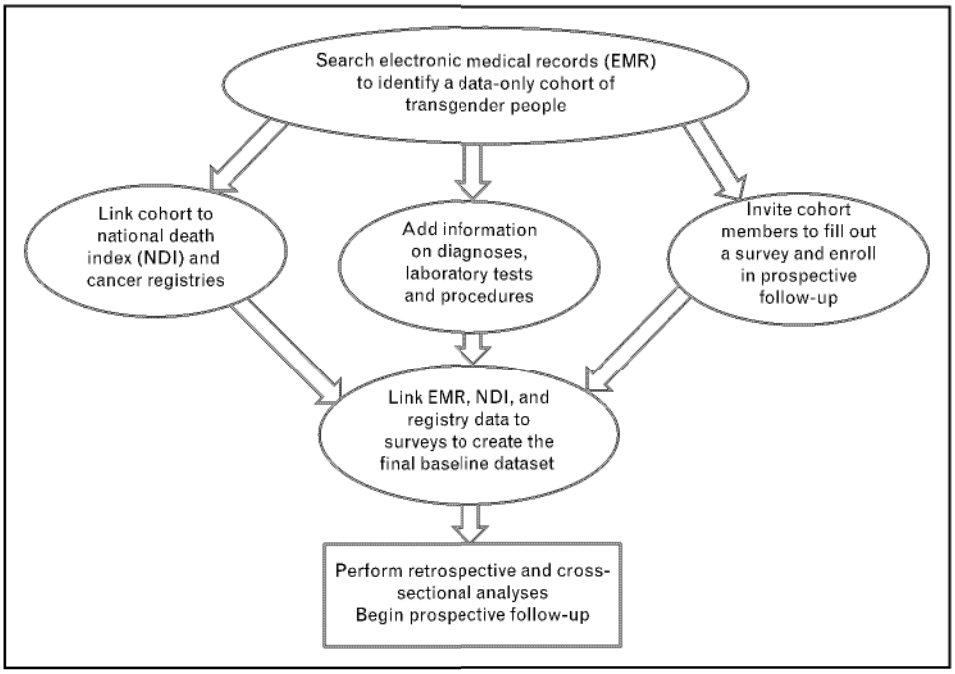

FIGURE 2. A flow diagram depicting data collection and design of a mixed retrospective/prospective health systems-based study.

CLINIC-BASED APPROACH

A clinic-based approach uses institutions that provide care to the patient population of interest. An example of successful implementation of this approach is the European Network for the Investigation of Gender Incongruence (ENIGI). ENIGI is a collaboration of several Western European gender identity clinics [37,38▪,39,40]. The project recruits and prospectively follows people that apply at these gender identity clinic of ages 17 years or older from clinical entry (before initiation of hormonal therapy or surgical gender affirmation) onward. Data collection procedures include periodic administration of survey instruments, systematic abstraction of medical records, and acquisition and storage of biospecimens [39].

Clinic-based studies of US transgender patients will also benefit from the experience of other US clinic-based multicenter projects such as the Centers for AIDS Research [41]. One approach would be to establish a multisite cohort study of transgender patients by joining federally qualified health centers (FQHCs), also known as community health centers [42]. For example, Fenway Health in Boston, Massachusetts is a FQHC that served more than 1700 unique transgender patients in 2014 [43]. Other FQHCs with large transgender patient populations are located in most major cities, including Callen-Lorde Community Health Center in New York and similar centers in Philadelphia, Washington, Chicago, Los Angeles, and San Francisco.

A clinic-based approach offers excellent opportunities for in-depth data collection, biospecimen acquisition, and both patient and provider-reported information. Many clinics, particularly community health centers, also serve underserved transgender subgroups such as uninsured or underinsured individuals, racial/ethnic minorities, patients with nonbinary gender identities, and HIV-infected patients. Putting together a large clinic-based cohort requires multiple study sites, and per participant cost and effort is relatively high; however, scientific knowledge to be gained is high.

VENUE-BASED APPROACH

Developed in the mid-1990s, venue-based sampling combines outreach activities with standard methods of sampling to study hard-to-reach groups [44]. Following success of this approach in several cities [45], venue-based sampling was adapted for the National HIV Behavioral Surveillance studies of MSM [46].

Venue-based methods are currently applied in the ongoing federally funded multisite study 'Identity Development, Risk, and Resilience among Gender Diverse Populations.' The study uses purposive, venue-based sampling to recruit transgender

Table 1. Data need and research priorities

Data need in transgender health research:
Implementation of uniform collection of gender identity data, using the two-step method (Table 2). Uniform collection of sexual orientation and sexual behavior data will also allow improved resolution when defining cohorts
Reliable and valid measures to examine health disparities by transgender status, and reliably assess exposures (e.g., gender affirmation and treatment) and health outcomes for transgender people
Standardization of terminology to allow direct comparisons between studies
Involvement of community and care provider stakeholders in every stage of research design, implementation and evaluation to provide appropriate context and insure that research methods are relevant, adaptable, and culturally appropriate
Large sample size to enable well powered statistical analyses (statistical conclusion validity)
Longitudinal prospective data to allow follow-up over time (opportunity for nested and ancillary studies)
Representation of hard-to-reach subgroups and diverse transgender people in terms of age, race/ethnicity, socioeconomic status, gender identities (examine health disparities and identify mediators for future interventional studies)
Methodological needs in transgender health research:
Measures and data collection – identifying transgender people, standardized data collection in clinical settings (implement the two-step method), skip patterns for trans-specific data (anatomy inventory)
Prospective longitudinal cohort – design engine (supports nested and ancillary studies)
Interventional studies – Sequential, Multiple Assignment, Randomized Trials designs, cluster randomized clinical trials, implementation science (alternative models to individual-level randomized trials)
Treatment outcomes – gender affirmation, hormones, surgical interventions, and health
Fit methodology to study population – acceptability and ethnics of research with transgender people (observational vs experimental designs)

people in three US cities (New York, San Francisco, and Atlanta). Venues include commercial establishments (e.g., bars, coffee shops, and beauty salons) and outdoor spaces (e.g., streets and parks); groups (e.g., community organizations and groups organized around culture, sports, and seniors); and events (e.g., Lesbian, Gay, Bisexual, Transgender Pride). Sampling is stratified by age and gender identity, while maximizing ethnic and racial diversity. The goal of the study is to test an adaptation of the minority stress model to investigate vulnerability, risk, and resilience in the context of transgender identity development across the lifespan [47].

Access to hard-to-reach participants identified via venue-based recruitment can improve generalizability and allow correcting selection biases [48]. This approach enables a single study team to cover an entire city or geographic area. Limitations include difficulty of maintaining high response and retention rates, and problems with recruiting large numbers of participants.

OTHER METHODOLOGICAL ISSUES IN TRANSGENDER HEALTH RESEARCH

In addition to selecting an appropriate sampling strategy, additional methodological issues that need to be considered in transgender health studies include defining the target population, using optimal study design for the research question, routinely collecting gender identity data, identifying and recruiting transgender people for participation in research, developing accurate measures and efficient data collection protocols, and using consistent terminology. A summary of these issues is presented in Table 1.

Routine collection of gender identity data is critical for transgender health clinical practice and research. The two-step method is recommended [15,49▪], including by the World Professional Association for Transgender Health [50]. The two-step method asks questions about current gender identity and assigned sex at birth (Table 2) [50]. Cross-tabulating these items allows for different sex and gender combinations to identify transgender patients. Such an approach has been found to identify twice as many transgender people as a single-question method [51].

Enrollment of a large multisite cohort of US transgender patients has not yet been executed. Such a cohort could act as a vehicle and infrastructure for multiple analyses and ancillary studies. A series of protocols for identification, recruitment, and follow-up of diverse transgender people in age, racial, ethnic, and socioeconomic backgrounds, and with diverse gender identities could be developed. It is conceivable that such a multisite research project could enroll a cohort study with as many as 10 000–25 000 participants (Fig. 3). Sample size considerations for such a multisite cohort study are summarized in Table 3 [52–54].

Table 2. Routine data collection using the two-step method

About the Two-Step Method

Standardization of data collection is critical for transgender health clinical practice and research. The two-step method is recommended, including by the World Professional Association for Transgender Health (WPATH). The two-step method asks questions about both assigned sex at birth and current gender identity. Cross-tabulating these questions allows for different sex and gender combinations to assess transgender health.

Recommended Two-Step Method [50]

Question 1: How do you describe your gender identity? (check one)
- ❑ Male
- ❑ Female
- ❑ Transmale/ Trans Man/ Female-to-male (FTM)
- ❑ Transfemale/ Trans Woman/ Male-to-female (MTF)
- ❑ Genderqueer/ Gender Nonconforming
- ❑ Different Identity: Please State: _____

Question 2: What sex were you assigned at birth, on your original birth certificate?
- ❑ Male
- ❑ Female

Cross-tabulating these questions gives a two by six (2x6) contingency table with 12 cells demonstrating different sex and gender combinations.

	Assigned sex at birth	
Current gender identity	Male	Female
Male	Cisgender	Transgender*
Female	Transgender*	Cisgender
Transmale/ Trans Man/ Female-to-male (FTM)	--	Transgender*
Transfemale/ Trans Woman/ Male-to-female (MTF)	Transgender*	--
Genderqueer/ Gender Nonconforming	Transgender*	Transgender*
Different Identity: Please State: _____	Transgender*	Transgender*

Cisgender = Nontransgender.

Cisgender = nontransgender. *Adding these cells results in overall prevalence of transgender.

In addition to supporting within-cohort analyses, the study could also identify comparable reference groups of cisgender males and females to conduct comparative studies, including nested case-cohort designs.

In a longitudinal cohort study of transgender patients, additional data can be obtained through a variety of methods during follow-up. Linkages with external data sources such as the National Death Index, cancer registries, and Medicare and Medicaid may offer an efficient way of assessing morbidity and mortality. In addition, new diagnoses and changes in medications, procedures, and test results can be obtained from periodic reviews of medical records, using electronic data searches and abstraction methods [35,55]. A number of important outcomes, such as quality of life and satisfaction with care, can only be obtained by self-report (in-person, or via mailed or online surveys) as commonly done in other areas of comparative effectiveness research [56–58]. Rich data can also be obtained through collection of biological specimens, a *sine qua non* for contemporary cohort studies [59–61]. Availability of a biorepository in a multisite cohort study would offer a variety of opportunities for case-cohort and nested case-control studies.

A priority in transgender health research is evaluation of risk and benefits of gender affirmation therapies, such as hormones and surgical interventions. Although randomized clinical trials of gender affirmation are not always possible or ethical, multiple areas of equipoise remain. For example, one could design and implement clinical trials comparing different delivery modes and schedules for hormonal therapy. Another area that lends itself to interventional studies is patient management. Practice-level randomized studies could test various patient navigation methods or physician-decision algorithms aimed at standardizing and optimizing gender affirmation including referrals, hormonal treatment, and postsurgery management and follow-up.

In the absence of randomized studies, some of the questions in transgender health can be answered

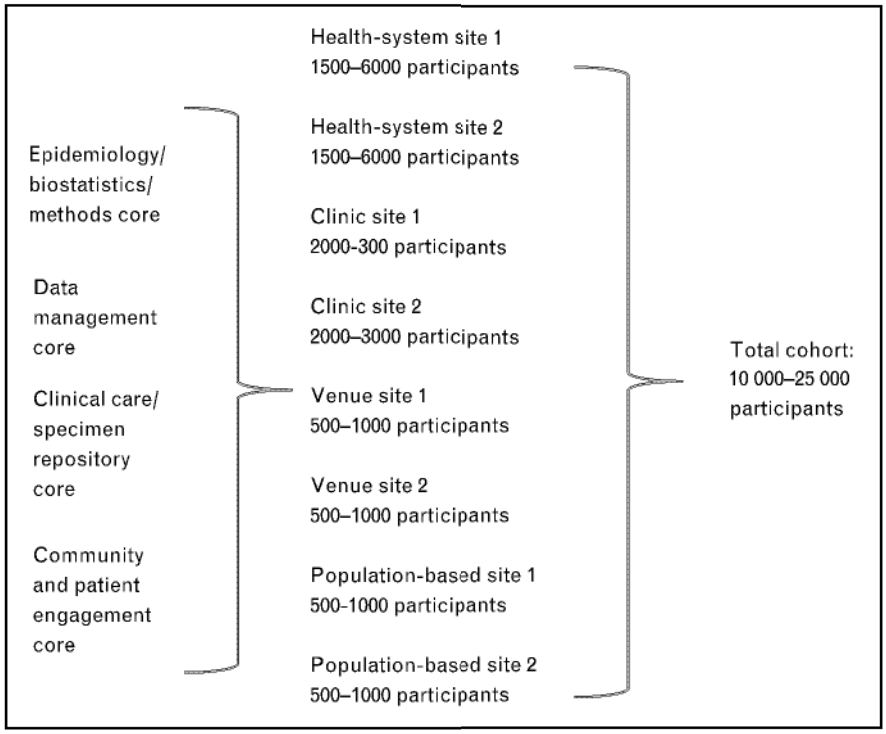

FIGURE 3. A concept of a multisite US national transgender cohort study.

Table 3. Anticipated sample sizes required for risk ratios of various magnitude assuming binary outcomes, statistical power of 80%, and a range of outcome occurrence estimates among the nonexposed (P_0)[a]

Two-sided α-error = 0.05, exposed-to-unexposed ratio = 1 : 10			
P_0[**]	**RR = 1.5**	**RR = 1.75**	**RR = 2.0**
0.005	7290	3688	1874
0.01	3541	1639	933
0.05	686	312	179
Two-sided α-error = 0.01, exposed-to-unexposed ratio = 1 : 10			
P_0[**]	**RR = 1.5**	**RR = 1.75**	**RR = 2.0**
0.005	10847	4812	2789
0.01	5268	2435	1388
0.05	1021	464	266
Two-sided α-error = 0.05, exposed-to-unexposed ratio = 1 : 1			
P_0[**]	**RR = 1.5**	**RR = 1.75**	**RR = 2.0**
0.005	15813	7396	4678
0.01	7686	3814	2321
0.05	1475	718	437
Two-sided α-error = 0.01, exposed-to-unexposed ratio = 1 : 1			
P_0[**]	**RR = 1.5**	**RR = 1.75**	**RR = 2.0**
0.005	23528	11004	6956
0.01	11437	5674	3454
0.05	2194	1068	650

[a]Each cell shows number of exposed study participants.

[**]A P_0 of 0.5% corresponds to an approximate annual incidence of prostate cancer among natal men over 50 years of age or a 15-year risk of ovarian cancer in natal women over 40 years of age [52]. A P_0 of just under 1% is an estimate of all-cause mortality in the United States [53], and a P_0 of about 10% is prevalence of diabetes mellitus in US adults [54].

Table 4. Recommended terminology for various descriptors, based on identified or affirmed sex[a]

Sex identity	Sex assigned at birth	Term	Androphilic[b] orientation identity	Gynephilic orientation identity	Mixed sexual orientation identity
Female	Female	Cisgender woman	Heterosexual/straight	Homosexual/lesbian	Bisexual/pansexual/queer
Male	Male	Cisgender man	Homosexual/gay	Heterosexual/straight	Bisexual/pansexual/queer
Female	Male	Trans(gender) woman	Heterosexual/straight	Homosexual/lesbian	Bisexual/pansexual/queer
Transgender female/ transfemale/male-to-female	Male	Trans(gender) woman	Heterosexual/straight	Homosexual/lesbian	Bisexual/Pansexual/queer
Male	Female	Trans(gender) man	Homosexual/gay	Heterosexual/straight	Bisexual/pansexual/queer
Transgender male/ transmale/female-to-male	Female	Trans(gender) man	Homosexual/gay	Heterosexual/straight	Bisexual/pansexual/queer
Nonbinary/fluid/ genderqueer	Male	Trans feminine spectrum individual	Varies by individual	Varies by individual	Varies by individual
Nonbinary/fluid/ genderqueer	Female	Trans masculine spectrum individual	Varies by individual	Varies by individual	Varies by individual
Gender identity not listed here (avoid using the word 'other')	Either	Varies by individual	Varies by individual	Varies by individual	Varies by individual

[a]An increasing proportion of transgender people have an identity and sexual orientation identity outside of historical binaries. The term 'queer' describes a range of fluid and nonbinary gender and sexual identities and may be used in combination with the terms listed to describe particular subpopulations.
[b]Note: Transgender men and women may identify only as 'male/female' or as 'transgender male/female.' Androphilic and gynephilic are terms used to describe sexual orientation identity. Androphilic describes sexual attraction to men or masculinity. Gynephilic describes sexual attraction to women or femininity. The terms are used to identify a person's attraction without attributing gender identity or sex assignment to the individual. Cisgender refers to being nontransgender. This table refers to sexual orientation identity – additional questions regarding sexual behaviors and sexual organs involved in the sexual practices are recommended in clinical settings.

through observational comparative effectiveness research or implementation science methods [62]. To achieve this goal, data capture should include a full history of hormonal exposures and surgical procedures, therapy received both within and outside of professional care settings, and gender-affirming treatments both in the USA and abroad. Validated tools are needed to standardize collection of these patient data elements.

Regardless of study design or research question, there is a need for standardized terminology to describe transgender identity and history. Demographic groupings by gender identity should be grounded in current best practices to ensure appropriate comparisons across genotypic, phenotypic, and identity categories. Table 4 contains specific identity terminology recommendations, taking into consideration the increasing proportion of transgender people who have an identity and sexual orientation outside of historical binaries. Terminology for gender-affirming treatments should also be consistent and descriptive.

A critical feature of research with transgender people is patient centeredness [63]. Engaging local transgender community members from the start will ensure that study design and data collection methods are feasible and acceptable to participants [35]. Moreover, in longitudinal studies, for example, in a prospective cohort, long-term follow-up and ability to recontact participants are keys to success given attrition is the primary threat to validity [64]. Ways of maximizing retention and protocol adherence should be explored though formative qualitative and pilot studies, as in other areas of research with hard-to-reach populations [65,66]. Transgender health studies will likely benefit from applying community-based research principles to work 'with' not 'on' transgender people [67] in the design, implementation, and dissemination of research and to foster trust and synergy between researchers and local communities [68,69].

CONCLUSION

Transgender health research would benefit from methodological advances that ensure adequately powered statistical analyses, representation of hard-to-reach subgroups, a consistent agreed upon shared lexicon, unified protocols across studies for collecting data on treatment and health outcomes over time,

ability to pool data across sites, and ample opportunities for ancillary and nested studies, including clinical trials. Based on the strengths and limitations of different approaches discussed in the previous sections, some transgender health studies should be health systems-based, some clinic-based, some should conduct venue-based sampling, and some should deploy hybrid designs. It is expected that studies will have different methodological strengths and address diverse aspects of the transgender health research agenda. Broadening methodologies used in transgender health research represents a key next step to further scientific and clinical knowledge and advance health equity for transgender people.

Acknowledgements

None.

Financial support and sponsorship

This work was supported in part by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health (R13HD084267), the Endocrine Society, the Tawani Foundation, the World Professional Association for Transgender Health (WPATH), and the Program in Human Sexuality at the University of Minnesota Medical School. The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health, the Endocrine Society, WPATH, or the Department of Veterans Affairs.

Dr Reisner was partially supported through a Patient-Centered Outcomes Research Institute (PCORI) Award (CER-1403-12625). Dr Goodman was partially supported through a PCORI Award (AD-12-11-4532) and by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health under award number R21HD076387. All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of PCORI, its Board of Governors, or Methodology Committee. Likewise, the content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflicts of interest

There are no conflicts of interest.

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Approach to the Patient: Transgender Youth: Endocrine Considerations

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Compelling studies have demonstrated that "gender identity"—a person's inner sense of self as male, female, or occasionally a category other than male or female—is not simply a psychosocial construct, but likely reflects a complex interplay of biological, environmental, and cultural factors. An increasing number of preadolescents and adolescents, identifying as "transgender" (a transient or persistent identification with a gender different from their "natal gender"—ie, the gender that is assumed based on the physical sex characteristics present at birth), are seeking medical services to enable the development of physical characteristics consistent with their affirmed gender. Such services, including the use of agents to block endogenous puberty at Tanner stage 2 and subsequent use of cross-sex hormones, are based on longitudinal studies demonstrating that those individuals who were first identified as gender-dysphoric in early or middle childhood and who still meet the mental health criteria for being transgender at early puberty are likely to be transgender as adults. Furthermore, onset of puberty in transgender youth is often accompanied by increased "gender dysphoria"—clinically significant distress related to the incongruence between one's affirmed gender and one's "assigned (or natal) gender." Studies have shown that such distress may be ameliorated by a "gender-affirming" model of care. Although endocrinologists are familiar with concerns surrounding gender identity in patients with disorders of sex development, many providers are unfamiliar with the approach to the evaluation and management of transgender youth without a disorder of sex development. The goals of this article are to review studies that shed light on the biological underpinnings of gender identity, the epidemiology and natural history of transgenderism, current clinical practice guidelines for transgender youth, and limitations and challenges to optimal care. Prospective cohort studies focused on long-term safety and efficacy are needed to optimize medical and mental health care for transgender youth. (*J Clin Endocrinol Metab* 99: 4379–4389, 2014)

Case Presentations

Case 1

Patient 1 is a 13-year-old phenotypic male who was referred to the Child and Adolescent Gender Center (CAGC) Clinic with gender dysphoria. The parents report that as early as 3 years of age, the patient stated, "I am a girl" and asked why he had a penis if he was a girl. The patient subsequently insisted on a girl's name and the use of the female pronoun and would only wear girls' clothing. The parents acquiesced to the patient's requests while at home but initially insisted on a male presentation outside of the home. The patient experienced significant anxiety and depression throughout the middle childhood years, which worsened with the onset of puberty. Medical and mental health histories were otherwise unremarkable. By searching for information on the Internet, the family became aware of the CAGC and asked their pediatrician to initiate a referral so the patient could receive "pubertal blockers." After a series of mental health evaluations from a qualified child psychologist/gender specialist at the

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received April 1, 2014. Accepted August 7, 2014.
First Published Online August 20, 2014

Abbreviations: AR, androgen receptor; BMD, bone mineral density; BSTc, central part of the bed nucleus of the stria terminalis; CAH, congenital adrenal hyperplasia; CAIS, complete androgen insensitivity syndrome; DEXA, dual-energy x-ray absorptiometry; DSD, disorder of sex development; FTM, female-to-male; GID, gender identity disorder; GnRH, gonadotropin releasing hormone; INAH 3, interstitial nucleus of the anterior hypothalamus 3; MTF, male-to-female; SOC, standards of care; T, testo

CAGC, it was determined that the patient had severe gender dysphoria and would likely benefit from putting puberty "on hold" to provide an additional period of time for self-awareness and understanding. In addition, the family interacted with a CAGC advocacy specialist who worked with the child's school to provide training for teachers, parents, and students to establish a safe and tolerant environment for the patient. Physical examination demonstrated normal male genitalia with Tanner stage 2 pubic hair and early pubertal testes (5 cc, bilaterally). The remainder of the physical examination was entirely within normal limits. The patient and family were advised of the potential risks (including likely effects on bone mineralization and on fertility) and benefits of pubertal suppression with gonadotropin releasing hormone (GnRH) agonists. Baseline laboratory studies confirmed that the patient was in early puberty. Serum calcium, phosphorous, alkaline phosphatase, and 25-hydroxyvitamin D were all in the normal range. Bone mineral density (BMD) by dual-energy x-ray absorptiometry (DEXA) scan was 0.5 SD below that of an age-matched reference population for whole body, lumbar spine, and proximal femur. GnRH agonist treatment was prescribed; however, despite multiple appeals, this medication was denied by the family's insurance company.

Case 2

Patient 2 is a 16-year-old phenotypic female referred to the CAGC with long-standing gender dysphoria and a stated preference to be referred to with the male pronoun. In retrospect, the patient felt that he had "always been a boy" but did not reveal these feelings to family or friends for fear of rejection. The onset of puberty was accompanied by significant anxiety and depression, prompting referral to a therapist who was not knowledgeable about gender dysphoria in adolescents and thought the patient was likely "gay." The patient felt less anxious after decisions to wear a binder to hide the breasts and to wear loose-fitting "masculine" clothing. However, recurring monthly menses were accompanied by heightened anxiety. The patient became increasingly depressed and contemplated suicide. The patient eventually told his parents that he was not gay, but realized he was "transgender." The patient was subsequently referred to the CAGC for evaluation and management. Medical and mental health histories were otherwise unremarkable. Physical examination revealed Tanner 5 breasts and pubic hair and normal pubertal external female genitalia; the remainder of the physical examination was unremarkable. Mental health assessment confirmed that the patient was transgender with severe gender dysphoria. After detailed discussions with the medical team, in conjunction with ongoing mental health support, the patient and family opted for treatment with GnRH agonists to suppress the hypothalamic-pituitary-gonadal axis, with cessation of menses. Shortly thereafter, with continuing GnRH agonist therapy, the patient was treated with increasing doses of testosterone (T), achieving T blood levels in the mid-normal range for adult males. The patient's gender dysphoria and suicidal ideation fully resolved, and the depression was markedly reduced.

Background

Definitions

Although a person's "sex" refers to the physical attributes that characterize biological maleness or femaleness (eg, the genitalia), "gender identity" refers to a person's fundamental, inner sense of self as male or female (and is not always binary). The medical and mental health literature contain ample references to "gender assignment"/"natal gender" (1–3) on the one hand, and to "sex assignment"/"birth sex"/"sex of rearing" (2–5) on the other, sometimes leading to confusion. The gender assignment (or natal gender) is based on the "initial assignment as male or female," usually at birth (1), which, in turn, in the absence of a disorder of sex development (DSD), is typically based on the appearance of the external genitalia. Although sex of rearing can be assigned at birth, gender identity can only be assumed, and not, in fact, known until an individual achieves a particular level of psychological development and self-awareness. "Transgender" has been defined somewhat differently by the American Psychiatric Association and by the World Professional Association for Transgender Health (WPATH). In the former, transgender refers to a person who transiently or persistently identifies with a gender different from their natal gender (1). As defined in the standards of care (SOC) from WPATH, transgender (adjective) describes "a diverse group of individuals who cross or transcend culturally defined categories of gender" (6). In the WPATH SOC, "transsexual" (adjective) describes "individuals who seek to change or have changed their primary and/or secondary sex characteristics through feminizing or masculinizing medical interventions (hormones and/or surgery), typically accompanied by a permanent change in gender role" (6). Transsexual has also been used to describe a person who identifies as a member of the gender opposite to that assigned at birth (7, 8), but who has not necessarily sought medical and/or surgical interventions. In contrast, "gender-conforming" (sometimes used interchangeably with "cisgender") refers to a person whose gender identity is congruent with the natal gender. "Gender behavior"

doi: 10.1210/jc.2014-1919

(sometimes referred to as "gender role") is not equivalent to gender identity (7, 8). In fact, most youth with gender-nonconforming behavior will not turn out to have a transgender identity (9, 10). Previously referred to as "gender identity disorder" (GID) in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV, this term has now been replaced with "gender dysphoria" in DSM-5, with distinct diagnostic criteria for "gender dysphoria in children" and "gender dysphoria in adolescents and adults" (specifying with or without a DSD) (1). Replacing "disorder" with "dysphoria" depathologizes the transgender identity and focuses instead on dysphoria as the clinical problem (1). It should be noted that most patients with gender dysphoria do not have a DSD. Whether in children or adolescents, a core feature of gender dysphoria is "a marked incongruence between one's experienced/expressed gender and assigned gender" of at least 6-month duration (1). "Sexual identity" (or "sexual orientation") is often confused with "gender identity." Both are distinct aspects of human development. While sexual identity pertains to the individuals to whom one is sexually attracted, gender identity indicates who one "is" as male, female, or somewhere on the gender continuum. Just as gender-conforming individuals may have a heterosexual, homosexual, or bisexual orientation, the same holds true for transgender individuals.

Prevalence of transgenderism/transsexualism

Limited data exist regarding the prevalence of transgenderism/transsexualism. Recent data for natal adult males suggest a prevalence ranging from 1:7000 to 1:20 000, and for natal adult females a prevalence ranging from 1:33 000 to 1:50 000, and these are thought to represent "modest underestimates" (1). In The Netherlands, among the population age 15 years and older, a prevalence of 1:11 900 for male-to-female (MTF) and 1:30 400 for female-to-male (FTM) transsexualism has been reported (11). Such data were derived from patients diagnosed as transsexual by mental health professionals (11). Prevalence estimates in Singapore and Thailand were significantly higher (12, 13). Equivalent studies in North America have not yet been reported. However, a recent report from Massachusetts suggests that the prevalence of transgenderism may be more common than previously thought. In a survey of 18 to 64 year olds (n = 28 662) in a "representative household sample" carried out between 2007 and 2009, participants were presented with a commonly accepted definition of transgender and were provided with more detailed information if requested (14). Of those surveyed, 131 (0.5%) self-identified as transgender (14). Although prevalence data for younger transgender adolescents are lacking, multidisciplinary clinics for transgender youth and adolescents in Europe and North America have seen a steadily increasing demand for services in recent years (15–18), with a ratio of phenotypic males to females close to 1:1 (17).

Psychiatric co-morbidities and impact of family support

Transgender youth and adolescents are at significantly increased risk for life-threatening behaviors. Interviews of transgender youth in New York City (n = 55; MTF = 31, FTM = 24) demonstrated that 45% had experienced suicidal ideation, whereas 26% had attempted suicide (19). A recent report from Ontario, Canada, of transgender youth and young adults ages 16 to 24 years (n = 84) assessed the impact of the degree of parental support on mental health outcomes (20). Satisfaction with life and self-esteem were significantly greater in transgender youth whose parents were "very supportive" vs those whose parents were "somewhat to not at all supportive" (20). In addition, depression and suicide attempts were significantly decreased in transgender youth whose parents were supportive in comparison to those whose parents were not supportive (20). However, even with supportive parents, transgender youth still have a significant risk for depression (20), perhaps in part from their experience of transphobia from members of their communities and a feeling that they don't fit in.

Current Concepts of the Biology of Gender Identity

Numerous studies from a variety of biomedical disciplines— endocrine, genetic, and neuroanatomical— have begun to shed light on the biological underpinnings of gender identity. Results of these studies support the concept that gender identity is not simply a psychosocial construct, but likely reflects a complex interplay of biological, environmental, and cultural factors.

Although most transgender patients do not have a DSD, studies of gender identity outcome within the endocrine discipline have been principally carried out in patients with a variety of DSDs, primarily exploring the role of prenatal and postnatal androgens in gender identity development. For example, studies in 46,XX patients with "classical" congenital adrenal hyperplasia (CAH) caused by mutations in *CYP21A2*, resulting in 21-hydroxylase deficiency and varying degrees of genital masculinization, demonstrate a greater than expected number of patients with gender dysphoria, "atypical gender identity," or who were transgender (21–23). In an interview study of 43 patients ages 3–18 years, gender identity scores indicated

that 11.6% of patients had scores outside the range of control girls; no correlation was found between gender identity and degree of genital virilization or age of genital surgery (21). In a larger meta-analysis of 250 patients with 46,XX 21-hydroxylase deficiency leading to virilizing CAH and who were raised female, 94.8% of patients reported a female gender identity without gender dysphoria, whereas 5.2% reported either a male gender identity or gender dysphoria (22). As with an earlier study (21), there was no apparent correlation with the degree of genital masculinization and gender identity outcome (22). A study of adult women with classical 21-hydroxylase deficiency demonstrated a relationship between severity of disease and gender identity outcome. Of 42 patients with the salt-wasting form, three (7.1%) either had gender dysphoria or had changed gender to male; no gender dysphoria was seen in less severely affected individuals (23). These and other studies demonstrate that most 46,XX patients with virilizing CAH from 21-hydroxylase deficiency appear to have a female gender identity. However, the finding that 5.2–11.6% of such patients have gender dysphoria, an atypical gender identity, or are transgender would appear to be much more common than expected based on the reported prevalence of FTM transsexualism, implying that there is some role for prenatal/postnatal androgens in gender identity outcome (21–23). It is noteworthy that in 46,XX individuals with virilizing CAH from 21-hydroxylase deficiency, prenatal androgens are more likely to affect gender behavior and sexual orientation than gender identity (24, 25).

The potential effects of prenatal and postnatal androgen exposure on gender identity outcome and "gender role change" have also been explored in other hormonal and nonhormonal DSDs. For example, in 5α-reductase-2 deficiency among 46 XY individuals raised female, a gender role change from female to male (typically after puberty) was reported in 56–63% of the patients (26). Gender role changes from female to male were also reported in 39–64% of 46,XY individuals raised female with 17β-hydroxysteroid dehydrogenase-3 deficiency (26). In the largest series of patients with 5α-reductase-2 and 17β-hydroxysteroid dehydrogenase-3 deficiency reviewed by Cohen-Kettenis (26), individuals undergoing gender role change from female to male had intact testes, implying a potential role of prenatal as well as postnatal androgen exposure in gender identity outcome (27, 28). Among "nonhormonal" DSDs, gender identity outcome has been studied in patients with cloacal exstrophy, penile ablation, and penile agenesis (29, 30). A study of patients with 46,XY cloacal exstrophy reported that the majority (eight of 14) who had undergone neonatal sex reassignment to female (castration) subsequently declared a male gender identity and that two patients raised as males remained male (29). However, this study has been criticized for methodological concerns in the assessments of gender identity and gender dysphoria (30). A literature review of patients with 46,XY cloacal exstrophy found that of 51 patients assigned female, the majority (65%) were living as female, whereas 14% were living as female but with possible gender dysphoria, and approximately 22% were living as male (30). In addition, of 16 males with penile agenesis assigned female at birth and of seven males with penile ablation reassigned to female in infancy or early childhood, the majority were living as female (30).

Taken together, these studies of gender identity outcome in hormonal and nonhormonal DSDs indicate that gender identity is not solely dependent on prenatal and postnatal androgen exposure; however, the occurrence of gender identity change (in comparison to the natal gender) at a rate significantly higher than would be expected in the general population supports some role of prenatal and possibly postnatal androgens in gender identity development. It should be noted that potential limitations of all these survey/questionnaire-based studies to assess gender identity include a person's degree of self-awareness and one's willingness to disclose this information in the study context.

In contrast to studies that support some role of androgens in male gender identity, a case report in a 46,XY individual with complete androgen insensitivity syndrome (CAIS) challenges the concept that androgen receptor (AR) signaling is required for male gender identity development (31). Although individuals with CAIS typically have unambiguous female genitalia and a female gender identity, an individual with CAIS, associated with an unambiguous female phenotype and an *AR* gene mutation resulting in a premature stop codon, was found to have a male gender identity (31). The authors acknowledge that this patient may have had a postzygotic de novo *AR* gene mutation (the mother's DNA was not available) and could theoretically have brain mosaicism (with a normal AR in the brain); however, this was considered unlikely given that the same *AR* gene mutation was found in both the patient's blood and fibroblasts (31).

With respect to genetics and gender identity, heritability of transsexualism has been suggested from studies describing concordance of transsexualism in monozygotic twin pairs and in father-son and brother-sister pairs (32, 33). A larger study of survey responses from parents of twins (96 monozygotic pairs and 61 dizygotic pairs, ages 7–14 y) demonstrated a 2.3% prevalence of clinically significant GID (34) (based on DSM-IV criteria). These authors reported that heritability accounted for 62% of the variance for GID in their twin sample (34). A more recent

doi: 10.1210/jc.2014-1919

study supporting a role for genetic factors in gender identity outcome demonstrated a 39.1% concordance for GID (based on DSM-IV criteria) in 23 monozygotic female and male twin pairs, with no concordance in 21 same-sex dizygotic female and male twin pairs or in seven opposite-sex twin pairs (35). With respect to specific genes, association studies with transsexualism have been inconsistent and lacking strong statistical significance. In one study of 29 MTF transsexuals and 229 male controls, an association was found with a longer dinucleotide CA repeat in intron 5 of the *ERβ* gene in the transsexuals vs controls ($P = .03$), but no associations were found with polymorphisms in the *AR* (CAG repeat length) and the aromatase (*CYP19*) (TTTA repeat length) genes (36). A larger study (112 MTF transsexuals and 258 male controls) did not find an association of transsexualism with the *ERβ* gene or the *CYP19* gene but did find that the MTF transsexuals had a longer trinucleotide CAG repeat in exon 1 of the *AR* gene vs controls ($P = .04$) (37). A study from Japan (74 MTF and 168 FTM transsexuals with 106 male and 169 female controls), however, did not find any significant associations of transsexualism with polymorphisms in five candidate genes (the same polymorphisms noted above for *AR*, *CYP19*, and *ERβ*, as well as polymorphisms in *ERα* and the progesterone receptor) (38). A single study reported a positive association between a single nucleotide polymorphism in the *CYP17* gene and FTM transsexuals but not in MTF transsexuals (39).

With respect to a neurobiological basis for transsexualism, numerous studies have reported brain differences in transsexual individuals vs controls. It is well-established that there are "sexually-dimorphic" brain structures—eg, cell groups in the anterior hypothalamus (eg, interstitial nucleus of the anterior hypothalamus 3 [INAH 3]) and the central part of the bed nucleus of the stria terminalis (BSTc) that have different morphological characteristics in males and females (40, 41). In addition, there is some evidence for a "sexual-orientation dimorphic" brain structure. In 1991, it was reported that the INAH 3, which, in addition to being twice as large in heterosexual men vs women, was also found to be twice as large in heterosexual men vs homosexual men (40). This study was criticized for its relatively small sample size, potential influence of HIV on INAH 3 size, and the fact that the characterization for INAH 3 in the initial study was only for volume and not cell number. A subsequent study with a larger sample size (particularly for controls) confirmed that INAH 3 was significantly larger in presumed heterosexual males vs presumed heterosexual females and demonstrated that INAH 3 was not affected by HIV status (42). However, no difference was found in INAH 3 neuronal number based on sexual orientation, although there was a trend for decreased volume and increased cell density in the INAH 3 of homosexual vs heterosexual men (42).

Recent studies have supported the concept that there may also be "gender-dimorphic" brain structures, which segregate not according to physical sex but rather according to gender identity (41, 43). The BSTc, known to be larger in men than in women (independent of sexual orientation), had a female appearance in a group of MTF individuals (41, 43). Potential limitations of this study were a small sample size and the fact that many of the MTF individuals had received estrogen treatment (43). Of note, however, were the findings observed in several controls. A male with a feminizing adrenal tumor producing high blood levels of estrogen nonetheless had the male BSTc pattern, as did two T-deficient males who were orchidectomized for prostate cancer; furthermore, a female with a virilizing adrenal tumor producing high blood levels of androstenedione and T nonetheless had the female BSTc pattern, as did an 84-year-old MTF individual who had never received any estrogen or antiandrogen treatment (43). Despite the above-noted study limitations, the inclusion of critical controls with sex steroid variations and an untreated MTF individual lends some support to the concept that the observed BSTc differences in the transsexual individuals were intrinsic and not simply a consequence of sex steroid milieu (43). However, it should be noted that the sexually dimorphic differentiation of the BSTc in humans is not present until puberty, in contrast to rats, where such differences in the BST occur in the early postnatal period and apparently require perinatal differences in T levels (44, 45). Given that many transgender adolescents experience significant gender dysphoria before puberty (and before sex differences in BSTc volume emerge), the relationship between BSTc volume and gender identity would appear to be unclear.

Subsequent studies have explored brain differences in transsexual adults who had not yet received cross-sex hormone treatment (46–49). One study of gray matter volumes by magnetic resonance imaging noted that the right putamen volume was sexually dimorphic and reported that the volume of the right putamen in MTF individuals was larger than in control males and within the average range for control females (46). A subsequent study, however, did not confirm these findings but reported that the putamen volume in MTF individuals was smaller than in both male and female cisgender controls (49). With respect to sexually dimorphic white matter structures (eg, parts of the superior longitudinal fasciculus), magnetic resonance imaging studies using fractional anisotropy found that patterns in transsexual individuals were closer to individuals who had the same gender identity rather

than the same physical sex (47). In addition, in studies where hypothalamic blood flow was activated by smelling odorous steroids in a sexually dimorphic manner, the response in MTF individuals not yet treated with cross-sex hormones (estrogens) was closer to that of control women than control men (48). A potential limitation in the gray and white matter studies is related to brain functional plasticity. It has been demonstrated that changes in both white matter microstructure and gray matter can be induced by training/experience in healthy human adults (50, 51); thus, it would be difficult to know with certainty whether any observed brain differences between transgender and cisgender individuals are intrinsic or a consequence of experience.

Natural History of Transgenderism in Youth/Adolescents

Longitudinal studies have demonstrated that most gender-dysphoric prepubertal youth will no longer meet the mental health criteria for gender dysphoria once puberty has begun (9, 10). Although gender "fluidity" may be a contributing factor, the lack of persistence of gender dysphoria in most gender-dysphoric prepubertal youth undoubtedly reflects the heterogeneous nature of this group. In fact, many such individuals will turn out to be homosexual (natal males, in particular) rather than transgender (1, 5, 9, 10). Recent studies have attempted to identify factors that predict gender dysphoria "persisters" vs "desisters" (52). Persisters reported relatively greater degrees of gender dysphoria and were more likely to have experienced social transition (to their affirmed gender) during childhood (52). Furthermore, persisters "believed they were" the other sex, whereas desisters "wished they were" the other sex (52). The limitations in prediction of persistence, coupled with the observation that most gender-dysphoric children will not become transgender adolescents or adults, have led some investigators to promote efforts to encourage gender-dysphoric children to accept their natal gender (53). In contrast, a model of care that "affirms" a child's gender expression is thought to have a more optimal mental health outcome (54). Long-term outcome studies are needed to resolve these differences in approach to the care of gender-dysphoric prepubertal youth.

Diagnostic and Therapeutic Strategies

Assessment

Although the symptoms of gender dysphoria will decrease or disappear in most gender-dysphoric youth after initiation of puberty, persistence of gender dysphoria implies a very high likelihood that such individuals will be transgender as adults; in fact, the emergence or worsening of gender dysphoria with onset of puberty is thought to have significant diagnostic value in the determination of being transgender (55). It is noteworthy, however, that with the advent of gender-affirming medical interventions (as detailed below), awareness of such treatment options may positively impact and, thus, limit the degree of dysphoria that might otherwise accompany the onset of puberty in a transgender individual. It is therefore essential that gender-dysphoric youth undergo a thorough psychodiagnostic evaluation by a qualified mental health provider. An important role of the mental health/gender specialist is not only to determine the presence or absence of gender dysphoria but also to evaluate for psychiatric comorbidities. Although there is an increased prevalence of autism spectrum disorder in clinically referred gender-dysphoric children in comparison to the general population (56) (and, conversely, increased "gender variance" in referred children with autism spectrum disorder) (57), most gender-dysphoric children and adolescents do not have an underlying severe psychiatric illness (55).

Management

Guidelines from The Endocrine Society (7) and the WPATH SOC (6) provide direction for the comprehensive management of two distinct pediatric transgender populations likely to seek medical services: an early pubertal group (Tanner 2/3) and a late pubertal group (Tanner 4/5).

Early pubertal transgender youth

Pioneering studies from The Netherlands, first published in 1998, have examined the consequences of pubertal suppression with a GnRH agonist (classically used for the treatment of precocious puberty) in early/midpubertal gender-dysphoric adolescents (58–61). The rationale for such fully reversible treatment is that additional time for gender exploration can be created without the pressure of ongoing pubertal development. Once completed, the physical changes of puberty cannot be reversed (by means other than surgical or, for voice, other than by voice training)—eg, low voice, Adam's apple, and facial features in phenotypic males and breast development in phenotypic females. Theoretically, preventing pubertal development that does not match a person's gender identity can lead to decreased gender dysphoria and can ultimately make the individual more "passable" as an adult. Subsequently, if the individual continues to identify as transgender, cross-sex hormones can be added while continuing GnRH agonist suppression of endogenous puberty, enabling the individual to experience only the physical changes of puberty that match the person's affirmed

doi: 10.1210/jc.2014-1919

Table 1. Hormonal Interventions for Transgender Adolescents (All Currently Off-Label for Gender Nonconforming/Transgender Youth)

A. Inhibitors of gonadal sex steroid secretion or action
  1. GnRH analogs: inhibition of the hypothalamic-pituitary-gonadal axis (FTM and MTF)
    a. Leuprolide acetate im (1- or 3-mo preparations) or sc (1-, 3-, 4-, or 6-mo preparations) at dose sufficient to suppress pituitary gonadotropins and gonadal sex steroids
    b. Histrelin acetate sc implant (once-yearly dosing, although may have longer effectiveness)
    c. Other options: goserelin acetate sc implant (4- or 12-wk preparations); nafarelin acetate intranasal (multiple daily doses) also available, but no reported use in this population
  2. Alternative approaches
    a. Medroxyprogesterone acetate orally (up to 40 mg/d) or im (150 mg every 3 mo): inhibition of hypothalamic-pituitary-gonadal axis and direct inhibition of gonadal steroidogenesis (FTM and MTF)
    b. Spironolactone (25 to 50 mg/d with gradual increase to 100–300 mg/d orally, divided into twice daily dosing): inhibition of T synthesis and action (MTF)
    c. Cyproterone acetate (gradual increase up to 100 mg/d orally; not available in United States): inhibition of T synthesis and action (MTF)
    d. Finasteride (2.5–5 mg/d orally): inhibition of type II 5 α-reductase, blocking conversion of T to 5α-dihydrotestosterone (MTF)
B. Cross-sex hormones
  1. MTF: estrogen—17β-estradiol
    a. Transdermal: twice weekly patches (6.25 μg [achieved by cutting a 25-μg patch] with gradual increase to full adult dose)
    b. Oral/sublingual: daily (0.25 mg with gradual increase to full adult dose of 6–8 mg/d)
    c. Parenteral im (synthetic esters of 17β-estradiol): estradiol valerate (5–20 mg up to 30–40 mg/2 wk) or estradiol cypionate (2–10 mg/wk)
  2. FTM: testosterone
    a. Parenteral im or sc (synthetic esters of T): T cypionate or enanthate (12.5 mg/wk or 25 mg/2 wk, with gradual increase to 50–100 mg/wk or 100–200 mg/2 wk)
    b. Transdermal (consider once the full adult T dose has been achieved parenterally): patch (2.5–7.5 mg/d) or 1% gel (2.5–10 g/d of gel = 25–100 mg/d of T)

gender identity (6, 7). The Endocrine Society guidelines and WPATH SOC endorse the use of pubertal blockers (using GnRH agonists) at Tanner 2/3 in individuals experiencing a significant increase in gender dysphoria with onset of puberty (6, 7). Although age-specific guidelines for subsequent interventions are not delineated in the WPATH SOC, the Endocrine Society guidelines suggest that cross-sex hormones can be initiated at about the age of 16 years (the legal age for medical decision-making in some countries), whereas surgical procedures (with the exception of mastectomy) should be deferred until the individual is at least 18 years of age (7). The primary risks of pubertal suppression in these individuals include adverse effects on bone mineralization (which can theoretically be reversed with cross-sex hormone treatment), compromised fertility, and unknown effects on brain development (55, 59). It is important to ensure adequate intake of calcium and vitamin D, with routine monitoring of 25-hydroxyvitamin D levels. Despite the recommendation that cross-sex hormone treatment not be initiated before age 16 years, not only could delaying such treatment until that age be detrimental to bone health, but keeping someone in a prepubertal state until this age would isolate the individual further from age-matched peers, with potentially negative consequences for emotional well-being. Thus, gender centers at our institution and elsewhere are studying the impact of cross-sex hormone treatment initiation at 14 years of age (which approximates the upper end of the age range for normal pubertal onset in natal males and 1 year beyond the upper end of the age range in natal females). In this group, sex steroids are increased gradually over the course of 2–3 years.

Limited available outcome data support the above-noted Endocrine Society and WPATH recommendations. A prospective follow-up study from The Netherlands assessed 70 gender-dysphoric adolescents (33 MTF, 37 FTM), average age 13.65 years (range, 11.1–17 y) at initial assessment, who were Tanner stage 2–3, had lifelong gender dysphoria that increased with puberty, had stable psychological function, and were supported by their environment (59, 60). These adolescents were studied at the initiation of GnRH agonist treatment (mean age, 14.75 y), and approximately 2 years later, just before starting cross-sex hormones (60). Depressive symptoms decreased, general mental health functioning improved, no subjects withdrew from pubertal suppression, and all went on to cross-sex hormone treatment (60). In a separate report, BMD in the lumbar spine, femoral neck, and total body was followed in a small number of gender-dysphoric adolescents during 2 years of GnRH agonist alone and for an additional 2 years of combination treatment with GnRH agonist and cross-sex hormones (59). BMD (g/cm^2) did not

change significantly during treatment with GnRH agonist alone, although z-scores decreased; during combination therapy with GnRH agonist and cross-sex hormones, absolute BMD increased, as did z-scores (59). A 22-year follow-up of the first described gender-dysphoric adolescent treated with GnRH agonist and cross-sex hormones reported overall psychological well-being with no clinical signs of adverse effects on brain development; furthermore, BMD was within the normal range for both sexes (61).

Late pubertal transgender youth

Not infrequently, some transgender adolescents first come to medical attention when they are late pubertal (Tanner 4/5). Such FTM individuals can be treated with T alone, whereas MTF individuals are optimally treated with an agent that blocks T secretion and/or action, concurrent with the use of estrogen (6, 7, 62, 63). Although too late to block endogenous pubertal development, GnRH agonists can nonetheless be used to suppress the hypothalamic-pituitary-gonadal axis, potentially enabling the use of lower doses of cross-sex hormones to induce phenotypic transition to the affirmed gender, thereby decreasing potential toxicities associated with cross-sex hormone treatment. In this older cohort (having already experienced the full or near-full puberty associated with their physical sex), cross-sex hormone regimens may be increased to full replacement doses over a shorter interval than used for the younger cohort that had been initially treated with pubertal blockers at Tanner 2/3. Although GnRH agonists are the preferred option for pubertal suppression in both the early and late pubertal individuals, this treatment is costly and often inaccessible. Table 1 lists options for pubertal suppression and cross-sex hormone treatment. With specific respect to estrogen treatment, 17β-estradiol (transdermal, oral, or parenteral) is preferred to conjugated (eg, premarin) or synthetic estrogens (eg, ethinyl estradiol), given that conjugated and synthetic estrogen levels cannot be monitored in the serum and that ethinyl estradiol (in comparison to 17β-estradiol) is associated with an increased risk for venous thromboembolic disease and death from cardiovascular causes (64, 65). MTF individuals treated with estrogen may have impaired insulin sensitivity and hyperprolactinemia (7). Principal risks associated with T treatment in FTM individuals include cystic acne, polycythemia, hypertension, an atherogenic lipid profile, and possible decreased insulin sensitivity (7). Surveillance recommendations for desired as well as adverse effects during treatment with pubertal blockers alone and in combination with cross-sex hormones are adapted from the current Endocrine Society guidelines (7) and are summarized in Table 2.

Table 2. Monitoring During Pubertal Suppression and During Cross-Sex Hormone Treatment

Measure	Frequency
A. Pubertal suppression	
1. Physical exam: height, weight, Tanner staging	T 0 and every 3 mo
2. Hormonal studies: ultrasensitive LH, FSH, estradiol/T	T 0 and every 3 mo
3. Metabolic: calcium, phosphorous, alkaline phosphatase, 25-hydroxyvitamin D (see also Ref. 6)	T 0 and yearly
4. Bone density: DEXA	T 0 and yearly
5. Bone age	T 0 and yearly
B. Cross-sex hormone treatment in previously suppressed patients or in late pubertal patients not previously suppressed	
1. Physical exam: height, weight, Tanner staging, blood pressure (for FTM, in particular); monitor for adverse reactions	T 0 and q 3 mo[a]
2. Hormonal studies: ultrasensitive LH, FSH, estradiol/T	T 0 and q 3 mo[a]
If MTF, also monitor Prolactin	T 0 and yearly
3. Metabolic: calcium, phosphorous, alkaline phosphatase, 25-hydroxyvitamin D, complete blood count, renal and liver function, fasting lipids, glucose, insulin, glycated hemoglobin	T 0 and q 3 mo[a]
If MTF on spironolactone, serum electrolytes (potassium)	T 0 and q 3 mo[a]
4. Bone density: DEXA (if puberty previously suppressed)	T 0 and yearly[b]
5. Bone age (if puberty previously suppressed)	T 0 and yearly[b]

Modified from W. C. Hembree, et al: Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2009;94:3132–3154 (7), with permission. © The Endocrine Society.

[a] Every 3–12 months after the first year.

[b] Until puberty is completed.

It should be noted that some Tanner 4/5-transgender adolescents present for medical services before 16 years of age. As with the group treated with GnRH agonists at early puberty, we and others are studying the consequences of cross-sex hormone treatment at 14 years of age. Occasionally, some gender-dysphoric youth first come to medical attention when they are Tanner 4/5, but < 14 years of age. Such individuals would be candidates for pubertal blockers (eg, to stop menses in an FTM adolescent), but without supportive outcome data, not currently candidates for cross-sex hormone use under most circumstances.

It is essential that any use of pubertal blockers and cross-sex hormones includes an informed consent process and a discussion about implications for fertility. Transgender adolescents may wish to preserve fertility, which

doi: 10.1210/jc.2014-1919

may be otherwise compromised if puberty is suppressed at an early stage and the patient completes phenotypic transition with the use of cross-sex hormones.

Controversies and Areas of Uncertainty/ Barriers to Ideal Practice

The ability to provide optimal health care to gender-dysphoric/transgender youth is limited by areas of uncertainty, controversies, and barriers to state-of-the art practice. Only limited safety and efficacy data currently exist, with virtually no published data on the use of pubertal blockers in gender-dysphoric individuals < 12 years of age or cross-sex hormones in transgender youth < 16 years of age. Furthermore, randomized controlled trials for hormonal interventions in gender-dysphoric youth have not been considered feasible or ethical (66). The clinical practice guidelines that currently exist are based on best available evidence, with significant reliance on expert opinion. A 2011 report from the Institute of Medicine of the National Academies in the United States has endorsed the need for prospective, longitudinal safety and efficacy studies of medical interventions in gender-nonconforming/transgender youth (67). Barriers to implementation of current clinical practice guidelines include the fact that pubertal blockers and cross-sex hormone treatments are off-label in gender-dysphoric youth and are expensive, and coverage is often denied by insurance companies. Furthermore, whereas an increasing number of clinical programs have emerged in recent years, there are many geographic regions in which such services do not exist, limiting access to care and often requiring patients and families to travel long distances. In addition, access to optimal care may be limited by a lack of training of providers and by prejudice and misunderstanding on the part of family, community, and medical and mental health professionals.

Returning to the Patients

Despite insurance denials after multiple appeals, our 13-year-old Tanner 2/3 gender-dysphoric MTF patient and family were determined to have access to pubertal suppression with GnRH agonist therapy. They decided against alternative approaches to block T production or action and instead purchased the least expensive GnRH agonist option out of pocket. The patient's gender dysphoria has markedly reduced since initiating pubertal suppression.

Our 16-year-old Tanner 5 transgender FTM patient has continued to do well on GnRH agonist treatment to suppress the hypothalamic/pituitary/ovarian axis and on weekly sc T injections for phenotypic transition. Monitoring at 3-month intervals has thus far shown no toxicities associated with hormonal interventions; the gender dysphoria and suicidal ideation continue to be fully resolved, and the patient's depression continues to be reduced.

Conclusions

Transgender youth represent an often marginalized and misunderstood population. Compelling studies have demonstrated that gender identity is not simply a psychosocial construct, but likely reflects a complex interplay of biological, environmental, and cultural factors. The recent replacement of "disorder" with "dysphoria" in DSM-5 removes the connotation that a transgender identity itself is pathological and focuses instead on dysphoria as the clinical concern. The best available evidence indicates that mental health comorbidities in gender-dysphoric youth significantly diminish or resolve when such individuals are subject to a gender-affirming model of care, optimally delivered in a multidisciplinary clinical setting. Prospective cohort studies focused on long-term safety and efficacy are needed to optimize medical and mental health care for transgender youth.

Acknowledgments

I thank my colleagues at the UCSF Child and Adolescent Gender Center for their shared commitment and passion for this work. I am inspired by the courage of our patients, who want nothing more than to be themselves, and by their parents and other family and community members who support them.

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Disclosure Summary: The author has nothing to disclose.

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CORRESPONDENCE

Oocyte Cryopreservation in a Transgender Male Adolescent

TO THE EDITOR: Since the effects of gender-affirming therapy on fertility are unknown, multiple medical societies endorse the preservation of fertility in persons who identify as transgender.[1-3] In transgender male adolescents (with a natal female sex), the pubertal transition to female sex can lead to gender dysphoria, which is often treated with gonadotropin-releasing hormone (GnRH) agonists to prevent pubertal development. This presents a unique clinical challenge of providing effective preservation of fertility without exacerbating gender dysphoria and undesired pubertal development if GnRH agonists are discontinued. In addition, the practicality of cryopreservation of oocytes is uncertain in patients who have not completed puberty. Here, we describe our multidisciplinary approach to cryopreservation of oocytes in a transgender male adolescent who was receiving GnRH agonist therapy and who wished to have genetically related children.

GnRH agonist therapy was initiated when the patient was 14 years of age, when the pubertal stage was classified as Tanner stage 2 (with stages ranging from 1 to 5 and higher stages indicating more advanced pubertal development),[3] and he was referred to a reproductive endocrinologist at 16 years of age. The patient was counseled to discontinue GnRH agonist therapy, given concern that his degree of pubertal development was inadequate to allow effective maturation of oocytes for cryopreservation; however, he opted to continue therapy during the period in which the oocytes were obtained and cryopreserved. Additional discussion detailed the process of future use of cryopreserved oocytes, including the potential use of donor sperm and the role of a gestational carrier.

The baseline gonadotropin levels were consistent with GnRH agonist suppression (serum follicle-stimulating hormone level, 0.89 mIU per milliliter; serum luteinizing hormone level, 0.07 mIU per milliliter). Since he did not want to undergo transvaginal ultrasonography, transabdominal ultrasonography and measurements of serum estradiol levels were used to monitor the patient's response to therapy. Doses of follitropin alfa and low-dose human chorionic gonadotropin were adjusted until the patient had a maximum estradiol level of 1204 pg per milliliter (4420 pmol per liter) on cycle day 30. After induction of oocyte maturation with recombinant human chorionic gonadotropin, five oocytes were retrieved while the patient was under conscious sedation; four mature oocytes were cryopreserved.

Distressing side effects of this process included vaginal bleeding for 7 days after oocyte retrieval and unanticipated breast development, which regressed within 3 months. The patient reported depressed mood and brief passive suicidal thoughts in response to these symptoms. The multidisciplinary team (including pediatric and reproductive endocrinologists, clinicians in adolescent medicine, and psychologists) moni-

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tored the patient for resolution of these symptoms. Testosterone therapy was then initiated as planned. The patient and his parents were satisfied with the process and outcome, although the prognosis regarding his fertility was guarded given the small number of oocytes that were cryopreserved.

This case stresses the importance of education regarding preservation of fertility in transgender youth. This involves a thorough discussion of the risks and benefits of discontinuation of GnRH agonists as well as counseling regarding potential adverse effects.

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

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DOI: 10.1056/NEJMc1813275

Low Incidence of Hospital-Onset *Clostridium difficile* Infection in Sickle Cell Disease

TO THE EDITOR: Patients with sickle cell disease have defects in immune function; they are frequently hospitalized for painful vaso-occlusive crisis and are often given empirical antibiotic treatment for fever in this setting. They also have intestinal dysbiosis.[1] Health care facility–associated *Clostridium difficile* infections might be expected to be more common among patients with sickle cell disease than in other patient populations.

We performed a retrospective cohort study involving adult patients with sickle cell disease who were admitted to Westchester Medical Center in Valhalla, New York, from January 2015 through November 2018. A total of 106 patients (87% of whom were either homozygous for hemoglobin S or had hemoglobin S β+ thalassemia and 13% of whom were heterozygous for hemoglobin S [hemoglobin SC]), representing 365 total consecutive hospital admissions, were included. Patients who underwent allogeneic stem-cell transplantation were excluded from the analysis.

In total, 70% of the admissions were for sickle cell–related complications and 56% were readmissions. There were 54 female patients and 52 male patients, and the median age of the patients was 26 years (range, 17 to 68). The mean length of stay in the hospital was 10.2 days (median, 7; range, 1 to 93). The total number of patient-days in the hospital for this cohort was 3727. Overall, 454 courses of antibiotics were administered during 180 hospitalizations (49%). The total number of days on which antibiotics were administered was 1598, and 1984 units of blood were administered. The most frequently used antibiotics were ceftriaxone, azithromycin, vancomycin, piperacillin–tazobactam, and cefepime.

A Cepheid Xpert *C. difficile* real-time polymerase-chain-reaction (PCR) assay targeting the toxigenic B gene was used to analyze samples from patients who had two or more loose stools in 24 hours in the absence of laxative use. A diagnosis of *C. difficile* infection was made if the PCR was positive in the absence of other conditions that could account for the diarrheal illness. Incidence rates, confidence intervals, and statistical differences were calculated with the use of MedCalc statistical software. Although data on readmissions were recorded accurately during the study period for patients with sickle cell disease, similar data were not available for patients in the hospital-wide group; many hospitalizations over the 4-year study period were readmissions. To allow for this, we opted to consider all admissions as being independent in our calculations of confidence intervals in both groups.

Published data on *C. difficile* infection in hospital-wide populations have shown incidence

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Article *in* Sexual and Relationship Therapy · April 2014

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October 2013

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Approved by Central Policy Committee: December 2012
Due for review: 2018

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Contents

Endorsements

The following organisations have endorsed the report:

- British Association of Urological Surgeons
- British Psychological Society
- Gender Identity Research and Education Society
- Gender Trust
- Press for Change
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Obstetricians and Gynaecologists
- Royal College of Paediatrics and Child Health*
- Royal College of Physicians
- Royal College of Speech and Language Therapists
- Royal College of Surgeons
- UK Council for Psychotherapy

*With respect only to discussion of children and adolescents, p. 20.


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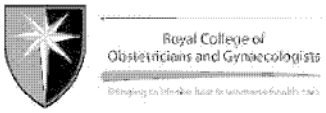
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Organisations providing consultation

Equality and Human Rights Commission

General Medical Council

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Ms Michelle Ellis	Service User, Gender Trust
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Ms Maxine Rathbone	District Nurse, Royal College of Nursing

1. Replaced by Mr David Ward.
2. Replaced by Dr Walter Bouman.
3. Replaced by Mr Dominic Walsh.
4. Replaced by Dr Philip McGarry.

Executive summary and recommendations

The provision of care for patients experiencing gender dysphoria is an excellent example of an area where multidisciplinary and interdisciplinary care is not only good practice but ensures that a wide choice of treatment pathways are offered, tailored to the needs of the individual patient. This intercollegiate document provides guidelines which we hope will optimise the clinical care pathways for patients who may need to access several medical and allied health professionals.

We herald a new approach to care which has evolved from a linear progressive sequence to multiple pathways of care which recognise the great diversity of clinical and presentation needs. Central to the new way of working for healthcare professionals is the recognition of patient-centred care that will result in flexible treatment options, hopefully increasing the likelihood of good outcomes, reduced morbidity and improved quality of life for patients. The joint participation in goal-setting and regular follow-up is crucial to winning the support of both patients and clinicians. Practitioners have a duty of care to enable individuals to make competent, fully informed decisions and choices. Providers of services have a positive duty to support this patient-centred approach which is enshrined in the UK equality and human rights legislation.

Our recommendations are clearly enshrined in the principles of accessibility of services without undue and unnecessarily long waits, the provision of high-quality services with proper cooperation and working practices between a number of clinicians, with clear recognition of the diverse needs of patients and a recognition of a variety of needs depending on the patient's particular gender transition. For some, this means helping individuals achieve real harm reduction which has caused considerable conflict between parties in the past. We strongly emphasise the establishment of clinical partnerships between both patient and clinician, and between clinicians. With this in mind, clinical governance processes must be set up in accordance with current National Health Service (NHS) good practice guidelines.

Owing to the adoption of the patient-centred recommendations within this publication we hope that patients will feel less need or inclination to avoid seeking professional medical assistance throughout their process of transition. There are already examples of good clinical practice where such recommendations are part of standard practice. The World Professional Association for Transgender Health's (WPATH) standards of care for transsexual, transgender and gender non-conforming people have informed these UK standards of care (World Professional Association for Transgender

Health, 2011). The endorsement by several medical Royal Colleges, allied medical professional societies and service user groups sends a strong signal for the adoption of these guidelines across the UK and beyond.

RECOMMENDATIONS

1 The principle of multidisciplinary and interdisciplinary teams and networks who work and collaborate in the provision of services for persons with gender dysphoria is paramount. These services may operate out of different venues and locations and engage in regular governance review.

2 A multidisciplinary team or network will have terms of engagement, rules of confidentiality and regular supervision. Patients will be consulted and involved in clinic and network decision-making and policy development.

3 The multidisciplinary team will usually act as a focus for a network of clinicians in a region.

4 The transfer of care of patients from adolescence to adulthood services should be immediate and wherever possible through joint appointment.

5 Transfer between services and across the lifespan without undue delay is essential.

6 Each team should have specific link clinicians and this would cover all disciplines including links with learning disability services, district nursing, etc.

7 Patients shall be expected to retain responsibility for their decisions after receiving informed advice with regard to reversible and irreversible interventions.

8 Persons with gender dysphoria have a right to counselling and psychotherapeutic practice as part of the overall package of care.

9 Adult persons with gender dysphoria should have equal access to the full range of available help and services irrespective of ethnicity, cultural background, age or disability. Services should be sensitive to a variety of ethnic and cultural needs.

10 There remains a paucity of research in the field. Research should be encouraged and funding set aside to offer specific grants looking at outcome and satisfaction with interventions and transition.

11 Service provision and clinical best practice for persons with gender dysphoria is underwritten by promoting patient autonomy and patient choice embedded in the NHS Constitution (Department of Health, 2013), and by ensuring that patients' human rights and right to equality, protected under legislation, are complied with by both decision makers and practitioners concerned with service provision and treatment.

Introduction

Establishment of the working group

In 2003 the Royal College of Psychiatrists established a working group with the remit of developing good practice guidance for the delivery of professional standards of care, within the UK and Ireland, for individuals whose phenotype is inconsistent with their gender identity. Because of the multiplicity of the specialist roles it was decided to convene representatives from other medical Royal Colleges and related disciplines. Representation from patient groups was invited. The group met in London and Sheffield and consulted with a large number of individuals and agencies.

The working group invited submissions from individual contributors on a number of topics, and the contents of the appendices reflect the current views or advice of the individual contributors in consultation with others, but not necessarily with the consensus of all members of the committee.

This document may be used in conjunction with commissioning guidelines prepared under the auspices of current international, national and local guidelines, including those prepared by the Parliamentary Forum on Gender Identity and the WPATH standards of care (World Professional Association for Transgender Health, 2011).

The process of treatment aims to achieve an improved quality of life. As such all procedures, including surgery, should be viewed as possible steps within a unique patient-centred process.

At the end-point of specialist treatment, which will vary depending on the needs, the individual patients will continue to be treated in primary care. It is not the remit of this document to cover this in detail. However, it is essential that primary care providers of endocrine treatment and monitoring understand that patients who experience, or have experienced, gender dysphoria must not have their endocrine treatment stopped, unless there are medical reasons for doing so. The fact that these medications are in the main not licensed for this use is not a reason to withhold this treatment. Religious beliefs or cultural mores must not be used to withhold, withdraw or denigrate treatment.

Guidance is given to ensure best practice across all NHS organisations which either commission or provide treatment and health services for individual patients. Guidance must comply with the NHS Constitution (Department of Health, 2013) and equality and human rights legislation. It must also support the rights of individuals who have been living long-term in the role that accords with their gender identity to have their current needs met without being required to repeat earlier steps in their journey, such as psychological assessment for diagnostic purposes.

DEFINITIONS

Definitions in the ICD-10 (World Health Organization, 1994) are under review.

The expression of gender characteristics that are not stereotypically associated with one's assigned gender at birth is a common and culturally diverse human phenomenon that should not be judged as inherently pathological or negative.

Non-conformity may be associated with prejudice, causing psychological distress. This distress is not inherent in being transsexual, transgender or gender non-conforming.

Gender dysphoria is the distress associated with the experience of one's personal gender identity being inconsistent with the phenotype or the gender role typically associated with that phenotype. This distress, when present, might give rise to an individual seeking clinical consultation. There are gradations of gender experience between the binary 'man' or 'woman', some of which cause discomfort and may need medical intervention; others may need little or none. There is growing recognition that many people do not regard themselves as conforming to the binary man/woman divide and that this will have an impact on their treatment. Self-descriptions include: pangender, polygender, neutrois and genderqueer. A few people who reject the gender concept altogether, and see themselves as non-gendered, may require gender-neutralising treatments from appropriate clinical services.

Any general practitioner (GP) involved in the overall care of transgender patients should usually be on the GP register of the General Medical Council (GMC) (or non-UK equivalent). General practitioners may have, or may gain, specialist interest through experience of working in the field, continuing professional development and specialist courses.[5] All doctors registering with the GMC should follow guidance on standards of professional conduct (General Medical Council, 2013*a*):

- multidisciplinary working (paras. 35–38; see also General Medical Council, 2012)
- continuity of care (paras. 44–45)
- working in partnership with patients and treating them as individuals (paras. 46–52)
- treating patients fairly and without discrimination (paras. 56–64)
- being honest and trustworthy in communication with patients (para. 68).

Similarly, a specialist nurse practitioner is a registered nurse who gains experience working as part of a gender identity team either in a gender identity clinic or other gender-specialist clinical network.

TERMINOLOGY

Language in the field of gender dysphoria is constantly evolving as understanding and perceptions of these conditions change. Different usage

5. The World Professional Association for Transgender Health suggests a range of ways to enhance continuing professional development: 'attending relevant meetings, workshops, or seminars; obtaining supervision from a mental health professional with relevant experience; or participating in research related to gender nonconformity and gender dysphoria' (World Professional Association for Transgender Health, 2011: p. 22).

exists between communities and even side by side within communities. The terms transgender or trans are sometimes used as umbrella terms to cover a wide variety of atypical gender experiences which sometimes lead to a permanent change of gender role but may not necessarily lead to surgical intervention.

Throughout this document, with the exception of material contained in quotation marks (or where according to context, reference is made to 'men' or 'women'), the terms 'trans woman' and 'trans man' are used in accordance with representation made to this working group by patients and relate to those who have yet to receive a Gender Recognition Certificate or to undergo genital surgery. A pre-genital operation individual or one yet to receive a Certificate who has been assigned as a female at birth on the basis of genital appearance, but who later identifies as a man, may be described as a trans man. Similarly, a pre-genital operation individual or one yet to receive a certificate who has been assigned as a male at birth, but who later identifies as a woman, may be described as a trans woman. It is important to note that many people, after receiving the appropriate medical care, do not identify as trans, but simply as men and women. For ease of reference, an individual who has received a certificate is referred to herein as having been 'certificated'.

People who are transitioning, or who have transitioned, to live according to the gender role that is consistent with their gender identity, should be addressed according to the name and style of address (Mr, Mrs, Miss or Ms) deemed to be correct by them. If personnel, whether medical or administrative, are in any doubt, they should ask individuals discreetly how they wish to be addressed.

When the word transsexual is used, it should be as an adjective, for example transsexual individual, transsexual people or someone who is transsexual.

Prevalence

Gender variance is not uncommon. A survey of 10 000 people undertaken in 2012 by the Equality and Human Rights Commission found that 1% of that population was gender variant to some extent. This figure cannot necessarily be assumed to be representative of the whole population. Historically, more pre-gender surgery or pre-certificated women sought treatment than men but this difference is reducing and some gender identity clinics are reporting numbers that are close to parity.

Gender variant people and gender non-conforming people do not necessarily have gender dysphoria and the population shows great diversity. It would be wrong to assume that there is a typical pre-gender operative or pre-certificated woman or man. Increasing numbers of individuals now present at an earlier stage in life;[6] equally there are many who may have lived with their dysphoria for decades before feeling confident enough (or having the opportunity) to seek to resolve their issues. Gender variance knows no social, ethnic, religious or socioeconomic boundaries but is likely to be more hidden in some cultures than in others.

6. The numbers of children attending the Tavistock Gender Identity Development Service is rising by 32% per annum (2007–2012) (K. Josha, personal communication, 2012). Those who continue to experience or present in adolescence as experiencing gender incongruence are extremely likely to require adult services.

Good practice

Availability and accessibility of services

Patients are presumed, unless proven otherwise, capable of consenting to treatment.

Regardless of location, there should be a competent and effective gender identity service that is readily accessible within the geographic region or reasonable travelling time thereof. The waiting times for access to such services should be in line with those for other patients and tertiary clinics in the region. Although in practice patients may not wish to be treated by a gender identity service a long way from their home location, they should have the choice of accessing any gender identity service, gender specialist[7] or surgeon in the country.

People should have direct access to primary care and be referred by their GP for secondary and tertiary health provision as is clinically appropriate, and in the same way as for any other patients. Only when the patient needs access to a gender identity service provider would the National Specialist Commissioning Group become involved. Clinical commissioning groups may also need to liaise with other commissioners to coordinate gender care.

When accessing treatments or procedures for medical conditions other than gender dysphoria, patients should be referred directly to a specialist surgeon/consultant without being required to attend a gender identity service or have compulsory psychiatric assessment. This includes referral to oncologists, gynaecologists, endocrinologists, urologists and plastic surgeons. This is not an exhaustive list but an example of frequently used services.

Where a patient moves from one commissioning area to another, funding and treatment should continue without interruption and gender-role changes undertaken by that person must be taken into account by treatment providers in the new area.

Gender consultants and specialists should recognise the expertise and opinion of colleagues in other gender identity services when a person transfers from one gender identity service provider and another. The patient may, of course, seek a separate, independent opinion.

Where people have successfully completed a verifiable long-term change of gender role and later decide to undergo surgery, for instance phalloplasty, they should not be reassessed regarding their social role or rediagnosed for gender dysphoria and, unless there are physical or

7. Gender specialists may be from many different clinical backgrounds, some specialising in mental health: psychologists, psychiatrists, counsellors or therapists, but they may also be GPs, endocrinologists, nurses, etc.

psychological contraindications, should be deemed ready for surgery. The referral by the GP should be to a specialist gender dysphoria practitioner.

Patients have the same right as other patients to private treatment in the UK or in Europe, funded by the NHS,[8] as long as proper letters of referral are obtained and the proposed provider abroad meets contemporaneous standards of care.

Commissioning

Those responsible for commissioning healthcare should ensure that the population for which they are responsible has access to comprehensive gender identity services, which include multidisciplinary input from primary care, specialist clinicians working within a team or network, endocrine and surgical specialties. In establishing specialised services (e.g. in setting up a gender clinic or primary care clinical network), it is essential to obtain appropriate patient and stakeholder representation and input into the decision-making and policy development at all stages, in conjunction with the relevant commissioners and providers. Patients must be offered a choice of clinically appropriate treatments.

Gender treatment should be established on a multidisciplinary basis and may include input from GPs, psychology, psychiatry, psychotherapy, nursing, speech and language therapy, endocrinology, dermatology, surgery, social work and other related professions. Working in cooperation with other specialist practitioners or colleagues, even if on a different site, and affiliation with peer review and supervision networks, should be the goals of all clinicians. In addition to involving patients, clinicians should facilitate or provide information about assistance available to partners and families.

Commissioning across regional boundaries should be consistent. Undue delay should be prevented and the risk of patient harm reduced. In principle, this should be achieved by offering the full range of treatment options and recognising that not all patients will request hormones and/or gender reconstructive surgery. Facial hair removal for women contributes to successful transition. Hair removal from donor sites that are relevant to genital surgery should also be funded to promote successful outcomes. Any individual with an intersex condition, including chromosomal anomalies, should be offered equal access to gender-specialist providers. Many long-term patients, especially those successfully discharged years previously from a gender identity service, are eligible and entitled to be directly referred for gender reconstructive surgery (see pp. 24–26) including chest reconstruction and hysterectomy for men.

Legal rights

All UK service providers are subject to the Equality Act 2010, the Human Rights Act 1998 and the Gender Recognition Act 2004. The implications

8. In the case of *Watts v. Bedford Primary Care Trust & Secretary of State for Health* [2006], the concept of 'undue delay' arises when the delay is based on an 'arbitary time frame, rather than a medical decision'. These circumstances render the NHS funding authority liable for the cost of the treatment undertaken privately, so that the patient has to be reimbursed.

of this are that any treatment guidelines promulgated which do not have due regard for this legislation would risk being illegal in their application to treatment. Providers and commissioners of treatment in the public sector are bound by the public sector equality duty. This means that the attitudes of clinicians, the manner and timing of their service delivery and the choice of treatments offered must be consistent with that duty. The legislation requires that patients are treated with dignity and are allowed personal autonomy.

Steps must be taken to eliminate discrimination (direct or indirect), harassment or victimisation within service provision against those with 'protected characteristics', including 'gender reassignment', and also those who are perceived as being or are associated with such patients, such as partners, spouses, significant others and family members.

These aspects of the law are relevant where unfavourable comparisons with other groups of patients may be drawn without objective justification, and where matters of patient autonomy, dignity and choice are engaged. There is a positive obligation to ensure that there is fair access to clinical treatment under all circumstances. This would include the provision of alternative appropriate clinical care where indicated.

The European Court of Human Rights, in *Goodwin v. United Kingdom* [2002] and *I v. United Kingdom* [2007], (under Articles 8 and 12) gave a strong indication to the UK government and all other agencies that they are under a positive obligation to treat such patients with respect and dignity in all areas of their lives, and to accord them equal rights and status with all other citizens. In the UK, patients are protected by the Human Rights Act 1998, which derives from, and must be compliant with, the European Convention on Human Rights. The Act protects individuals against unwanted intrusion into their private lives (Article 8). In *R (on the application of AB) v. the Secretary State for Justice and Another* [2010], the court held that a pre-operative gender woman committed to a life sentence for offences committed as a man, namely manslaughter by reason of provocation and attempted rape, was entitled to be transferred to an all-female prison pursuant to her human rights.

Once patients formally change their names and style of address, all GP, gender identity clinic, hospital and NHS records should be amended to reflect this change. A Gender Recognition Certificate is not required for this change to be effected. Some patients obtain a statutory declaration or a deed poll to mark their name change, but this is not obligatory, and treatments must not be made contingent on providing this type of documentation. A simple statement of intent will suffice. The fact that a patient is intending to undergo or is undergoing treatment for gender dysphoria must not be divulged to other health professionals and colleagues outside of the treating team and only within it if strictly necessary. Establishing a relationship of trust between trans individuals and their clinicians is especially important and assurance of confidentiality and secure record-keeping is paramount. Medical necessity in order to save life is an exemption from this rule of law or where as part of a medical team there is a need to know. Caldicott procedures must be followed (Caldicott, 1997).

In the UK, individuals may apply to the Gender Recognition Panel for a Gender Recognition Certificate. Applicants applying under this process must demonstrate that they have had a diagnosis of gender dysphoria and that they have lived in the gender role that is congruent with the gender identity for at least 2 years. Once a Gender Regulation Certificate has been issued, the applicant must, in accordance with the provisions of that certificate, be identified as a man or a woman and not a 'trans man' or 'trans woman'.

The issue of the certificate does not affect things done, or events occurring, before the certificate is issued (Section 9(2) Gender Recognition Act 2004).

A Gender Recognition Certificate provides a right to marry someone of the opposite gender or to enter into a civil partnership with a person of the same gender. The Act also makes consequential changes to the law with regard to social security, benefits and pensions.

Section 22 of the Gender Recognition Act 2004 was introduced to protect the rights and privacy of transsexual individuals pursuant to Article 8 of the European Convention on Human Rights and makes it a strict liability criminal offence for a person who has acquired protected information in an official capacity to disclose that information to any other person. This information relates to a person who has made an application for a Gender Recognition Certificate and considerable care needs to be taken regarding keeping secure the notes and medical records of the individual patients. According to Section 9 of the Act, once a full Gender Recognition Certificate has been issued, the person's gender becomes for all purposes the acquired gender so that if the acquired gender is the male gender then the person's gender becomes that of a man, and, if it is the female gender, the person's gender becomes that of a woman, and the persons must be so described.

Statutory Instrument 2005 No. 635 introduced some additional exceptions to Section 22 so that it is not an offence for the disclosure to be made by a health professional if it is made for medical purposes and the person making the disclosure really believes that the individual has given consent to the disclosure or cannot give such consent. 'Medical purposes' includes the purposes of preventive medicine, medical diagnosis and the provision of care and treatment. There may still be gender-specific treatment such as that related to screening for breast or prostate cancer where surgery has not taken place. A 'health professional' means a registered medical practitioner, a registered dentist, a registered pharmaceutical chemist, a registered nurse, a person who is registered under the Health Professionals Order 2001 as a paramedic, or operating department practitioner. It also includes a person working lawfully in a trainee capacity in any of the professions specified.

Referral process

Gender dysphoria services are usually provided by specialist clinicians. The support of a GP who is prepared to be proactive in supporting referrals for treatment and to enter into collaborative care arrangements is essential.

Specialist clinicians and gender clinics should provide patients and referrers with details about clinic services and protocols.

Adults with gender dysphoria should have equal access to the full range of available help and services irrespective of ethnicity, cultural background or disability, without discrimination. Certain groups will have additional specialist requirements (e.g. patients with intellectual disabilities; see Appendix 1).

Those who need NHS gender identity services for the first time should be referred by the GP, or they may be referred by a psychologist, non-specialist psychiatrist or sexual health centre via a GP to a gender service provider, for diagnosis and/or opinion about how the patient's needs may be met from a range of options. Where patients' acute needs cannot be met by a specialist service within a reasonable and safe time frame, they may be referred as an interim measure to a local endocrinologist and for mental

health support as appropriate, prior to being seen by a specialist gender identity clinic.

Those in prison should have access to both local mental health services for non-gender care and a gender identity specialist. This document may be used in conjunction with guidelines prepared by the Ministry of Justice (2011) and/or a prison's own specific guidelines.

Collaborative working

Primary care continues to be central to the delivery of medical and psychological care to the majority of patients. It is desirable for a single practitioner to adopt the lead role to facilitate coordinated care. General practitioners are likely to undertake this role. Under new commissioning arrangements it is particularly important that treatments provided locally are coordinated with those provided by tertiary services. All information should be shared with the GP, and patients should be copied in to all letters between clinicians.

Treatment in this field is particularly holistic in the degree to which different specialties may be involved. There is no necessity for specialists to work together under the same roof. Indeed, patients may not experience the full benefits of choice and emergent expertise if their options are constrained in such a fashion. Nevertheless, it is desirable that practitioners should establish protocols for working together.

In whatever way the multidisciplinary approach is organised, whether at a gender identity clinic or by a group of health professionals locally, the patient's choice of service provider should not be unreasonably limited, and delivery must not be unreasonably delayed.

Waiting times

As a matter of good practice, service providers should take all reasonable steps to provide the patient with a realistic understanding of the time scales involved. Patients should have confidence that their treatment will progress in the agreed time scale. Service providers should also continually seek ways to help guarantee deadlines. Liability for 'undue delay' arising from non-clinical circumstances may fall on the commissioners. In such circumstances, private treatment undergone by the patient may also become the responsibility of the NHS (*Watts v. Bedford Primary Care Trust & Secretary of State for Health* [2006]).

Patient focus and flexibility: informed consent and outcomes

The idea of empowering people to make informed choices about their own healthcare is a strong principle within modern healthcare thinking. It is embodied in the NHS Constitution (Department of Health, 2013) and throughout current health and social care legislation.

Care should be taken to respect the patient's autonomy for decision-making at all times. In law, 'informed consent' and 'competence to consent'

mean that the patient must comprehend the nature, purpose and effect of the procedure to be undertaken. Throughout all stages of treatment, the clinician has a responsibility to inform patients of the options, benefits, potential unwanted side-effects and health risks of the treatment, in terms that can be readily understood. The advantages and disadvantages of not undertaking treatment should also be discussed. Patient information documentation should be provided in a timely manner. It is in line with best practice that consent forms for treatment are signed and dated by patient and by clinician.

Treatment must be patient-centred and should recognise the individual's preferences, needs and circumstances. Treatment must not be prescriptive and should allow clinically safe choices for individuals. Patients should be accorded a substantial role in determining the kinds of treatments that are appropriate for them. This may include choices regarding pace and sequence of treatment and service providers. A relevant specialist should support the individual in making those decisions. A flexible approach to care, meeting an individual's needs, is recommended. In cases of disagreement between the clinician and the patient, there is an automatic right to the provision of an independent second opinion by another specialist working in the field.

There is growing recognition that many people do not regard themselves as conforming to the binary man/woman divide. This will affect their treatment choices. A few people who reject the gender concept altogether and see themselves as non-gendered may require gender-neutralising treatments from appropriate clinical services. Therefore, not all of these elements of treatment will be necessary or desirable in every case, nor will their sequencing conform rigidly to a standard pattern. For some people extensive surgery may not be appropriate or possible.

Treatment involving a combination of hormone administration and usually some combination of gender-confirming surgical procedures, following psychological assessment and accompanied by psychological support, is deemed to lead to good outcomes.

A study using the post-genital-surgery end-point showed only a 3.8% regret rate and indicates that regrets are few (Landén *et al*, 1998). The study revealed that regrets were more likely where there was a lack of family support. A review of more than 80 qualitatively different case studies over 30 years demonstrated that the treatment is effective (Pfäfflin & Junge, 1998). Lawrence (2003) found that the most significant factor for regret was a poor surgical outcome. Smith *et al* (2005) undertook a prospective study and found that no patient was actually dissatisfied, 91.6% were satisfied with their overall appearance and the remaining 8.4% were neutral. This study did indicate that women who had lived as heterosexual men before transitioning to live as women were at risk of fewer satisfactory outcomes. This was particularly the case where physical appearance and psychological functioning were unfavourable and the gender dysphoria experienced was inconsistent. Those with added difficulties were at greater risk of dropping out of treatment altogether and those that continue may need additional therapeutic guidance up to and even after surgery.

Factors that help to support successful outcomes are a consistent gender identity and psychological stability before and after surgery, adequate psychological preparation and transition at an early age (De Cuypere *et al*, 2006), including properly informed consent about benefits, risks and outcomes. A survey in the UK showed a high level of satisfaction (98%) following genital surgery (Schonfield, 2008). Two studies on

outcomes in women and men showed that they function well on a physical, emotional, psychological and social level (Weyers *et al*, 2009; Wierckx *et al*, 2011). Overall, there are a number of studies that report extremely high transgender patient satisfaction with genital reconstructive surgery.

Children and adolescents

These guidelines do not directly address the needs of children and adolescents. However, it is recommended that the transfer between adolescent and adult services is achieved through liaison between these services, so that treatments that have been initiated for adolescents may continue without interruption. Where treatment has not yet been undertaken, it may be started in a timely manner, taking account of the young person's clinical and social history.

Reversible hormone-blocking interventions (gonadotrophin-releasing hormone analogue) for adolescents in the early stages of pubertal development have now been introduced in the UK (2011) at the Tavistock Gender Identity Development Service, under a research protocol. This service works in liaison with the Paediatric and Adolescent Endocrinology Service at University College London Hospital. Some young people may be prescribed cross-gender hormones before they transfer to adult services. The British Society for Paediatric Endocrinology and Diabetes' position statement recommends that the care of adolescents should be offered within a specialist multidisciplinary team on an individual basis (British Society for Paediatric Endocrinology and Diabetes, 2009). Other publications supporting hormone-blocking intervention in early puberty include those from the Vrije Universiteit Medical Center in Amsterdam, The Netherlands, whose team pioneered this approach (de Vries *et al*, 2006; Cohen-Kettenis *et al*, 2011).

Further resources include the American Endocrine Society's clinical practice guidelines (Hembree *et al*, 2009) and the WPATH standards of care (World Professional Association for Transgender Health, 2011).

Clinical governance

Specialist gender clinics or clinical networks should operate on the principles outlined in this document. Policies and protocols are subject to official assessment of equality in their delivery of service. Clinics will be required to adhere to the principles of clinical governance, including regular clinical supervision of staff, patient satisfaction audit and continuous professional development. Patients' involvement is required at all stages of policy development. All staff should be able to demonstrate regular appraisal of their professional practice in accordance with their regulatory bodies.

Services must have transparent complaints procedures, and outcomes must be audited. Records must be made of remedial actions taken and those records must be made available.

Overview of recommended procedure

Initial referrals, assessments and support

GP consultation and overview

Initial assessment, for a patient with no previous diagnosis of gender dysphoria, by a GP or any member of the primary care team should use the holistic model. The GP should take a full history, including a mental state assessment. Any distress experienced by the patient should be acknowledged during the assessment. The GP has the additional advantage of possessing a record of the patient's longitudinal medical history, which should be reviewed to aid diagnosis. Once a provisional diagnosis is reached, the GP should discuss with the patient any preference they may have for a particular way forward.

A routine general and sexual health screen should be offered. Before commencing hormones, blood tests should be done in accordance with Appendices 2–4. A full physical examination should be offered by the hormone-prescribing clinic or by the GP in collaboration with the specialist team initiating endocrine treatment. The prescribing physicians should satisfy themselves that a recent clinical examination has been recorded in the medical notes. Genital examination may cause distress to the individual and may be declined by the patient: such refusals should be respected in all cases and the matter recorded in the clinical records of both the specialist clinic and the GP.

Patients frequently find it difficult to confide their feelings of gender dysphoria to their GP, often because it is the family GP or practice, and fear of ridicule, guilt or shame as well as other pressing social factors prevent them from seeking help and treatment. These factors and the anticipated delay in obtaining treatment on the NHS have led to increasing numbers of people self-medicating. Hormones and hormone-blockers are readily available via the internet. The medical practitioner or specialist must consider the risks of harm to the patient by not prescribing hormones in these circumstances. The WPATH standards of care (World Professional Association for Transgender Health, 2011) suggest the prescribing of a 'bridging' prescription on an interim basis for a few months while the patient is referred to a gender specialist and an endocrinologist.

Individuals without any significant co-existing conditions that might amount to a contraindication, who have successfully lived as men for an agreed length of time, may be referred directly by the GP to a gynaecologist of choice to discuss hysterectomy and oophorectomy. However, the surgical method used will need to take account of any future genital reconstructive surgery, so advice should be sought from the specialist surgeon who will

provide phalloplasty, if known. It is generally advisable to avoid causing scars on the lower abdomen, in case this area later becomes a donor site for phalloplasty.

This guidance in no way prevents GPs from prescribing hormones or hormone replacement treatment to any group of patients, rather it seeks to encourage GPs to acquire relevant specialist knowledge through best practice which is required to support patients in their care.

Patients who defer surgical interventions, but who have symptomatic gender dysphoria, and who have been on hormones for 12 months or more (unless unable to take them), should not be regarded as new patients. They may be referred for surgical interventions after prompt review by a gender specialist.

A patient may present to a GP having had gender reconstructive surgery such as chest reconstruction, breast augmentation or genital surgery and they may require scar revision or nipple repair. As this type of surgery is a continuation of the original funded surgery, a direct referral to a surgeon of choice should follow. Gender identity clinic referrals or approval is not required.

Initial specialist assessment

Initial assessment of patients with possible gender dysphoria includes a general medical and mental health interview, with specific attention to psychosexual history and current functioning. A record is required of lifelong mental functioning including any history of disorder. Recollections of childhood gender-typed behaviours, and childhood and adolescent cross-gender dressing with possible erotic accompaniment are elicited. Attempts to conform to cultural gender expectations are described. The current marital or other relationship status as well as extended family situation is discussed. Steps already taken are noted and acknowledged to the patient. Drug use is recorded. Information is provided to the patient.

Although some patients may be living part-time or even full-time in the new role when they first seek help from a clinician, many will not have changed their gender role. Change of role must be taken into account when endocrine treatment is being considered, but administration of hormones is not contingent on role change and patients should not have to take this step or be obliged to make a commitment to it. When gender role change is not planned at that time, there should be a clearly documented treatment plan that is regularly reviewed.

Gender dysphoria may be confirmed in different ways, for instance by engaging in a period of therapy with a counsellor, psychotherapist, psychologist or a psychiatrist. This can take place in either primary or secondary care settings.

Patients must have experienced persistent gender dysphoria in order to be eligible for endocrine treatment. Psychotherapeutic support may continue during ongoing hormone administration. Where endocrine treatment helps patients to cope in the long term with gender dysphoria, this treatment may not be withheld or withdrawn because the individual, for whatever reason, chooses not to change the gender role full-time or at all (Byne *et al*, 2012).

At first presentation, others may have already changed their social gender role, commenced endocrine treatment or had some surgery. This must be recognised and individual circumstances accommodated in the overall treatment programme. Implementation will depend on patients'

circumstances, steps taken and how successful they have been in consolidating their gender role. It is possible that no supervision of living in the new role will be required because effectively it has already taken place and is verifiable.

Men whose breasts are causing them distress and who have a diagnosis of gender dysphoria or have a Gender Recognition Certificate may need to have chest reconstruction around the same time as the change of gender role. Breast binders may be worn, but this can be painful and problematic. Binders restrict breathing and may have significant physical consequences. Damage to the breast tissue is also caused, so that chest surgery may be more complicated and less successful. Balanced against early surgery, the administration of testosterone for 6 months may improve the outcome of surgery.

Counselling/psychotherapy

The role of counselling or psychotherapy by the counsellor, psychotherapist, psychologist or psychiatrist should be to facilitate the process of exploration for the patient. Psychological therapies should be available to be used as part of the patient's treatment programme. It should enable people, through a variety of approaches, to be clearer about their gender identity including whether they want to commence, continue or reverse treatment.

Therapeutic support

In the following situations it is desirable to provide psychological or psychotherapeutic interventions for patients.

- Assessment prior to gender transition, hormone and surgical treatment should include a psychological assessment and formulation including a development history, an account of psychological attitudes to gender and sexuality, and an understanding of any other psychosocial issues that may be responsive to psychological interventions.
- People wishing to consider gender transition but hampered in the decision-making process should have the opportunity for psychological exploration either directly with a gender identity specialist or independently through a consultation with a psychological therapist.
- Some patients with gender dysphoria may have psychological issues beyond gender identity. Such individuals may require in-depth exploration of these wider issues. If these are related to a mental health diagnosis, they may need treatment prior to or, more usually, in parallel with, the gender treatment process. Cessation or suspension of gender treatment by the treating team can only occur where there is evidence that a mental health condition is giving rise to a misdiagnosis of gender dysphoria or renders the patient untreatable until their condition is reasonably well controlled.
- In the course of gender treatment, patients may become depressed or have to face psychosocial issues in reaction to external factors. As with any other individuals, they may benefit from psychological interventions in any of a number of different models of psychotherapy.
- At any stage of treatment, patients may need to explore their gender identity issues within a psychotherapeutic process. This may be

provided outside a gender identity service, and this is especially valuable when it can be accessed locally on a frequent, regular basis. The gender identity clinic may request the GP to make a local referral.

- Post-operatively, people may wish to have emotional support or psychotherapy. Some people experience depression post-operatively. In these circumstances, support should be offered and may be provided within a gender identity service or in another psychotherapeutic setting.

THE CHANGE OF GENDER ROLE

The progression from one gender role to another usually requires input from specialist services to support changes in social, family, domestic and work life.

A verifiable period of time, usually at least 12 months, living in a gender role that is congruent with the gender identity is a requirement for those who seek genital surgery. Some people have already changed their gender role before seeking medical help. Others may wait until they have been on hormones for a few months or sometimes years (Byne *et al*, 2012). Where people can demonstrate that they have already been living in role, this must be taken into account by clinicians.

The quality of life in the new role is assessed through discussions about the patient's ability to function in areas such as employment, voluntary work, education and training or some other stable, social and domestic lifestyle, and to adopt a gender-appropriate first name.

Clinicians require verifiable documentation or evidence of the gender role change. However, care should always be taken to avoid breach of confidentiality in this regard.

Patients should be given the opportunity to discuss which surgical options would be best for them. This can be achieved by an appropriate referral during this time to consult with a specialist surgeon. Where possible, patient choice should be taken into consideration. To avoid unnecessary delay, the consultation may occur before the required period of living in the new role is achieved. This also provides an opportunity to determine the outline of donor site hair removal which promotes good outcomes. Some surgery such as facial feminising surgery and thyroid cartilage reduction may be undertaken at any time.

USE OF MEDICAL OPINIONS

OPINIONS AND ELIGIBILITY CRITERIA FOR GENDER TREATMENTS

Opinions are required at the crucial stages of commencing hormone therapies and referral for surgical procedures. The following apply to all medical and surgical intervention:

- persistent and well-documented gender dysphoria
- capacity to make fully informed decisions and to consent to treatment
- if significant medical or mental health concerns are present, they must be reasonably well controlled.

Endocrine treatment

The decision to proceed with endocrine treatment will usually involve a single opinion from a member of the gender identity team or network. Patients should have a written copy of this decision. However, the GP or other medical practitioner involved in the patient's care may prescribe 'bridging' endocrine treatments as part of a holding and harm reduction strategy while the patient awaits specialised endocrinology or other gender identity treatment and/or confirmation of hormone prescription elsewhere or from patient records.

Surgery

It is important that surgeons responsible for major, irreversible operations do not merely rely on referrals but, in addition, satisfy themselves that this is an appropriate proposed procedure for the person concerned (see 'Genital surgery for men', p. 30, for donor site hair removal).

Best practice expects that opinions and recommendations given by a gender identity clinic or consultant in one area of the country are portable and accepted by other gender identity clinic providers, surgeons and consultants elsewhere in the country.

If the person has an interim or full Gender Recognition Certificate, they have, by definition, lived in the gender role that is congruent with their gender identity for at least 2 years, and have satisfied the Gender Recognition Panel that they intend to do so for the rest of their lives. They are therefore eligible to proceed with surgery, including genital surgery, subject to a single medical opinion from a physician who has long-term knowledge of the patient, on the basis of informed consent.

Surgery applicable to men only

- Chest reconstruction requires a single opinion from a gender specialist. Patients should have a written copy of the referral letter.
- Hysterectomy and/or salpingo-oophorectomy requires two opinions, usually from members of the gender clinic team or network (one letter may have two signatories). The second opinion may also be from a GP with a special interest or the patient's own GP. Patients should have a written copy of the decision and referral letter(s). Eligibility criteria are as listed on p. 24, plus:
  - 12 months' continuous endocrine treatment as appropriate to the patient's goals (unless the patient has medical contraindications or is otherwise unable to take hormones). (None of these criteria would apply to medical conditions requiring advice, opinion or treatment from a gynaecologist or oncologist where direct referral is appropriate.)
- Vaginectomy, urethroplasty, phalloplasty, metoidioplasty, testicular prosthesis and/or scrotoplasty requires two opinions, usually from members of the gender clinic team or network (one letter may have two signatories). The second opinion may also be from a GP with a special interest. Patients should have a written copy of the decision and referral letter(s). Eligibility criteria are as on p. 24, plus:
  - 12 months' continuous endocrine treatment as appropriate to the patient's goals (unless the patient has medical contraindications or is otherwise unable to take hormones);

- at least 12 months' living continuously in a gender role that is congruent with the gender identity.

Surgery applicable to women only

- Augmentation mammoplasty requires a single opinion from a gender specialist or GP with a special interest. Patients should have a written copy of the referral letter. Eligibility criteria are as listed on p. 24, plus:
  - it is recommended that patients have 18 months of a therapeutic level of feminising hormones (see Appendices 2 and 4) prior to breast augmentation surgery, to maximise breast growth and to obtain better aesthetic results.
- Penectomy, orchidectomy, vaginoplasty, clitoroplasty and/or labiaplasty requires two opinions, usually from members of the gender clinic team or network (one letter may have two signatories). The second opinion may also be from a GP with a special interest. Patients should have a written copy of the decision and referral letter(s). Eligibility criteria are as listed on p. 24, plus:
  - 12 months' continuous endocrine treatment as appropriate to the patient's goals (unless the patient has medical contraindications or is otherwise unable to take hormones). It is desirable for the patient's circulating hormone levels to be the same before surgery as will be the case afterwards;
  - at least 12 months' living continuously in a gender role that is congruent with the gender identity.

Factors conducive to successful outcomes

Peer support and mentoring

Societal prejudice can impair overall health and well-being, whereas peer support can reduce social isolation and distress. Peers can play an important role in providing support and encouraging the use of helpful organisations and resources. Because many people may be more comfortable talking to those who have been through similar experiences, they are more likely to trust their help and accept their advice. Clinicians should provide information on local and national resources.

Family support

There is evidence that for many people, family support is an important aid to successful transition. Clinicians should provide information about accessing family support. Regional clinics could facilitate setting up family workshops (see Appendix 5).

Hair treatments

Facial and body hair removal, hair transplantation and provision of hairpieces where appropriate will prevent risk of harm and help a woman live more successfully (see Appendix 6).

Image in the new social gender role

It is important for those experiencing gender dysphoria to have confidence in their ability to succeed in the new social gender role. The chances of success, especially during the early stage of gender role adjustment, will be considerably reduced where there is a poor self-image. This factor may have a negative impact on decisions about future treatment. Continual fear and exposure to risk of harm affects self-image and should be minimised and reduced by best practice throughout service provision.

Speech and language therapy

Speech and language therapists working with people aim to develop voice and communication skills that are congruent with age, physical appearance and consistent with the expectation of both the individual and society for that person's gender identity. Speech and language therapists may be involved in the care of both women and men (see Appendix 7).

Facial feminisation surgery

Facial feminisation surgery is considered by some to be an essential part of the transition process by women. This procedure involves cranial surgery and, depending on the amount of work undertaken, can take anything from 5 to 12 hours. Surgery can encompass scalp advancement, brow repositioning, removal of brow bossing on the forehead, re-contouring the orbital rim, cheek surgery, rhinoplasty, upper lip lift and the re-shaping of the jaw and chin.

Guidelines for hormone interventions

Hormone prescribing in this field, according to the principles below, and under the guidance of a specialist service, has been shown to be safe and can be undertaken mainly in primary care. Accepting the desire for the guidelines to be evidence based, there is a great paucity of such evidence. Hormone support is based on traditional patterns of treatment.

Only recently are treatment programmes being introduced based on the care of patients with endocrine gonadal disorders unrelated to gender dysphoria. In some people experiencing gender dysphoria, the changes associated with endocrine treatment may be sufficient and the person may not proceed to make other social changes or undergo any surgery.

Hormone support should be carried out as part of the care from a team or network that includes a clinical endocrinologist or using clearly developed protocols (see Appendices 2–4), with access to an endocrinologist if necessary. Endocrinologists involved should be conversant with the management of patients with gonadal disorders not due to gender dysphoria such as is encountered in patients with chromosomal, pituitary, adrenocortical or gonadal diseases.

Full discussion of fertility issues should precede endocrine treatment. There should be no differentiation between gamete storage in patients and the general population (see Appendix 8).

There should be awareness of the recently described complications of excessive and prolonged gonadal steroid replacement in menopausal women

especially if given in excessive amounts (Marjoribanks *et al*, 2012). Wherever possible, physiological end organ response should be the aim of any endocrine treatments. This should be based on management of circulating hormone levels to allow accurate and individual dose titration together with suppression of the hormone effects associated with the undesired gender. Treatment should be flexible and patient-led as far as is consistent with clinical safety and with the agreement of the prescriber, accompanied by a full explanation of the principles behind the treatment regimen and taking account of the individual's views of their needs.

Close liaison between the specialist clinician and GP should be maintained at all times. Physical assessment and ongoing haematological, endocrinological and biochemical monitoring is essential, preferably under agreed collaborative care protocols. As with all women, patients taking oestrogen therapies should be advised about breast awareness.

All patients receiving hormone therapies should be regularly reviewed to ensure that clinical well-being is maintained.

Choice of hormone preparation, method of delivery and dosage should be in line with current understanding of minimum health risks and maximum efficacy. The endocrine treatment protocols outlined in Appendices 2–4 are designed to deliver optimum results in the safest way, and should be suitable for the majority of people.[9] Additionally, research in this area is limited, and since the aim is to achieve greater comfort for the person, clinicians should respond flexibly to the individual's reaction to treatment, and it may be necessary to vary products and dosages accordingly. If necessary, this may be under specialist care.

Some patients may obtain hormones from the internet or other agencies. The clinician should discourage patients from using such sources but may offer monitoring and advice on the effects of such agents. The clinician should assist patients in obtaining hormones from properly authorised sources. A harm-reduction approach should be taken. Accordingly, hormones should not be stopped. A bridging prescription may be appropriate, and blood tests and health checks are undertaken to screen for contraindications.

When patients move between clinical services, appropriate endocrine treatment should continue to be offered.

For women the mainstay of therapy is oestrogen therapy and suppression of androgen secretion and action (see Appendix 2). For men, the mainstay of therapy is androgen therapy and suppression of oestrogen secretion and action (see Appendix 3).

Where androgen endocrine treatment results in high haemocrit and/or high haemoglobin or red blood cell levels, often called secondary polycythaemia, the man must not be denied androgen treatment. This is especially important when the man has had a hysterectomy or salpingo-oopherectomy. Polycythaemia is generally easily manageable by venesection or the alternative response may be to titrate and reduce the androgen dosage and/or the androgen peaks by using a short-acting topical androgen.

9. When prescribing an unlicensed medication, the GMC advise doctors that they must: be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy; take responsibility for prescribing the medicine and for overseeing the patient's care, monitoring, and any follow up treatment, or ensure that arrangements are made for another suitable doctor to do so; and make a clear, accurate and legible record of all medicines prescribed and, where you are not following common practice, your reasons for prescribing an unlicensed medicine (General Medical Council, 2013*b*: paras. 67–70).

Aftercare

Long-term monitoring should be offered once the patient is stabilised at the agreed end stage of the gender transition. Monitoring of the endocrine treatment should be directly available to the patient, without psychiatric or psychological involvement unless requested. A summary of commonly used preparations is listed in Appendix 4.

Surgical interventions

Genital reconstructive surgery

This is also termed gender reassignment surgery, sex reassignment surgery, gender realignment surgery and gender reconstructive surgery.

It is the surgeon's responsibility to determine that a referred patient's physical and mental well-being is sufficiently robust to undergo such a major irreversible procedure. The surgeon must see a copy of the opinion(s) confirming that genital or chest surgery should be offered in the circumstances specified in 'Opinions and eligibility criteria for gender treatments', pp. 24–26. A single opinion may suffice for a person with a Gender Recognition Certificate or of equivalent standing. If surgeons have doubts about the appropriateness of the surgery, they should consult with the referrer(s) before undertaking any procedure.

Role of the nursing team

The role of the nurse working with patients with gender dysphoria includes pre- and post-operative care. Ideally, contact would be made prior to surgery to establish a professional relationship between both parties. Information should be shared on aftercare.

Post-operative care consists of wound and physical care. Support to the patient, relatives, friends and carers may be offered. This may only be necessary for a short period of time until the patient has recovered both mentally and physically, and ready to resume normal life.

It is important that the nurse has knowledge of the needs of patients with gender dysphoria and of the surgery that is involved. It is desirable for the nurse to be able to liaise with the other disciplines.

It is essential that the hospital-based nursing team makes appropriate referral to the community team prior to discharge.

Genital surgery for women

Within the UK, feminising vaginoplasty (penectomy and bilateral orchidectomy with construction of a sensate clitoris, labia majora and vaginal formation) is in most cases performed as a single-stage procedure using tissue obtained from the penis and scrotum. When there is insufficient skin available (e.g. micropenis or more commonly, long-term endocrine treatment), the vagina may be constructed from bowel segments, usually the sigmoid colon. Patients who lack sufficient functional depth following an inversion penile scrotal skin vaginoplasty may also be candidates for salvage colonic vaginoplasty (see Appendix 9).

Hair removal from the donor site may be needed in many types of gender reconstructive surgery and will need to be undertaken well before surgery.

GENITAL SURGERY FOR MEN

Patients may request genital surgery as the final stage of reassignment. There are many options that can be tailored according to the patient's request. Patients who wish to have penetrative intercourse will need a total phalloplasty to house a penile prosthesis. Some patients do not wish to have a urethra and are content to sit to void, and this will reduce complications and the number of operations required.

Patients should have an in-depth discussion with regard to the current techniques. They should be shown photographs of typical results and, if possible, be able to speak to individuals who have had the desired operation. Patients should have the opportunity to choose any of the clinically appropriate techniques even if this means referral to another centre either in Europe or elsewhere (see Appendix 10). Currently, the Belgian technique for the forearm phalloplasty is a single-stage technique, whereas the British technique requires two shorter admissions several months apart. Both techniques defer implanting prostheses to an additional stage about a year after the original phalloplasty.

Hair removal from the donor site may be needed in many types of genital surgery. The surgical team will advise about the areas to be epilated which will depend on the surgical practice and the available tissue. This takes time and should be initiated well in advance of the proposed surgery.

CHEST SURGERY FOR WOMEN[10]

Surgery is usually undertaken as a day case, under general anaesthetic. The incision is either placed submammary or in the axilla and a saline or silicone gel prosthesis is inserted into a submuscular pocket, or sometimes subglandularly if there has been a good response to hormone therapy. Implants are designed for a female chest and therefore tend to be rather narrow for the broad male chest. Also, males tend to have their nipples rather lateral in position compared with females.

The principal complication is encapsulation or hardening around the prosthesis which occurs in one in ten cases.

CHEST SURGERY FOR MEN[10]

In small-breasted patients who have good, thick skin on their breasts, mastectomy can be achieved through a periareolar incision. Using this procedure it is difficult to achieve the correct amount of reduction. In some, an over-reduction is achieved which in most cases cannot be corrected as a secondary procedure.

For most patients, however, a more extensive reduction is required, removing the breast as an ellipse and trying to place the scar in the submammary groove – the nipple is repositioned as a free graft. Although

10. Written by Mr Dai Davies, Royal College of Surgeons.

this gives a more obvious scar it is an easier and more predictable operation to undertake and patients, on the whole, are happier with this approach.

The operations are usually done with a one-night stay, as there is a slight risk of haematoma, and then managed on an out-patient basis after that. Follow-up usually continues to 6 months when a decision may be made as to whether any small adjustments are required. These are usually done under local anaesthetic. If a patient requires phalloplasty then there is an argument for undertaking mastectomy at the time of the phalloplasty, as the spare skin can be used to resurface the forearm when a radial forearm free flap is undertaken.

Follow-up and general medical care

Men and women should be offered information on breast awareness and screening as advised by current national guidelines.

Women should be offered advice as appropriate in relation to prostatic disease as prostatectomy is not part of genital reconstructive surgery.

Men should be offered ongoing screening for cervical disease (if relevant) as advised by current national guidelines and remain on the cervical cytology recall service.

The risk of developing ovarian carcinoma if the ovaries remain *in situ* once androgen therapy commences is unknown but unlikely to be different to that of nulliparous women whose lifetime risk is slightly greater than that of women who have been pregnant. Endometrial cancer is a high risk for men who have a uterus while their body is aromatising 'unopposed oestrogen' derived from testosterone. In this respect it is assumed that they will have the same negative response as natal females with a uterus who have the same 'unopposed' oestrogen exposure. It is generally recommended that men consider hysterectomy after 4–5 years on testosterone due to this increased risk. Some men in this situation, and also those with a familial history, may request a hysterectomy much sooner due to increased risk.

In view of increased risk of reduction of bone mass secondary to treatment, bone densitometry should be offered as appropriate, as advised by current national guidelines.

Access to all other medical services should be on an equitable basis with those offered to all other individuals in similar circumstances.

Patients should continue to be seen by psychological and surgical specialists for as long as necessary. The opportunity should be provided for direct referral back to specialist clinicians or clinics at any time in the future if requested.

Appendix 1 The needs of people with intellectual disabilities who have gender dysphoria*

Within this section, the needs of people with an additional diagnosis of intellectual disability will be identified. For clarification, an intellectual disability will be defined as having an IQ of 70 or below, as outlined in ICD-10 (World Health Organization, 1994) or where a health or social care learning disability service has recognised the need for involvement.

This document has clearly outlined the process required for assessment and access to treatment for individuals requiring gender reassignment treatment. However, the needs of people with intellectual disabilities are often greater, not only in accessing services but in understanding that the condition, treatment and consequences can be difficult, as outlined by the Department of Health (2001), and such individuals often require additional support to access treatment by learning disability services. Individuals referred should have the opportunity for the following.

- A person-centred plan implemented by the learning disability service which would outline their holistic needs including the gender need.
- Access to counselling/psychotherapy prior to referral to a gender clinic, with further counselling/psychotherapy provided if not accepted for treatment.
- Access to counselling/psychotherapy will be required if accepted for treatment. This may not need to be a constant service. However, it would be needed prior and during the real-life experience, prior to and at the start of hormone treatment, and pre and post any surgical treatment.
- Counselling/psychotherapy should be provided, where possible, by a professional who has experience of both intellectual disability and gender identity issues. Where this is not possible, supervision should be sought from a suitable source where the experience is available.
- A support network will be required for the individual which might be identified from the person-centred planning group to support the individual throughout the gender treatment process. This support network should include a community learning disability nurse and/

*Written by Mr Daniel Wilson, CONSENT (Consultancy, Sexuality Education and Training).

or social worker and an advocate support worker. This support will be provided during the entire gender reassignment process.

- Where learning disability services are involved, the individual's capacity to consent to treatment should be considered and assessed by the multidisciplinary team. Lack of capacity to consent is not a reason to stop the referral process. However, a decision to act in the individual's best interests should be considered.
- Gender clinics that have concerns about an individual having an intellectual disability and their ability to understand and consent should refer the individual to their local learning disability service for assessment of intellectual disability. If diagnosed with an intellectual disability, the services described earlier should be implemented.

Appendix 2 Guidelines for hormone therapy for gender dysphoria in trans women and post-genital operation or gender recognition certificated women*

Suppression of testosterone secretion and provision of oestrogen therapy

It has been traditional to use the androgen receptor-blocking drug cyproterone acetate or the potassium-retaining diuretic spironolactone, which has similar effects, to suppress the effects of circulating androgens such as testosterone, dihydrotestosterone, androstenedione and dehydro-epiandrosterone (DHEA). There may be problems, however, with the use of cyproterone acetate, which is, at least in part, dose dependent. High doses of cyproterone acetate are associated with glucocorticoid effects, although this is more apparent in children and adolescents than adults. Hepatotoxicity is recognised in animal models on long-term therapy and indeed hepatic tumours occur in rats. Although this has not clearly been seen in humans, hepatic dysfunction does occur rarely. The Medicines and Healthcare products Regulatory Agency has issued a warning of potential risk of (multiple) meningiomas (Medicines and Healthcare products Regulatory Agency, 2009). Cyproterone can also cause depression. Spironolactone causes elevated potassium and low sodium levels in the blood. There are alternative and preferable ways of suppressing secretion of endogenous androgens and their effects.

Instead of using cyproterone acetate, a more effective alternative is to use depot injections of analogues of the gonadotrophin-releasing hormone. Examples of this would be depot goserelin or leuprorelin. A usual dose of goserelin would be the use of a subcutaneous implant of 3.6 mg once every 4 weeks or 10.8 mg every 3 months. This produces reversible 'chemical gonadectomy'. By super-stimulation of the pituitary, the gonadotrophin-releasing hormone receptors on the pituitary are downregulated and the pituitary rapidly becomes unresponsive, leading

*Written by Professor Mike Besser, Royal College of Physicians.

to cessation of secretion of the gonadotrophins. Leuteinizing hormone and follicle-stimulating hormone levels fall to hypopituitary levels and testosterone and dihydrotestosterone levels decline to very low levels equivalent to a post-gonadectomy state. If the treatment is stopped, the receptors regenerate and gonadotrophin secretion resumes. There is therefore a state of reversible hypogonadism. Gonadotrophin-releasing hormone therapy may be continued until gonadectomy. Secretion of the circulating adrenal androgens, androstenedione and DHEA is not suppressed but they have low androgen potency but may be converted to testosterone and dihydrotestosterone. If necessary, their effects may be mitigated by the use of finasteride, a drug which inhibits the conversion of testosterone to the much more active dihydrotestosterone. In the rare event of persisting effects of androgenisation, a low dose of cyproterone or spironolactone could be introduced since these compounds block the androgen receptor. Suppression of the levels of androgens and their effects given this way allows the full effect of administrated oestradiol to become apparent without the use of excessive dose. Circulating levels of testosterone and, ideally, dihydrotestosterone levels should be monitored to ensure they are suppressed to well below the normal male range.

Oestradiol therapy should normally be used in association with suppression of androgen secretion.

Oral doses of oestradiol 1–6 mg/day are commonly required. Circulating oestradiol levels should be monitored to make sure that appropriate levels are achieved and that the dose given is not excessive – levels at 24 h after a dose of oestradiol should be in the upper half of the normal follicular phase serum oestradiol levels. It is wise to check circulating lipid levels and liver function tests since some patients experience obstructive hepatotoxic effects of oestradiol. Blood pressure should be monitored. If surgery is to be undertaken, it is usual to stop oestrogen replacement therapy 4 weeks prior to surgery.

Oestrogen replacement therapy has traditionally been given using oral equine oestrogen mixtures or ethinyloestradiol. Neither of these is physiological for the human and there is a major problem in that they cannot be measured effectively in relation to physiological human circulating levels of oestrogen. These adverse features are avoided if oestradiol is used. Oestradiol is a physiological hormone in women and the physiological levels in the circulation are well established. Different patients require different doses to achieve the female physiological level of circulating oestradiol in the upper half of the normal follicular phase of the normal menstrual cycle (e.g. anything from 1 mg to 6 mg per day by mouth). Different laboratories report different normal ranges for hormonal assays depending on the methods used. Clinicians should use their local laboratory normal range for follicular phase serum oestradiol levels – a representative range for the upper half of the follicular range is 300–400 pmol/l or 80–140 pg/ml. Levels higher than this may be associated with the established side-effects of excessive oestrogen, particularly thromboembolism, hypertension and myocardial infarction. Physiological levels should be able to produce the desired phenotypic changes, particularly if the circulating androgen levels and their effects are suppressed. Transcutaneous oestradiol using 50–150 mcg patches two or three times a week can be used and monitored serum levels of oestradiol at 48 h after application of a patch should be in the upper half of the normal follicular range. Oestradiol gel (two or three measures daily) can also be used and serum monitoring should occur at 24 h.

Biochemical and haematological markers

See Appendix 4.

Physical assessments

Before commencing hormones, a full physical examination should be offered by the GP or hormone prescribing clinic. The prescribing physician should satisfy themselves that a recent clinical examination has been recorded in the medical notes.

Genital examination may cause individual distress and may be declined by the patient: such refusals should be respected in all cases.

Routine screening for prostate malignancy should be offered in accordance with current good practice guidelines and specifically where persistent urinary symptoms are reported.

Five-year monitoring for breast cancer should be undertaken. Breast awareness information should be offered by the prescribing unit.

If gonadectomy is carried out, then the use of a gonadotrophin-releasing analogue must cease.

Appendix 3 Guidelines for hormone therapy for gender dysphoria in trans men and post-genital operation or gender recognition certificated men*

Suppression of oestrogen secretion and provision of testosterone therapy

The use of a long-acting analogue of a gonadotrophin-releasing hormone such as goserelin as detailed in Appendix 2 will rapidly but reversibly suppress leuteinizing hormone, follicle-stimulating hormone and ovarian function.

Testosterone replacement therapy can be started at the same time. It has been usual to use depot testosterone injections such as testosterone enantate or the mixed testosterone esters preparation Sustanon® 250 mg intramuscularly every 2–3 weeks. Sustanon® 250 mg has been approved for the supportive treatment of men. This dose may need to be increased and most patients are maintained well on 500 mg every 3–6 weeks. A more recently introduced depot intramuscular preparation of testosterone undecanoate can be given (Nebido® 1 g every 3 months). The basis of the dosage regimen should rely on the measurement of circulating testosterone levels just before an injection is given. The idea is to achieve a circulating testosterone level just prior to an injection at or below the lower end of the normal adult male range so that accumulation does not occur.

An alternative medication involves the use of a transdermal gel, which is applied daily in a dose of 5 g, rubbed usually on to the shoulders or loins after a morning shower or bath. Transdermal patches of testosterone can be used but are frequently poorly tolerated and may induce a reaction to the medication in the patch. Another alternative is oral testosterone undecanoate, but the dosage cannot be monitored effectively by using serum testosterone. This is because this preparation is absorbed across the gut into the lymphatic system and does not undergo 'a first pass' effect

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in the liver. Since the gut wall contains high levels of the enzyme 5-alpha-reductase, testosterone is converted to the much more biologically active dihydrotestosterone in the gut. Circulating testosterone levels are often at or below the normal male range, whereas dihydrotestosterone levels are supraphysiological for men on this preparation. Sometimes the oral preparation is preferred to transdermal or intramuscular administration and if this is the case, monitoring of the dosage should be based on circulating dihydrotestosterone levels in blood obtained 3–4 h after a dose. The doses of testosterone undecanoate vary from 40 mg three times a day to 80 mg twice daily.

Men treated with androgens should have monitoring of haemoglobin and haematocrit since high haemoglobin levels may be induced with high doses. It is unusual to get liver dysfunction on these preparations.

If gonadectomy is carried out, then the use of a gonadotrophin-releasing analogue must cease.

Biochemical and haematological markers

See Appendix 4.

Physical assessments

Before commencing hormones, a full examination should be undertaken. The prescribing physician should satisfy themselves that a recent clinical examination has been recorded in the medical notes.

Genital examination is not necessary if a pelvic ultrasound is undertaken. This should ideally be done transvaginally but may be transabdominal if the patient objects to the former.

Breast monitoring should continue in accordance with current good practice guidelines.

Appendix 4 Hormonal treatment: a suggested collaborative care protocol

Endocrine normal ranges differ between different laboratories as methods of assay are not always the same. Clinicians should use their local laboratory ranges when interpreting results as reported. Levels quoted here are indicative only. Monitoring should normally take place in a primary care setting.

Women

Monitoring tests

Patients should be encouraged to stop smoking, take regular exercise, have a sensible diet and consume no more than 14 units of alcohol per week.

Baseline

Blood pressure, full blood count, urea and electrolytes, liver function tests, fasting blood glucose, lipid profile, serum free thyroxine T4, thyroid-stimulating hormone, testosterone, oestradiol (less than 100 pmol/l) and prolactin (50–400 mU/l).

Monitoring

On a 6-monthly basis for 3 years and then yearly depending on clinical assessment and results. Provision of prescription is contingent on patients understanding the risks and benefits that may result due to the need to take the following tests: blood pressure, full blood count, urea and electrolytes, liver function test, fasting glucose, lipid profile, testosterone, serum oestradiol 24 h after a tablet or 48 h after a patch (levels should be in the upper half of the normal follicular range, 300–400 pmol/l) and prolactin (less than 400 mU/l).

Medication

In the first instance, a specialist clinician will provide the prescription or, if the GP is in agreement with collaborative care prescribing and the patient

attends a gender specialist service, this will be supervised by the gender specialist who has obtained valid consent. Typical prescriptions would be for:

- oestradiol (1–6 mg orally daily)

OR

- oestradiol gel (two to four measures daily) or patches (50–150 mcg, two to three times per week), particularly for patients over 40 years (lower risk of thrombosis). Dosage of oestrogen depends on the results of monitored circulating oestradiol levels (see p. 34);
- goserelin 3.6 mg implant subcutaneously once every 4 weeks or 10.8 mg implant once every 12 weeks, or an alternative gonadotrophin-releasing hormone agonist – inhibits secretion of pituitary gonadotrophin and testosterone secretion.

Additional therapies, which may be helpful, include:

- cyproterone acetate[11] (50–100 mg orally daily) – it is much less satisfactory than goserelin;
- Dianette® (1 tablet daily for 21 days; repeat after 7 gap days), which contains cypoterone acetate and an oestrogen;
- spironolactone[11] (100–400 mg orally daily) may be required for additional androgen receptor blockade – long-term use associated with liver dysfunction and possibly hepatoma risk (animal data);
- progesterone is not usually indicated since no biologically significant progesterone receptor sites exist for biological males. Medroxyprogesterone acetate (100 mg orally twice daily) or dydrogesterone (10 mg orally twice daily) has been used;
- finasteride (5 mg orally daily) – blocks conversion of testosterone (which may derive from adrenal androgens in the absence of secreting testes) to the more active dihydrotestosterone. It can discourage male pattern hair loss and testosterone-dependent body hair growth.

Surgery

- Stop hormones 4 weeks before surgery and cover with a single dose of subcutaneous goserelin 3.6 mg. Hair regrowth can occur when the effects of goserelin wear off after approximately 4 weeks.
- Hormones should be resumed 4 weeks post-operatively if there are no complications, namely oestradiol tablets or patches for patients over 40 years (see above).
- Anti-androgen usually not required but androgens may still be significantly derived from adrenals – finasteride can be prescribed if androgen effects are still of concern after approximately 6 months.
- Monitoring for osteoporosis, breast and prostate carcinoma required.
- Medication and tests needed for life on 6-monthly basis for 3 years, then yearly if well (see p. 39).

11. Cypoterone and spironolactone are not recommended for long-term therapy unless there are no good alternatives, as side-effects may occur (see p. 34).

Men

Monitoring tests

Patients should be encouraged to stop smoking, take regular exercise, have a sensible diet and consume no more than 14 units of alcohol per week.

Baseline

Blood pressure, full blood count, urea and electrolytes, liver function tests, fasting glucose, lipid profile, serum free thyroxine T4, thyroid-stimulating hormone, prolactin (less than 400 mU/l) and serum oestradiol and testosterone.

Monitoring

On a 6-monthly basis for 3 years and then yearly if well, depending on clinical assessment and results. Provision of prescription is contingent on patients understanding the risks and benefits that may result due to the need to take the following tests: blood pressure, full blood count (haemoglobin and haematocrit), urea and electrolytes, liver function tests, fasting glucose, lipid profile, serum oestradiol (for adequacy of suppression less than 70 pmol/l) and prolactin (less than 400 mU/l).

Serum testosterone should be at or below lower end of normal range (<10 nmol/L) just before next dose is due to avoid accumulation or inadequate dosage. If on oral testosterone, measure dyhydrotestosterone levels 3–4 h after a dose.

Medication

- Goserelin 3.6 mg implant subcutaneously once every 4 weeks or 10.8 mg pellet subcutaneously once every 12 weeks.
- Testosterone enantate or Sustanon® (mixed testosterone ester) 250–500 mg intramuscularly two to six times weekly depending on serum testosterone levels (see above).

  OR
- Testogel® (50 mg/5 g gel once daily – occasionally two doses are required), rubbed into the shoulders or loins after shower or bath.

  OR
- Testosterone undecanoate 120–160 mg/day orally or 1 g intramuscularly every 3 months.

Surgery

- Hormones do not need to be stopped pre-operatively.
- Androgen (testosterone) should be continued for life if there are no contraindications.
- Monitoring for osteoporosis, cervical and breast carcinoma is required.
- Medication and tests needed for life on 6-monthly basis for 3 years, then yearly if well (see p. 41).

Appendix 5 Family support*

Transsexualism within a family often puts huge strains on relationships, creating a high risk of rejection of the individual, just when support is most needed. Poor support from the family is a recognised prognostic factor for a person's experience of regret following gender reconstructive surgery.

Family members themselves experience complex emotions of shock, grief, anger, bewilderment, fear, guilt, denial and embarrassment. Partners and spouses, in addition, have to face the disruption to their sexual relationships. There may be mutual accusations of selfishness as the individual, sometimes after years of delay, focuses on achieving all transitional goals as quickly as possible, while the family grapples with an entirely unanticipated situation, and may seek to delay, or even prevent, transition. The denial of contact between people and their children causes great suffering, but it is not unusual, despite the research indicating that such contact is not harmful to a child, whereas loss of a parent is.

Support and education for families in the early stages of transition can often prevent deterioration of, or lead to significant improvements in, relationships by mitigating the experience of pain and loss. Family acceptance is an important, sometimes vital, ingredient in the successful rehabilitation of the individual in the new gender role. Engagement with the family should, therefore, form a part of the care package offered to individuals. However, this should only be implemented if and when the person is entirely comfortable with family involvement, and should not be a precondition to treatment.

Family support may best be provided by someone other than clinicians. A formula may be based on the workshops run by the Gender Identity Research and Education Society (www.gires.org.uk), assisted by Depend (www.depend.org.uk) and Mermaids (www.mermaidsuk.org.uk). The team leading the workshop should include parents, partners, a man and a woman. Families need an informal, caring and absolutely confidential setting in which to explore and share their emotions and fears with others in the same situation. The aims of the workshops are to encourage optimism about the future, to promote open discussion of the many difficulties faced by people, to lessen the tension between them and their families, and to enable families to support them.

*Written by Mrs Terry Reed, Gender Identity Research and Education Society.

Appendix 6 Hair treatment*

Androgens stimulate the conversion of fine vellus hair into large terminal hair in many regions of the skin following puberty. The growth of pubic and axillary hair is stimulated by low levels of androgens, probably of adrenal origin. Higher levels of gonadal androgens are needed to stimulate hair growth on the beard area, trunk and limbs and, in these sites, terminal hair growth is dependent on the potent androgen dihydrotestosterone, which is derived from circulating androgens (principally testosterone) by the action of the enzyme type II 5-alpha reductase. These changes are most pronounced in men but they also occur in some women, particularly those with hyperandrogenism. Paradoxically, androgens are also responsible for the progressive miniaturisation of hair follicles on the scalp that cause balding.

Men castrated before puberty do not show these androgen-dependent changes in hair growth. In men castrated post-puberty, some reversal may be seen. The degree of reversal appears to depend on the age at androgen ablation – in young men terminal hair growth may be fully reversed by gonadectomy but with increasing age the degree of reversal becomes progressively less (Hamilton, 1958). Limited studies in male castrates suggest that androgen ablation in men aged over 30 reduces terminal hair growth by less than 50%. The same considerations apply to male balding (Hamilton, 1942). These observations indicate that androgens alter gene expression in androgen-dependent hair follicles, which is not fully reversible in the absence of androgens. This view is supported by numerous studies on the treatment of female hirsutism with anti-androgens.

We may expect, therefore, that androgen ablation, either chemical or surgical, will produce a substantial degree of androgen-dependent hair growth reversal in young men, although there is likely to be interindividual variation in the response. Women may also be taking oestrogens. In other species, oestrogens inhibit hair growth but very little is known about the effect of oestrogens on human hair growth and we cannot assume that oestrogen therapy influences terminal hair growth. Where terminal hair growth is well established, androgen ablation will, at best, result in only partial reversal and other methods of hair removal may be needed. Methods such as shaving and waxing are widely used but their effect is, of course, temporary. To date there are only two methods of hair removal which have the potential to be permanent – electroepilation (electrolysis) and laser hair removal, neither of which is readily available on the NHS.

*Written by Professor Andrew Messenger, Royal College of Physicians.

ELECTROEPILATION

This is practised mainly by beauty therapists. It involves the insertion of a fine needle into each hair follicle individually; the follicle is then destroyed by thermal and/or electrolytic forces by the passage of an electric current through the needle. Electroepilation is slow and tedious, typically requiring repeated treatments over many months or years, but good results can be obtained if done by an expert. It is most suitable for treating small areas of unwanted hair growth, such as the chin or moustache area. It is not appropriate for treating hair growth over extensive regions of the skin, such as the chest or limbs.

LASER HAIR REMOVAL

Light energy from the laser source is absorbed by melanin in the hair roots and converted to heat, which then destroys the hair follicle. The laser source is applied to the skin surface and several follicles can be treated simultaneously, meaning it is a much more rapid treatment than electroepilation. Laser hair removal is most effective in those with dark hairs and fair skin, but modern lasers are also able to treat those with racially pigmented skin. It is not suitable for treating non-pigmented hairs. Laser hair removal is expensive and treating large areas of skin is still a major undertaking. Permanency is not guaranteed and, like electroepilation, repeated treatments may be needed. Side-effects include scarring, pigment changes in the skin and, rarely, increased hair growth. Effective treatment may require access to more than one type of laser.

TOPICAL AGENT

A topical agent containing the ornithine decarboxylase inhibitor called eflornithine is available. It has recently been licensed in the UK for treating facial hirsutism in women. There are no published peer-reviewed studies but data presented at academic meetings suggest that it reduces hair growth by about 20%. There is no information on its use in men. Continued treatment is needed to maintain the response.

Appendix 7 Speech and language therapy*

Referral

- Speech and language therapists should ideally work as part of a recognised multidisciplinary team, with established links to its members, especially psychotherapist colleagues.
- Only after a confirmed diagnosis of gender dysphoria has been established will a patient be assessed for suitability for voice and communication therapy.
- A referral to a speech and language therapist should only be accepted if the therapist is clinically competent in this specialised area.

Assessment and readiness for therapy

- Therapeutic intervention will be mindful of the physical limitations of the patient's vocal anatomy enabling change without causing vocal abuse/damage (Dacakis, 2002; Adler *et al*, 2006).
- Intervention will be timely and take into account the person's ability to participate in therapy (Söderpalm *et al*, 2004).
- It will be consistent with current research/agreed expert opinion.
- Any pre-existing voice difficulty will be treated before voice modification (Taylor-Goh, 2005).
- Regular therapy will usually commence when the patient is 'living in role' or transition is imminent in order to maximise voice/ communication changes.
- Case history will include a detailed voice assessment to gain values of both perceptual and objective measures where facilities are available.

*Written by Ms Jane Thornton, Royal College of Speech and Language Therapists.

THERAPEUTIC INTERVENTION (GENERAL)

- The amount of therapy required will be variable and take into account the patient's own expectations, their natural vocal ability and their commitment to therapy.
- Therapy contracts between therapist and patient are commonplace and can be re-negotiated at any point in the patient journey.
- Therapy may be offered on an individual basis or in groups (Chaloner, 2000), with use of biofeedback to support therapy. Different communication styles and situations will be addressed.
- Therapists will regularly evaluate progress in line with clinical practice guidelines.
- It is recognised that in some locations it may be the speech and language therapist who offers advice on style and appearance. Counselling/psychotherapy should be provided by appropriately trained team members.

THERAPY WITH WOMEN

The introduction of female hormones will have no effect on the male voice. Therefore, other factors known to mark the difference between male and female voices have to be enhanced to give the individual a more 'feminine' voice. Research has highlighted (Oates & Dacakis, 1997; Gelfer & Tice, 2013) key communication areas where males and females differ, for example voice quality, pitch, intonation, prosody, rate, articulation, resonance, language and non-verbal communication.

THERAPY WITH MEN

The introduction of male hormones in men will lower the pitch of the voice, although the degree and rate of change is variable (Van Borsel *et al*, 2000). Therapy may be offered at this time to help stabilise the voice and laryngeal support musculature that will have been physically altered by the male hormones. However, it is not simply lowering the pitch that will make the voice appear more masculine (see above). Other aspects of the voice/ communication will determine 'maleness' to the listener and these should be addressed during assessment.

SURGICAL INTERVENTION

WOMEN

- Pitch-changing surgery may be offered but this should only occur after speech and language therapy intervention and should be decided jointly by the consultant ear, nose and throat surgeon, psychiatrist, speech and language therapist and patient (Matai *et al*, 2003; Parker,

2008). There are various procedures of which, currently, the most preferred for women is cricothyroid approximation. This may precede or follow other types of gender-change surgery and should be followed by further voice-therapy review to optimise surgical results (Antoni, 2007). Objective results are variable at present (Wagner *et al*, 2003), although personal satisfaction rates are high (Kanagalingam *et al*, 2005).

- Thyroid chondroplasty may also be offered to reduce the prominence of the thyroid cartilage for cosmetic appearance (Sandhu, 2007).

Men

Pitch-changing surgery for men is not as well developed. There have been attempts to lower the pitch further with surgery (e.g. Isshiki type III thyroplasty), but both subjective and objective results are not favourable at present.

Support mechanisms and continuing professional development

- Adults with gender dysphoria are likely to form a small part of a voice therapist's case-load unless the therapist is attached to a gender clinic. It is therefore essential that access to specialist colleagues and national support networks is available.
- Regular updating of clinical skills is advised through designated courses, study days and individual learning opportunities.

Discharge

Discharge will be at the discretion of the speech and language therapist following discussion with the patient. Reasons for discharge may include any of the following:

- successful completion of the therapy aims and objectives
- no further progress deemed possible
- patient is unable to commit to therapy/practice required to achieve therapy goals.

Appendix 8 Storage of gametes*

If a person seeks advice on storage of gametes then they should be put in touch with a fertility centre offering licensed treatment. A list of centres in the UK can be found at the Human Fertilisation and Embryology Authority's website (www.hfea.gov.uk).

Gametes can only be stored if the provider has given appropriate informed consent. The implications of the storage of sperm or eggs will require careful counselling/psychotherapy. The provider will have to undergo testing for blood-borne viruses including HIV, hepatitis B and C. A support infrastructure, including hepatology services, should be available to deal with screening positive individuals.

The normal maximum storage period of gametes is 10 years. However, in the case of the transsexual individuals this can be extended up to a maximum of 55 years. Centres will normally contact all individuals with gametes in storage on an annual basis to ensure that continued storage is desired. It is the responsibility of the gamete provider to ensure that the clinic is aware of the individual's contact details for this purpose. The clinic may be required to destroy stored samples if the provider fails to keep in touch with the clinic.

Gametes can be stored only after appropriate consent has been given. The centre offering storage will be required to register with the Human Fertilisation and Embryology Authority the fact that sperm or eggs from the named provider have been stored in accordance with statutory guidance. Gametes can be stored for use in the treatment of a named individual, in the treatment of others (sperm/egg donation) or for research. If the specimen is to be used for treatment subsequently, then further counselling/psychotherapy and consent issues will have to be addressed before treatment can take place, including reference to the welfare of any child that might result from treatment.

Hormonal therapy has the potential to disturb the endocrine control of gametogenesis. It is advisable for individuals who wish to store gametes to stop therapy before provision of sperm specimens or undergoing treatment to procure eggs.

Storage of sperm

Providers of sperm will be expected to produce five to ten ejaculated semen samples over a period of several weeks. If sperm quality is satisfactory this

*Written by Dr Mark Hamilton, Royal College of Obstetricians and Gyneacologists.

will allow the samples to be split and stored in separate straws or vials, allowing for 10–15 cycles of opportunity for conception through artificial insemination in the future. If sperm quality is poor then discussion may be required regarding the use of assisted reproduction procedures such as *in vitro* fertilisation in the future. Should the individual be unable to ejaculate, the clinic may be able to offer alternative methods of obtaining sperm through surgical sperm retrieval or electro-ejaculation.

Storage of eggs

Egg quality, unlike sperm quality, is greatly influenced by the age of the female. Female fertility in the late 30s and beyond tails off dramatically and even *in vitro* fertilisation techniques are associated with poor success rates. In younger individuals the use of assisted reproductive technology techniques can be considered. Providers of eggs would be required to undergo a cycle of controlled ovarian stimulation leading to egg recovery in order to obtain a reasonable number of eggs for storage. The process of stimulation can take as long as 5 weeks to complete and involves injections of gonadotrophins to stimulate the ovary to generate multiple follicular development. Under ultrasound guidance and with sedation, vaginal oocyte retrieval can be performed. On average, between 8 and 12 eggs can be obtained in this way. Egg storage as a technique is not as reliable as sperm storage and pregnancy rates through the transfer of embryos derived from cryopreserved eggs are as low as 2% per egg frozen. If the egg provider has a male partner, consideration can be given to fertilising the eggs with his sperm. The generation of embryos in this way would offer the possibility of transfer of the embryos into a surrogate host. Embryo cryostorage is more reliable than egg storage and pregnancy rates of up to 20% per embryo transfer cycle can be anticipated with frozen embryos. Consent of the sperm provider for storage or use of embryos derived from his sperm is obligatory. Surrogacy raises further complex ethical questions, which require the input and expertise of counsellors trained in the field.

Storage of ovarian tissue

Freezing of ovarian tissue is experimental at present and it is unlikely that this will be available as a clinical service in the near future.

Changing or withdrawing consent

Any consent relating to the use and storage of gametes or embryos can be changed or withdrawn at any time by the person who gave the original consent as long as the gametes or embryos concerned have not already been used in treatment or research. The right to change or withdraw consent is an important part of effective consent in ensuring that clinics adhere to the wishes of the provider. Any consent for storage that is given to a clinic should include a statement of what should happen to the gametes or embryos in the event that an individual becomes mentally incapacitated or dies.

Appendix 9 Genital surgery for trans women or certificated women*

There is no level 1 or 2 evidence (Oxford levels) supporting the use of feminising vaginoplasty in women but this is to be expected since a randomised controlled study for this scenario would be impossible to carry out. A useful review of the evidence of the benefits and adverse outcomes of feminising vaginoplasty in female transsexuals is reported by Peter Day. In his report '593 possibly relevant articles in abstract form were identified of which 70 articles were retrieved in full text. Ten studies were selected for appraisal after the application of the inclusion and exclusion criteria. The study designs of the included studies comprised one systematic review, one prospective controlled study, one retrospective cohort study and seven quasi-experimental studies' (Day, 2002: p. 6). He concluded that 'gender reassignment surgery may benefit some carefully assessed and selected transsexual people who have satisfied recognised diagnostic and eligibility criteria, and have received recognised standards of care for surgery. More research is required to improve the evidence base identifying the subgroups of transsexual people most likely to benefit from sex reassignment surgery' (p. 7).

Positive outcomes in the non-controlled studies were reported in areas of cosmetic appearance, sexual functioning, self-esteem, body image, socioeconomic adjustment, family life, relationships, psychological status and satisfaction. However, these 'benefits' were not validated. Significant morbidity can include urethral stenosis or swelling from retained corpus spongiosum, vaginal stenosis or loss of vaginal depth due to necrosis of the penile skin flap, vaginal prolapse, lack of clitoral sensitivity or painful clitoral sensation, necrosis of labial flaps, patient concerns regarding cosmetic outcomes, thromoembolic events including deep venous thrombosis and pulmonary embolism which may be fatal, haemorrhage, and rectal injury requiring faecal diversion (Goddard *et al*, 2007). Rarely, a patient may request reversal of the genitoplasty.

Current retrospective short- and intermediate-term follow-up studies suggest about 80% of patients undergoing feminising vaginoplasty are pleased with the function and cosmetic outcome of their operation (Krege *et al*, 2001; Goddard *et al*, 2007; Tugnet *et al*, 2007). The remainder are pleased that they underwent surgery but report that their pre-operative expectations have not been met with post-operative reality. The majority of these patients may benefit from secondary surgery. It is clear therefore

*Written by Mr Tim Terry, British Association of Urological Surgeons.

that the vast majority of patients, at least in the short and intermediate term, derive important benefits from feminising vaginoplasty at a low risk of serious complications (Krege *et al* 2001; Lawrence, 2003). Other researchers have reported excellent outcomes from feminising vaginoplasty when stringent selection criteria are used and a good surgical result obtained (Green & Fleming, 1990; Eldh *et al*, 1997). However, the long-term surgical, psychological, social and sexual benefits/hazards remain unquantified. As such, it is important to undertake high-quality, multicentre, prospective, long-term studies to determine the risks/benefits of feminising vaginoplasty. Such studies should be restricted to specialist centres with a proven track record in gender reassignment surgery and standardised protocols for patient selection.

Appendix 10 Genital surgery for trans men or certificated men*

The current options available in the UK are listed below. Patients must be warned that all of the surgeries involve multiple stages, and complications may occur. Consent forms and information sheets, explaining all expected outcomes, including potential complications and risks, must be provided several weeks in advance of surgery.

Metatoidoplasty

This involves releasing the clitoris and bringing the urethra to its tip, thus forming a micropenis. The scrotum is fashioned and testicular prostheses inserted at a second stage. Patients will be able to stand to void but only 50% will be able to use a male urinal as the microphallus is too small. Otherwise it is a simple one- or two-stage operation, but penetration for sex is usually not possible due to phallus size.

Total phalloplasty

Pubic phalloplasty

A good-size phallus is fashioned from lower abdominal wall skin that has had laser hair removal prior to the initial operation. Alternatively, patients can use depilatory creams or shave the phallus. The urethra is formed from labial hairless skin in two stages but often the opening is 1–2 in from the tip of the phallus. All scars are low down on the abdomen and below the underpant line.

Forearm flap phalloplasty

The phallus is fashioned from the depilated skin of the forearm with a urethra incorporated within. The vessels and nerves of the forearm skin are divided and joined to vessels and nerves in the genital area. The phallus is sensate, is cosmetically realistic, and the patient can void from the tip of the phallus. The main disadvantage is the unsightly resulting scar on the arm that has been skin-grafted. Once the total phalloplasty has been completed and urethral continuity established, patients are offered testicular and penile prostheses and the formation of a glans. Often hysterectomy and oophorectomy can be performed at the same time as one of the stages, either by open or laparoscopic techniques.

*Written by Mr David Ralph, Royal College of Surgeons.

Appendix 11 Supplementary reading

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Cureus

Open Access Review Article

DOI: 10.7759/cureus.1984

Transgender Associations and Possible Etiology: A Literature Review

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Abstract

Transgender or gender dysphoria has been defined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), as distress resulting from the incongruence between one's experienced gender and one's assigned gender, along with a persistent and strong desire to be of another gender, and accompanied by clinically significant distress. Adolescents referred for evaluation often want hormonal therapy and several among them also express a desire for gender reassignment surgery. Furthermore, evidence shows that adolescents and adults with gender dysphoria without a sex development disorder, before gender reassignments, are at increased risk for suicide. For this review, a search of the English language scientific literature was conducted using the PubMed database. This summary discusses the associations and comorbidities of gender dysphoria and reiterates the evidence that its etiology is multifactorial. Transsexualism involves prenatal neuroanatomical changes, has a psychiatric association, and is found to be more prevalent in conjunction with schizophrenia and autism spectrum disorders. Childhood adversities and neglect are also linked to having a transgender identity. Moreover, the evidence favors a genetic predisposition. Likewise, there seems to be a growing concern with regards to the relationship between endocrine disruptors and transsexuals as well as other gender minority populations. More research needs to be done to understand the exact pathways.

Categories: Endocrinology/Diabetes/Metabolism, Internal Medicine, Medical Education
Keywords: transgender, gender identity disorder, gender dysphoria, transexualism, autism spectrum disorders

Introduction And Background

Transgender or gender dysphoria (GD) has been defined as clinically significant distress resulting from the incongruence between one's experienced gender, and one's assigned gender, along with a persistent and strong desire to be of another gender [1]. Adolescents referred for evaluation often request hormone therapy (HT) and many also express a desire for sex reassignment surgery (SRS). Evidence shows that adolescents and adults with GD without a sex development disorder before SRS are at increased risk for suicide. However, after SRS, the adjustment may vary, and suicide risk may persist [1]. GD has replaced the term gender identity disorder (GID) in the 2013 edition of the diagnostic and statistical manual of mental disorders, fifth edition (DSM-5), which itself has replaced "transsexualism" [2].

Received 12/11/2017
Review began 12/12/2017
Review ended 12/14/2017
Published 12/24/2017

The transgender community suffers from a lot of discrimination. In a survey in the United States, 19% of transgender people reported being denied medical care. Nearly half of those surveyed reported having to teach their medical providers how to care for the transgender persons [3]. It is imperative to perform more research regarding transgender status and associations in order to reveal the complex multifactorial etiology, improve the understanding among clinicians, and lead to better wellbeing for transgender individuals. GD involves neurodevelopmental changes and has psychiatric association including schizophrenia and autism. Childhood adversities are also associated with being transgender. Moreover, the evidence favors a genetic predisposition. A link with endocrine disrupting chemicals has also been suggested.

There are several transgender variants that exist historically in different cultures of the world [4]. They do not fit in the conventional definition of male or female; rather, they move between the two or are a combination of both genders. Vulnerable and insecure transgender individuals have been disregarded and marginalized by the mainstream society [4]. In a study in Bangladesh, 50 in-depth interviews and 20 key-informant interviews were conducted. Results revealed that transgender persons suffered from humiliation at school, social isolation, and difficulty getting a mainstream job. Moreover, family members of transgender persons felt uncomfortable with the feminine attitudes of male adolescents, especially when the family experienced negative and unpleasant societal expressions [4].

In the United States, individuals who identify as transgender experience similar adversities. A study including transgender and gender non-conforming individuals from all fifty states showed the presence of discrimination against transgender people [3]. Transgender people were living in extreme poverty. Forty-one percent of them reported attempting suicide as compared to 1.6% of the general popu

How to cite this article
Saleem F, Rizvi S W (December 24, 2017) Transgender Associations and Possible Etiology: A Literature Review. 10.7759/cureus.1984

expressed a transgender identity or gender non-conformity at schools reported harassment (78%), physical assault (35%), and sexual violence (12%). About one-sixth left school or higher education due to harassment. Of those who have transitioned to the desired gender, only 59% reported updating the gender on their driver's license or state identity documentation [3]. Likewise, human immunodeficiency virus (HIV) infection was found to be more prevalent in transgender community as compared to the general population. Fifty-seven percent of transgender persons experienced significant family rejection. Seventy-six percent have been able to receive HT, demonstrating their determination, ability to endure difficulties, and resolution to seek out sensitive medical providers. Over three-fourths reported feeling more comfortable at work and improved performance after transitioning, although these transgender people had the same rates of harassment at work as the general population [3].

In another survey conducted in medical students enrolled in the United States and Canada, 15.8% students from 152 institutions identified themselves as sexual and gender minorities. The most common reasons for concealing their sexual identity were privacy, fear of discrimination, and social norms [5]. Research in the United States on transgender people has mostly relied on convenience samples taken from urban HIV assessments as most of the health surveillance surveys do not have measures that allow transgender identification [6]. Conron, et al. indicated that transgender adults were more likely to be unemployed as well as living at less than or equal to 100% of the poverty index as compared to non-transgender individuals among the survey participants selected from the Massachusetts Behavioral Risk Factor Surveillance System. Also, transgender people are less likely to be overweight, but more likely to smoke [6]. When transgender people were compared to their non-transgender siblings, it was concluded that even when transgender and gender queer people are more highly educated in comparison to their non-transgender siblings, they do not have a corresponding increase in their income. Transgender people are more likely to experience harassment and discrimination than their non-transgender siblings. They have less social support from family than non-transgender individuals [7].

In 2014, the behavioral risk factor surveillance system (BRFSS) included an optional gender identity module and was adopted in nineteen states in the United States [8]. Transgender people's demographics from BRFSS data show that they make up to 0.53% of the population. They are more likely to be non-white and below the poverty line, as likely to be married (50.5% vs. 47.7%), living in a rural area (28.7% vs. 22.6%), less employed, and less likely to attend college (35.6% vs. 56.6%) as compared with the non-transgender individuals [8]. A larger proportion of individuals identify themselves as male-to-female rather than female-to-male or gender nonconforming. Overall, transgender respondents are not significantly different from the non-transgender population with regards to age, living in a rural area, marital status, or employment [8]. Another study to identify the transgender population in the United States based on Behavioral Risk Factor Surveillance System (BRFSS) data showed 0.6% adults (about 1.4 million) identifying themselves as transgender people [9]. Hawaii has the highest percentage occurring in 0.8% of adults, while North Dakota has the lowest percentage at 0.3%. The district of Columbia (DC) was not included in this dataset. DC has a notably high transgender percentage (2.8%) and is considered an outlier [9].

Review

Given the demographics and background of transgender people, a growing transgender population invites researchers to dig further into the etiology and comorbidities related to transgender people in order to improve the overall health of the transgender community.

Data sources

The review covers publication dates within the last ten years. A search of English scientific literature was conducted using PubMed. Studies involving transgender demographics, discrimination, transgender etiology, and associations were included.

Neuroanatomical etiology

Differences in the brain structures and brain functions that are related to gender and sexual orientation have been found to be associated with the pathoetiology of gender dysmorphic disorder. Sexual differentiation of the genitals takes places in the first trimester of pregnancy, and sexual differentiation of the brain starts during the second half of pregnancy. Therefore, it has been hypothesized that these two processes may play roles independently of each other that predispose an individual to transsexuality [10]. One working hypothesis behind GD is that the neuronal differentiation in the hypothalamic networks is altered [11]. Magnetic resonance imaging (MRI) of male-to-female transsexual conversion has shown a female-like putamen; this means that the transgender putamen has a volume that is larger than normal males but within the normal female range [12]. Combined positron emission tomography and MRI experiments have shown sexual dimorphism in hemispheric ratios and the pattern of amygdala connectivity [13]. Sex reversal of the INAH3, a subnucleus of the hypothalamic uncinate nucleus in transsexual people, is a probable marker of an early atypical sexual differentiation of the brain. Changes in INAH3 and the bed nucleus of the stria terminalis (BNST) may belong to a complex network that may structurally and functionally be related to normal sex differentiation [14].

Psychiatric associations

GD patients appear to have comorbid psychiatric disorders, most commonly anxiety and depressive disorders [1]. Studies done in Amsterdam, Ghent, Hamburg, and Oslo have shown that 70% of the individuals with GD are diagonised with lifetime DSM-IV-TR Axis I; mostly, affective disorders and anxiety problems [15]. In a survey in Iran, major depressive disorder (33.7%), specific phobia (20.5%), and adjustment disorder (15.7%) were found to be the three most prevalent disorders in GD patients requesting SRS. Bipolar mood disorder prevalence was 2.4%. The majority of the patients with GD were found to have psychiatric Axis I comorbidities [16]. The literature shows that, although psychiatric conditions are more prevalent, there are low rates of coexistent medical illness in GD. Depression is present in 34.4% of the patients. Moreover, transgender people are much less likely to attend a mental health professional [17].

HT in transgender people has been found to boost self-esteem, reduce depression, and improve quality of life [18]. Initiating HT in transgender people seems to have a positive effect in reducing stress levels as shown by the reduced cortisol levels, assessed by cortisol awakening response, measured before and twelve months after HT [19]. Likewise, there is a decrease in depression but slightly elevated anxiety in transgender children who have socially transitioned and are supported to live openly. These children now identify themselves as the gender "opposite" to their natal sex [20]. Studies also show a correlation of GD with eating disorders [21]. Further studies need to be done to further substantiate these claims.

Relation with autism spectrum disorder

Autism spectrum disorder (ASD) is more prevalent in GD than in the general population [1]. Evidence suggests a link between GD and ASD [22]. To study further, additional studies with larger sample size are needed [2]. Evidence shows that 5.5% of the GD patients showed ASD traits as compared to the general population [23]. The literature evidence as regards to the co-occurrence of ASD and GD is limited. This is important as paying attention to the development of gender identity formation in individuals with ASD from an early age may be helpful. Doctors should also help individual to explore his or her own gender narrative, rather than merely focusing on medical intervention [24].

Schizophrenia

There is growing evidence, although limited, suggesting that both GD and schizophrenia are neurodevelopmental disorders [25] and that they may share common causal mechanisms and risk factors. Both involve brain lateralization and pathways involved in sexual differentiation [26]. A study performed by Judge, et al. documents presence of schizophrenia in 3.67% patients with suspected or confirmed GD who were referred for HT consideration [17]. A college-based survey in China shows that GD is more prevalent in women. Also, the scale of correlations between compulsion and GD, and between GD and schizophrenia, is significantly greater in male participants [27]. However, not all studies have shown a correlation [16].

Baltieri and De Andrade reported a case of a transgender patient with schizophrenia and the risks of a potential diagnostic confusion. A 19-year-old woman was referred for SRS, having an eight-year history of undifferentiated schizophrenia and GD. After a more suitable antipsychotic treatment, her masculine behavior persisted but her desire to change her own genital organs decreased. The case points out the challenge of differentiation between pure identity disorders and transsexual feelings secondary to an ongoing psychopathologic process such as schizophrenia [28].

Toxoplasma

Rajkumar also observed an association between Toxoplasma infection, schizophrenia and GD based on studies suggesting an independent association of both schizophrenia and GD in prenatal toxoplasma [29-30]. He suggests testing the hypothesis serologically in GD. However, no hard data is available [26].

Childhood maltreatment

A growing body of evidence reports the association between childhood maltreatment and adult dissociative psychopathology [31-33]. In a study [34] performed in Florence, 109 patients meeting the criteria for male-to-female GD were interviewed for childhood maltreatment with regards to emotional abuse, neglect, physical abuse, and sexual abuse. A high proportion of transsexual subjects reported childhood maltreatment. Maltreated subjects also reported higher body dissatisfaction and showed a worse lifetime mental health. Nevertheless, approaching the issue of childhood neglect and maltreatment thoroughly can enable the patients to reflect on its impact on their lives and, eventually, its relevance on treatment decisions [34].

Role of endocrine disruptors

Another working hypothesis involves the role of endocrine disruptors in transgender etiology. In a letter to the editor, Bejerot, et al. suggested a hypothetical link between endocrine disrupting chemicals and transgenders [35]. They hypothesized a role for endocrine disruptors, especially phthalates. Phthalates are present in some plastics, and there has been an increased concentration in the environment in recent years.

Bejerot, et al. suggested that endocrine disruptors may be the cause of high fetal testosterone exposure leading to increased risk of ASD as well as GD [35]. More systematic investigations are required that may also elaborate mechanisms involved in brain development and sexual differentiation.

Research in rats has shown that endocrine disruptors like polychlorinated biphenyls (PCB) profoundly impair the sexual differentiation of female hypothalamus [36]. Also, there is a growing concern that the use of fragrance-containing daily lifestyle materials run parallel with the unprecedented rates of malignancies, neural ailments, teratogenicity, and transgender instances [37]. PCB exposure can lead to altered neuronal activity in hippocampus and identify it as potential environmental risk factors for neurodevelopmental disorders. The mechanism involves probable defects in neuronal Ca++ signaling, increased ryanodine receptor activity and dendritic growth in hippocampal neurons caused by PCP [38].

Genetics

Likewise, a genetic association has been proposed. Heritability of GD is suggested by evidence that has shown the familiality of transsexualism among non-twin siblings, and an increased concordance for transsexualism in monozygotic as compared with dizygotic same-sex twins [1]. In addition, research supports CYP17 as a candidate gene for female-to-male transsexualism and shows that loss of a female-specific CYP17 T-34C allele distribution pattern is linked with female-to-male transsexualism [39].

Conclusions

The literature on transgender people during the last decade provides a framework for the associations and comorbidities associated with transgender or GD. The research draws links between transgender people and changes in prenatal neuroanatomy. There is an association with psychiatric disorders, schizophrenia, and ASD. Transsexualism is linked to childhood maltreatment and adversities. Evidence also leads some to speculate that there are genetic predispositions. Furthermore, a working hypothesis exists with regards to possible association of endocrine disrupting chemicals and transgender identity or other gender-related issues. The evidence until today shows that transsexualism has a complex biopsychosocial etiology. There is a need for additional research to explore the myths and mysteries behind transgender identity to improve the understanding among clinicians, social activists and policy makers leading to better transgender health.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Article *in* Psychology and Health · February 2008

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Regret associated with the decision for breast reconstruction: The association of negative body image, distress and surgery characteristics with decision regret

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(Received 9 December 2005; in final form 17 November 2006)

Abstract
This study investigated the influence of psychosocial and surgical factors on decision regret among 123 women diagnosed with breast cancer who had undergone immediate (58%) or delayed (42%) breast reconstruction following mastectomy. The majority of participants (52.8%, $n=65$) experienced no decision regret, 27.6% experienced mild regret and 19.5% moderate to strong regret. Bivariate analyses indicated that decision regret was associated with negative body image and psychological distress – intrusion and avoidance. There were no differences in decision regret either with respect to methods or timing patterns of reconstructive surgery. Multinominal logistic regression analysis showed that, when controlling for mood state and time since last reconstructive procedure, increases in negative body image were associated with increased likelihood of experiencing decision regret. These findings highlight the need for optimal input from surgeons and therapists in order to promote realistic expectations regarding the outcome of breast reconstruction and to reduce the likelihood of women experiencing decision regret.

Keywords: *Breast reconstruction, decision making, decision regret, negative body image, intrusion and avoidance*

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ISSN 0887-0446 print/ISSN 1476-8321 online
DOI: 10.1080/14768320601124899

Introduction

Decisional challenges facing women with breast cancer

Diagnosis of breast cancer is typically associated with elevated levels of psychological distress (Butler, Koopman, Classen, & Spiegel, 1999). The period following diagnosis is particularly challenging, since compounding the shock associated with diagnosis is the necessity to make crucial and complex decisions regarding treatment (Reaby, 1998a). In deference to the fatal threat that cancer poses, many women decide to undergo mastectomy, as opposed to breast-conserving treatment (Al-Refaie et al., 2005). However, the negative association between mastectomy and poor body image and psychological distress is well documented (Arora et al., 2001; Yurek, Farrar, & Andersen, 2000). Hence, the opportunity to restore the appearance of her breasts through reconstructive surgery following mastectomy may serve to enhance the woman's sense of self (Neill, Armstrong, & Burnett, 1998). However, the choice for breast reconstruction is a highly complex one, entailing personal values, priorities and body integrity (Reaby, 1998b).

Factors affecting the breast reconstruction decision

Coincident with the decision to accept breast reconstruction is the necessity to choose between alternative methods and alternative timing patterns. The methods of reconstructive surgery currently practised comprise flap reconstruction, implant reconstruction and a combination of these procedures (Nano et al., 2005). Flap reconstruction involves transferring sections of a woman's own muscle tissue from a remote site in the body to the breast area; procedural risks include loss of blood circulation to the transplanted muscle tissue, infection and abdominal bulges (Clayton & Waller, 1996). Unfortunately, such sensations are likely to negatively affect body image and to act as a constant reminder of the reconstructive procedure and its association with breast cancer (Harcourt & Rumsey, 2004). Implant reconstruction involves placing a silicone-gel or saline-filled breast prosthesis either behind or in front of the chest muscle. Unsatisfactory outcomes may be associated with implant displacement, incorrect sizing and scarring (Andrade, Baxter, & Semple, 2001). Additional corrective surgeries may be necessary should post-surgical complications such as rupturing of the breast implant, tightening of scar tissue and infection arise (Roberts, Wells, & Walden, 1999). Hence, the choice for breast reconstruction is inherently complex with uncertainty in the outcomes of such surgery evident. The present study will assess whether any differences are evident in decision outcomes for women electing to undergo flap, versus implant, reconstructive surgery.

Reconstructive procedures may be carried out at the time of mastectomy (immediate), or delayed for many months or years (delayed); however, it is unclear which approach yields greater benefit in terms of outcome satisfaction (Andrade et al., 2001). Some evidence points to the superior benefits of immediate breast reconstruction in terms of enhanced body image

(Al-Ghazal, Sully, Fallowfield, & Blamey, 2000) and less psychological distress (Schain, Wellisch, Pasnau, & Landsverk, 1985), while other studies report similar benefits and overall satisfaction resulting from delayed breast reconstruction (e.g., Wilkins et al., 2000). This study will assess whether any differences are evident in decision outcomes for women electing to undergo immediate, versus delayed, reconstructive surgery.

The challenge for women facing the choice of breast reconstruction is the lack of clear evidence that the procedure will lead to a beneficial outcome (Keith et al., 2003). The reported benefits of breast reconstruction include restoration of femininity and a sense of feeling whole (Andrade et al., 2001) and positive psychosexual adjustment (Rowland, Dioso, Holland, Chaglassian, & Kinne, 1995). However, some studies report that reconstructive surgery may neither restore a woman's body image (Harcourt et al., 2003), nor increase her social adaptability (Rowland et al., 2000), or sexual functioning (Corsten, Suduikis, & Donegan, 1992).

Decision making and decision regret associated with breast reconstruction

With the emphasis on the patient's role in medical decision making, health decisions resulting in adverse or unfavourable outcomes may lead to the individual experiencing decision regret (Davison & Goldenberg, 2003; Sheehan, Sherman, Lam, & Boyages, in press). The extent to which an individual has participated in the decision-making process is arguably a more appropriate method for measuring one's sense of responsibility for the decision (Brehaut et al., 2003). Thus, the present study investigates participants' levels of influence over the decision for breast reconstruction.

In the context of prophylactic mastectomy, decision regret has largely been experienced in association with body-image disturbance, diminished sexual satisfaction, and procedural complications (Montgomery et al., 1999; Payne, Biggs, Tran, Borgen, & Massie, 2000). In terms of breast reconstruction, there is a paucity of research in the area of regret. Little is known of the extent to which women experience regret following breast reconstruction (Winer et al., 1993), or the psychosocial factors associated with regret (Yurek et al., 2000). The present study aims to characterise the extent to which women undergoing breast reconstruction experience decision regret and to identify individual differences in psychological factors and surgery characteristics associated with regret. It was hypothesised that negative body image and greater psychological distress, namely intrusion and avoidance, will be associated with increased decision regret.

Method

Participants and procedure

Potential participants were identified through the NSW Breast Cancer Institute (BCI) situated at Westmead Hospital, Sydney. Eligibility criteria for study inclusion were (a) breast cancer diagnosis and, (b) already undergone immediate

or delayed breast reconstruction following mastectomy. Study invitation letters were sent to 247 women, along with an information sheet and consent form. Following signed consent, participants were mailed a self-report questionnaire which they completed and returned. Eight invitation letters were returned undelivered, and three women were deceased. Out of 236 women, 140 agreed to participate (59.32%): 140 questionnaires were sent out, and of these, 123 were returned completed, giving a response rate of 52.12%. All participants had undergone breast reconstruction at various hospitals by the plastic surgeon associated with the BCI (T.L.).

Measures

Decision regret. Current experience of regret over the decision to undergo breast reconstruction was measured by the valid and reliable Decision Regret Scale (Brehaut et al., 2003), utilising a five-point Likert scale (1 = strongly agree to 5 = strongly disagree). Mean scores were converted by subtracting 1 and multiplying by 25. Scores ranged from 0 to 100, with a high score indicating greater regret. Cronbach's alpha was 0.90 in the present study.

Body image. Participants' current perceptions of their physical appearance resulting from breast reconstruction were measured by the valid and reliable 10-item Body Image Scale (BIS: Hopwood, Fletcher, Lee, & Al-Ghazal, 2001). Participants utilised a four-point Likert scale (0 = not at all to 3 = very much). Scores ranged from 0 to 30; high scores denote more negative perceptions of body image ($\alpha = 0.89$ for the present sample).

Distress: Intrusion and avoidance. The 15-item Impact of Event Scale (IES: Horowitz, Wilner, & Alvarez, 1979) was used to measure participants' current subjective distress related to their decision to undergo breast reconstruction. Participants utilised a four-point Likert scale (0 = not at all; 1 = rarely; 3 = sometimes; 5 = often), with scores ranging from 0–35 (intrusion scale) and 0–40 (avoidance scale). High scores indicate high levels of intrusive and avoidant responses, respectively. Due to high intercorrelations between the subscales ($r = 0.81$, $p < 0.0005$), a total distress score (i.e., summing the subscale scores) was used in all analyses. A 'subclinical' range of total scores is 0–8, 'mild' 9–25, 'moderate' 26–43 and 'severe' 44 and over. Cronbach's alpha was 0.93 in the present study.

Method and timing of breast reconstruction. Information was obtained regarding the method (implant vs. flap) and timing patterns (immediate vs. delayed) of breast reconstruction that participants underwent.

Demographic and medical history variables. Age, country of birth, highest level of education achieved and marital status were documented. Medical history comprised time interval since breast cancer diagnosis; breast cancer stage; time interval since mastectomy; treatment prior to mastectomy; treatment

post-mastectomy and/or reconstruction; and time interval since the last reconstructive procedure.

Social support. The valid and reliable 6-item Social Support Questionnaire (SSQ-6: Sarason, Sarason, Shearin, & Pierce, 1987) assessed 'available' social support and 'satisfaction' with support, a potential covariate in the present study. Participants utilised a six-point Likert scale (1 = very dissatisfied to 6 = very satisfied). Scores are averaged (range 1–6), with a high score indicating greater satisfaction. Cronbach's alpha was 0.85 (Availability) and 0.97 (Satisfaction) in the present study.

Mood. The Positive and Negative Affect Schedule (PANAS: Watson, Clark, & Tellegen, 1988) assessed current mood state. The PANAS comprises two 10-item scales of positive-affect (PA) and negative-affect (NA) rated on a 5-point Likert scale (1 = not at all to 5 = extremely). Scores for each subscale range from 10 to 50. Cronbach's alpha of the PA and NA subscales were 0.88 and 0.85, respectively. Mood was investigated as a potential covariate.

Decision influence. Participants were asked to choose one of the five following options that coincided with their level of influence over the decision for breast reconstruction: (a) it was totally my decision; (b) I was more influential in that decision; (c) the doctor and I equally shared the decision; (d) the doctor was more influential; and, (e) it was totally the doctor's decision. Decision influence was investigated as a potential covariate.

Data analyses

The Statistical Package for the Social Sciences (SPSS, version 11.5) was used for all statistical analyses. Bivariate analyses using the non-parametric statistical tests of Spearman's rank correlations (for continuous variables) and Pearson's chi-square tests (for categorical variables) explored the associations between outcome and all other variables. Non-parametric tests were utilised due to skewness of the decision regret variable and the large number of zero values preventing normalization using transformations. Decision regret was recoded into an ordinal variable with three levels (No regret, Mild regret, Moderate to Strong Regret) and multinominal logistic regression analyses were then conducted to determine the variables with which regret was most strongly associated. Variables correlating with decision regret $p \leq 0.1$ were fitted into the regression model. To reduce Type 1 error rate, the critical p-value for the multinominal logistic regression was $p \leq 0.025$.

Results

Descriptive data

Demographic and clinical characteristics for the sample are shown in Table I. The mean number of persons listed as supports was 4.48 (SD = 2.88, range 0–15)

Table I. Demographic and clinical characteristics of participants.

Variable	
Region of origin (%)	
Australia	67.5
Europe	17.2
North America	4.0
Middle East	3.3
New Zealand	2.4
East Asia	2.4
India	0.8
Pacific Islands	0.8
South Africa	0.8
Education (%)	
Less than 8 years of schooling	1.6
School certificate	37.4
Higher school certificate	15.4
Vocational/TAFE qualifications	20.3
University qualifications	24.4
Married or partnered (%)	74.0
Age (years)	
M	52.2
SD	9.7
Range	24.0–84.0
Time since breast cancer diagnosis (months)	
M	52.7
SD	48.5
Range	1.0–336.0
Clinical stage at diagnosis (%)	
0	6.5
I	13.8
II	21.1
III	7.3
IV	4.9
Could not report	45.5
Time since mastectomy (months)	
M	45.3
SD	43.2
Range	1.0–336.0
Breast-conserving treatment prior to mastectomy (%)	10.6
Adjuvant treatment prior to mastectomy	11.3
Adjuvant treatment post mastectomy and/or breast reconstruction (%)	62.6
Time since last reconstruction procedure (months)	
M	20.2
SD	15.5
Range	1.0–72.0
Reconstruction type (%)	
Implant	74.8
Flap	25.2
Reconstruction timing (%)	
Immediate	58.5
Delayed	41.5

and the mean satisfaction with support was 4.93 (SD = 1.22, range 1–6). The mean positive affect (PA) score was 32.19 (SD = 8.42, range 11–50), and the mean negative affect (NA) score was 14.10 (SD = 5.14, range 10–41). All women, except one, actively participated in the decision-making process to some degree. The majority (50.4%) reported that it was totally their decision to undergo breast reconstruction, while 48.7% participated in shared decision-making.

Decision regret. The average score on the Decision Regret Scale was 13.76 (SD = 20.40, range 0–95), comparable with Brehaut et al. (2003) (mean = 15.3). The majority of participants (52.8%) indicated no decision regret regarding their choice for reconstructive surgery. Of the remaining women, 27.6% indicated mild regret (score between 1 and 25) and 19.5% indicated moderate to strong regret (score of 26 or higher).

Body image. The majority of participants (55.3%) reported nil or 'little' negative perceptions of body image (i.e., indicated either 0 or 1 on each item of the BIS scale). The BIS mean score was 6.32 (SD = 6.23, range 0–28), comparable with Hopwood et al. (2001) (mean = 5.14). Of current participants reporting negative body image, the most frequently reported perceptions were feeling less sexually (23.6%) and physically (21.1%) attractive.

Total distress: Intrusion and avoidance. The mean IES total distress score was 8.86 (SD = 12.92, range 0–57), comparable to data of Tjemsland, Soreide and Malt (1998) for women with breast cancer 1 year post-operatively (mean = 8.8). The majority of participants (68.3%) reported a subclinical response to the impact of breast reconstruction. A mild-moderate distress response was indicated by 22.5%, while 8.8% indicated a moderate-severe distress response.

Method and timing of breast reconstruction. Of all participants, 92 (74.8%) had undergone implant reconstruction, and 31 had undergone flap reconstruction (23.6% TRAM flap, 1.6% latissimus dorsi flap). The majority of participants had immediate breast reconstruction (58.5%) as opposed to delayed reconstruction (41.5%).

Correlations with decision regret

Bivariate correlations among decision regret and other variables are shown in Table II. Decision regret was most strongly correlated with negative body image ($r = 0.40$, $p < 0.0005$) followed by total distress ($r = 0.33$, $p < 0.0005$). There were no discernible associations between levels of decision regret when comparing either the two methods of reconstructive surgery (implant vs. flap: $\chi^2(2) = 0.62$, $p = 0.74$) or the different timing patterns of reconstructive surgery (immediate vs. delayed: $\chi^2(2) = 1.20$, $p = 0.58$). Only two potential covariates correlated with decision regret, current mood state (PA) ($r = -0.18$, $p = 0.05$) and time interval

Table II. Bivariate correlations among decision regret and other variables.

Variable	1	2	3	4	5
(1) Regret	–				
(2) PA	−0.18*	–			
(3) Recon.	0.17*	−0.01	–		
(4) Body im.	0.40**	−0.37**	−0.06	–	
(5) Distress	0.36**	−0.13	−0.13	0.57**	–

Notes: PA = PANAS positive affect; Recon. = months since last reconstruction procedure; Body im. = body image; Distress = total distress. *$p < 0.1$; **$p < 0.01$.

Table III. Multinominal logistic regression summary table for decision regret.

Variable	β	SE	Wald χ^2	df	p	OR
Mild regret						
PANAS_PA	−0.05	0.03	2.70	1	0.10	0.95
Recon.	0.02	0.02	2.38	1	0.12	1.02
Body image	0.02	0.05	0.14	1	0.71	1.02
Total distress	0.04	0.03	2.09	1	0.15	1.04
Moderate to strong regret						
PANAS_PA	−0.01	0.04	0.05	1	0.82	0.99
Recon.	0.03	0.02	3.32	1	0.07	1.03
Body image	0.14	0.06	6.16	1	0.01	1.15
Total distress	0.05	0.03	3.23	1	0.07	1.05

Notes: PANAS_PA = positive affect; Recon. = months since last reconstruction procedure. SE = Standard error; OR = Odds ratio. Overall model $\chi^2(8) = 31.27$, $p < 0.0005$.

since participants' last reconstruction procedure ($r = 0.17$, $p = 0.06$), which were controlled for in subsequent analyses.

Analysis of variables associated with decision regret

Multinomial logistic regression analysis was conducted with the four variables that significantly correlated with decision regret, namely negative body image, total distress, PA and time since last reconstructive procedure (Table III). Overall, negative body image was significantly associated with decision regret ($\chi^2(2) = 7.15$, $p = 0.03$). As negative body image increased, the likelihood of experiencing moderate to strong regret, compared to no regret, increased ($\beta = 0.14$, OR = 1.15, $p = 0.01$). Total distress overall was not significantly associated with decision regret ($\chi^2(2) = 3.80$, $p = 0.15$), hence no further analyses were carried out to ascertain specific effects of total distress on the categories of regret examined. However, negative body image and total distress were significantly correlated ($r = 0.57$, $p \leq 0.01$), therefore total distress may have mediated the association between negative body image and decision regret.

Unfortunately, the restricted sample size prevented any mediational analyses being conducted on these data.

Discussion

Regret is increasingly being regarded as an important construct for evaluating health states and in respect of decision making in health care (Smith, 1996). Several studies have documented the impact that anticipation of regret can have on the process of decision making (e.g., Steginga, Occhipinti, Gardiner, Yaxley, & Heathcote, 2002), but less is known about the factors associated with regret following a medical decision such as surgical options for cancer (Brehaut et al., 2003). The present research sought to determine the association of negative body image and distress in relation to the experience of decision regret with respect to breast reconstruction. As hypothesised, women with negative body image were more likely to experience moderate to strong regret compared to those experiencing no regret. Decision regret is likely to reduce one's self-confidence and self-efficacy and instil feelings of remorse, guilt and shame. Greater regret may impede quality of life and contribute to poorer physical and psychological wellbeing (Clark, Wray, & Ashton, 2001). Hence, for women faced with a decision regarding breast reconstruction, the experience of regret has the potential to contribute to psychosocial dysfunction.

Whilst the present findings are in broad agreement with previous findings, demonstrating that heightened positive body image is associated with greater decision satisfaction (Baker et al., 2002), satisfaction/dissatisfaction are considered to be theoretically different constructs to decision regret. Dissatisfaction/disappointment has been found to result from unfulfilled expectations and causation by circumstances beyond anyone's control (Zeelenberg et al., 1998). In contrast, the present study is unique since it investigates the experience of decision regret, which arguably derives from two distinct theories: the first is in response to knowing or imagining that a more favourable outcome was attainable under the choice of an alternative action; the second derives from feeling responsible for making a poor decision and incurring self-blame (Connolly & Reb, 2005).

It is conceivable that women in the present study may have experienced decision regret as the result of unrealistic expectations concerning the aesthetic outcome of reconstructive surgery. Thereby, the provision to women of realistic information regarding outcome expectations and side effects of breast reconstruction may help reduce the subsequent experience of decision regret (Montgomery et al., 1999). To address this issue, surgeons in the clinical situation could intervene prior to decision making, by informing the patients and elaborating upon the contents of a decision aid, to detail the potential benefits and possible adverse outcomes associated with reconstructive surgery. This process could further involve visual inspection in picture format of women with and without breast reconstruction following mastectomy. Additionally, women could be given the opportunity to physically handle saline and silicone implants,

allowing them to feel the differences in texture and weight. This process requires that guidelines be in place to assist surgeons in the utilisation of proficient and consistent communication skills in order to effectively convey preparatory information.

In conjunction with the surgeons' educative input, psychotherapeutic intervention both prior to, and following, making a decision for or against breast reconstruction, may be of benefit. Prior to the decision, psychotherapeutic approaches could be used to recognise unrealistic expectations of breast reconstruction outcomes, allowing a woman to explore existing beliefs about self-image and the value she places on her breasts. In addition, therapeutic approaches may benefit women following the decision to undergo reconstruction. For women in the present study, negative body image was related to the experience of intrusion and avoidance. Participants frequently reported the use of avoidance mechanisms to try to deny unwanted thoughts and to minimise emotional distress. Consequently, allowing the woman to explore her thoughts and concerns regarding her body-reality, as well as her sense of wholeness and sexual identity, with a therapist may minimise the experience of negative self-perceptions post-reconstruction (Cohen, Kahn, & Steeves, 1998). Cognitive behavioural techniques may be particularly helpful post-reconstruction to restructure malfunctioning thoughts, perceptions, and ideals that a woman holds regarding the dimensions of her body (White, 2000). Future research is required to explore the efficacy of both surgeon-initiated and therapist-initiated interventions in minimising decision regret.

Limitations of the study

Although this research has implications for increasing our awareness of the possible reasons for decision regret, methodological shortcomings of the research approach exist. Due to the utilisation of a cross-sectional study design, information about causality cannot be obtained and determination of how regret status changes over time is not possible. The ability for the present findings to be generalised may be limited, since participants were recruited from one institution in Sydney, Australia, specialising in multidisciplinary breast cancer care, operated on by the same plastic surgeon, and were predominantly married. A degree of caution in interpreting the present findings is warranted since not all eligible women volunteered to participate in this study, which may have introduced the possibility of flawed data caused by a self-selection bias. Whilst the present study assessed the extent to which women experienced regret over their decision to undergo breast reconstruction, a limitation of clinical significance is the absence of an appropriately matched comparison sample of post-mastectomy women in order to assess regret resulting from their decision to not proceed with breast reconstruction. Such a comparison would have indicated the benefits or otherwise of reconstructive surgery, as reported by post-reconstruction women.

Future research is required to explore the contribution of other psychological factors that may influence decision regret, for example, outcome expectations and perceptions of sexuality pre-breast reconstruction. The importance such women place on physical and sexual aspects within existing or desired relationships may be associated with post-decision regret. Furthermore, post-reconstruction research concerning sexual adjustment and the impact that breast reconstruction has on dyadic relationships are considered worthwhile. In the context of prophylactic breast reconstruction, Lloyd et al. (2000) found that reconstructive surgery impacted male partners by way of increased stress, disruptions to family life, and conflicts between commitments to work, family and provision of support. Medical factors such as post-operative complications and physical side effects are also expected to be associated with decision regret; however, the investigation of such variables was beyond the scope of this study. The undertaking of collaborative studies incorporating researchers from psychological and medical backgrounds deserves attention.

Conclusions

Current results acknowledge occurrences of women experiencing regret that is associated with their decision for breast reconstruction, and demonstrate that negative body image is associated with decision regret. It is hoped that the present results will encourage surgeons and therapists to utilise optimal communication skill guidelines and techniques in order to provide women with comprehensive and realistic information concerning the benefits and limitations of breast reconstruction in order to dispel potentially unrealistic expectations regarding surgical outcomes.

Acknowledgement

The authors thank Dr Alan Taylor, Department of Psychology, Macquarie University, for his assistance and advice with respect to statistical analyses of the present data.

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