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TYPE:	Article CC:CCL
JOURNAL TITLE:	Endocrine practice
USER JOURNAL TITLE:	Endocrine Practice
ARTICLE TITLE:	Endocrine Treatment of Transsexual Persons: Extensive Personal Experience
ARTICLE AUTHOR:	Leinung, Matthew C;Urizar, Marco Fiore;Patel, Nile
VOLUME:	19(4)
ISSUE:	
MONTH:	
YEAR:	2013
PAGES:	644-650
ISSN:	1530-891X
OCLC #:	35074613

Processed by RapidX: 2/1/2022 5:43:16 AM

Original Article

ENDOCRINE TREATMENT OF TRANSSEXUAL PERSONS: EXTENSIVE PERSONAL EXPERIENCE

Matthew C. Leinung, MD; Marco Fiore Urizar, MD; Nilem Patel, MD**; Shannon Comley Sood, MD*

ABSTRACT

Objective: The Endocrine Society's recently published clinical practice guidelines for the treatment of transsexual persons acknowledged the need for further information on transsexual health. We report here the experience of one provider with the endocrine treatment of transsexual persons over the past 2 decades.

Methods: Data on demographics, clinical response to treatment, and psychosocial status were collected on all transsexual persons receiving cross-sex hormone therapy since 1991 at the endocrinology clinic at Albany Medical Center, a tertiary care referral center serving upstate New York.

Results: Through 2009, a total 192 male-to-female (MTF) and 50 female-to-male (FTM) transsexual persons were seen. These patients had a high prevalence of mental health and psychiatric problems (over 50%), with low rates of employment and high levels of disability. Mental health and psychiatric problems were inversely correlated with age at presentation. The prevalence of sex reassignment surgery was low (31% for MTF). The number of persons seeking treatment has increased substantially in recent years. Cross-sex hormone therapy achieves very good results in FTM persons and is most successful in MTF persons when initiated at younger ages.

Conclusion: Transsexual persons seeking hormonal therapy are being seen with increasing frequency. The dysphoria present in many transsexual persons is associated with significant mood disorders that interfere with successful careers. Starting therapy at an earlier age may lessen the negative impact on mental health and lead to improved social outcomes. However, significant barriers exist, such as insufficient insurance coverage, which limit comprehensive care. **(Endocr Pract. 2013;19:644-650)**

Abbreviations:
DVT = deep vein thrombosis; **FTM** = female-to-male; **GID** = gender identity disorder; **HBIGDA** = Harry Benjamin International Gender Dysphoria Association; **MTF** = male-to-female; **SRS** = sex reassignment surgery; **WPATH** = World Professional Association of Transgender Health

INTRODUCTION

Transsexualism (International Classification of Diseases [ICD]-10) (1), also referred to as gender identity disorder (GID) (Diagnostic and Statistical Manual of Mental Disorders [DSM]-IV) (2), may be defined as a discrepancy between a person's psychological gender (sex) and the morphological, biological, and social sex, which is often perceived as "non-self" and belonging to the opposite sex (3). The Harry Benjamin International Gender Dysphoria Association (HBIGDA, now known as the World Professional Association of Transgender Health, or WPATH) published the first clinical care guidelines in 1979. Recently, the Endocrine Society recognized the need to publish clinical practice guidelines (4) for the endocrine treatment of transsexual persons (5,6). This report

For accompanying editorial, see page 575-578

Submitted for publication June 15, 2012
Accepted for publication December 12, 2012
From the Albany Medical College, Albany, New York.
Address correspondence to Dr. Matthew Leinung, Division of Endocrinology, 25 Hackett Boulevard, MC 141, Albany, New York 12208.
E-mail: leinunm@mail.amc.edu.
*Current address: Miami Beach Community Health Center, Miami, FL 33141.
**Current address: 1866 N. Orange Grove, Suite 102, Pomona, CA 91767.
Published as a Rapid Electronic Article in Press at http://www.endocrinepractice.org on March 19, 2013. DOI:10.4158/EP12170.OR
To purchase reprints of this article, please visit: www.aace.com/reprints.

acknowledged the need for further studies on transsexual health and recognized as one problem the small sample size of many published reports. This was addressed further by an Institute of Medicine report issued in 2011 citing the need for more demographic data on transsexual persons (7).

We report here the personal experience and observations of one provider at one center in upstate New York obtained over the past 2 decades of endocrine treatment of transsexual persons.

METHODS

Prior to 2003, clinical and psychosocial data were collected from retrospective chart reviews. Subsequently, data were collected prospectively. Creation of the database was approved by the Albany Medical Center Institutional Review Board. All patients were seen at one point by a single provider (M.L.). Information sent from patients' mental health providers was incorporated into the database. Patients new to the clinic through 2009 were included in the analysis, and follow-up data were collated through 2010. Treatment followed HBIGDA/WPATH guidelines. All patients initiating physician-prescribed hormonal therapy in our clinic were evaluated by a mental health professional with experience in GIDs and were deemed appropriate for therapy according to HBIGDA/WPATH guidelines. Male-to-female (MTF) patients received oral estrogen consisting of either ethinyl estradiol (maximum dose, 100 μg daily) or conjugated equine estrogens (Premarin, maximum dose, 6.25 mg daily) until around 2006, when the vast majority were switched to oral 17β-estradiol. Estrogen doses were titrated upward until serum testosterone levels were suppressed to <100 ng/dL (final 17β-estradiol doses exceeded 6 mg daily in only 2 of 137 patients, who were titrated to 8 mg daily). An oral progestational agent (medroxyprogesterone acetate, 2.5 to 10 mg daily) was added if testosterone levels could not be adequately suppressed by oral estrogen alone. Spironolactone or finasteride was added for additional anti-androgen effect in 80% of cases. Doses of estrogen were lowered after sex reassignment surgery (SRS) or orchiectomy, and anti-androgen therapy was discontinued.

In female-to-male (FTM) patients, intramuscular testosterone, given generally every 1 to 2 weeks, was titrated to doses that generated blood levels in the normal age-adjusted male range. Limited attempts at using transdermal testosterone were not successful at achieving full gonadal suppression, and this option was abandoned until after oophorectomy.

For the purpose of this study, low-qualified workers were defined as those whose educational attainment level was a high school diploma or less. Workers classified as "Employed with high qualification" were defined as those with an academic degree conferred by a college or university.

Statistical Analyses

Data were analyzed using SPSS version 19.0. Chi-square tests were used to analyze categorical variables. Categories were collapsed when necessary to obtain expected values greater than 5. Fisher's exact test was used for two by two tables with small sample sizes. Kaplan-Meier survival analysis was used to study variables associated with time to surgery. The Mantel-Cox log rank test was used to test if the survival function was equal at different factor levels.

RESULTS

A total of 242 patients were seen up to 2010. Patient demographic data are shown in Table 1. Eighty percent (192) of these patients were MTF and 20% were FTM. The average age at presentation to our clinic was 36.3 years, and the average duration of follow-up with us was 4.7 years (average, 7.1 years since initiation of hormone therapy). The age at initiation of hormonal therapy and the age at presentation to the clinic were lower in the FTM group. Compared with FTM patients, a greater number of MTF patients had taken cross-sex hormone therapy prior to their initial visit with us (34% vs. 20%), including 19 MTF patients (9.8%) who admitted to starting hormonal therapy without a physician's supervision. Sixteen patients, all MTF, were human immunodeficiency virus (HIV)-positive (6.6%), and 14 of these 16 patients (88%) admitted to having started hormonal therapy without medical supervision.

Overall, 28% of patients were on disability and/or unemployed, with a higher rate seen in MTF patients (32% versus 14%). Nearly 10% of patients were students at the time of presentation. Forty patients were on disability (17%), the vast majority for mental health issues. Overall, psychiatric disease was present in 56.2% of all patients, consisting mostly of mood disorders (depression, dysthymia, adjustment disorder, mania). Age at presentation correlated inversely with the presence of psychiatric problems. The incidence of mood disorders was lower in those patients that began hormonal treatment by age 32 (36.3% versus 51.7%, Fisher's exact one-sided test; $P = .011$) (Fig. 1).

Whereas yearly totals varied, there was a clear increase over time in the number of persons presenting to the clinic (Fig. 2). In addition, the age at presentation dropped over the past decade (Fig. 3).

Of 192 MTF patients, 59 (31%) had some form of SRS (Table 2), including 47 (24%) vaginoplasties, 8 orchiectomies only, and 4 breast augmentations only (14 patients receiving vaginoplasty also had breast augmentation). The average time from initiation of hormone therapy to vaginal

Table 1
Demographic Data

	MTF	FTM	Total
Transsexual Population	192 (79%)	50 (21%)	242
Mean age at presentation to our clinic (years)	38.0 ± 12.5	29 ± 9.9[a]	36.3 ± 12.3
Mean (and maximum) duration of follow-up (years)	4.6 (19.9)	4.7 (21.2)	4.7
Mean (and maximum) time since initiation of therapy (years)	7.2 (36.4)	6.9 (39.5)	7.1
Age at initiation of hormone therapy (years)	35.5	27.5[a]	33.8
Hormonal therapy prior to initial visit	66 (34%)	10 (20%)	76 (31%)
Prior hormonal treatment w/o physician supervision	19 (10%)	0[a]	19 (7.8%)
Sex reassignment surgery	59 (31%)	32 (64%)[a]	91 (38%)
HIV-positive	16 (8.3%)	0[a]	16 (6.6%)
Employment	127 (66%)	34 (68%)	161 (67%)
Employed with high qualification	45 (23%)	10 (20%)	55 (22%)
Employed with low qualification	70 (36%)	18 (36%)	88 (36%)
Unemployed + disability	61 (32%)	7 (14%)[a]	68 (28%)
Disability	36 (19%)	4 (8%)[a]	40 (17%)
Unemployed	25 (13%)	3 (6%)[a]	28 (12%)
Students	10 (5.2%)	12 (24%)[a]	22 (9%)
Psychiatric disease	112 (58%)	24 (48%)	136 (56%)
Patient who started hormone therapy at <32-years-old	47 (54%)	13 (35%)	60 (49%)
Patient who started hormone therapy at >32-years-old	65 (62%)	11 (85%)	76 (64%)
Mood disorder	86 (45%)	20 (40%)	106 (44%)
Patient who started hormone therapy at <32-years-old	36 (41%)	9 (24%)	45 (36%)
Patient who started hormone therapy at >32-years-old	50 (50%)	11 (85%)[a]	61 (52%)
Drug and substance abuse	24 (13%)	3 (6.0%)	27 (11%)
Legal name changed	117 (61%)	26 (52%)	143 (59%)
DVT	5 (2.6%)	0	5 (2.1%)

Abbreviations: DVT = deep vein thrombosis; MTF = male-to-female; FTM = female-to-male.
[a] $P<.05$ for comparison of MTF to FTM.

surgery was 4.9 years, with a maximum of 13.4 years; for orchiectomy only, the average was 5.1 years, with a maximum of 11.5 years. For MTF patients who were followed more than 2 years since initiation of therapy, the percentage undergoing vaginoplasty was 29% (average length of follow-up in the 71% of MTF patients who did not undergo vaginoplasty was 7.5 years, with a maximum of 23.4 years). Among MTF patients with more than 10 years of follow-up (n = 45), 14 (31%) had vaginoplasty, 4 (9%) had orchiectomy only, and 2 (5%) had breast augmentation only, but 25 of these patients (55%) did not have SRS (including 5 patients who were HIV-positive). Of those 25 patients who did not have surgery, no fewer than 20 expressed a desire to have SRS of some kind. None of the breast augmentations and <5% of the vaginoplasties and orchiectomies were paid for by insurance.

Of 50 FTM patients, 32 (64%) had one or more gender-related surgeries, which included 27 bilateral mastectomies and 21 hysterectomy plus ovarectomy procedures.

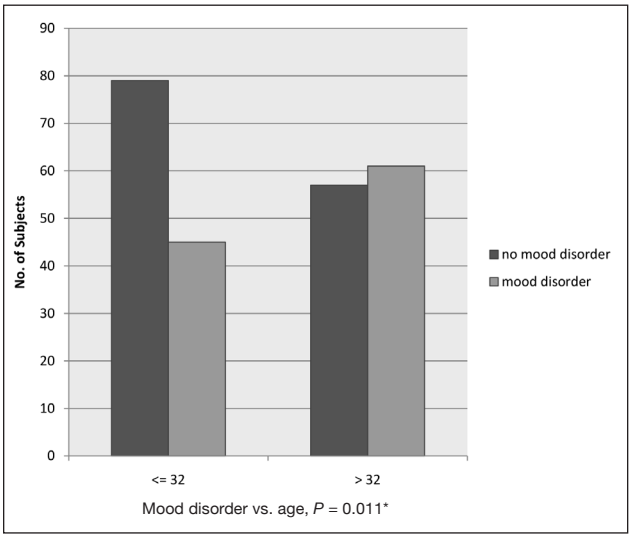

Fig. 1. Mood disorders at age of initiation of cross-sex hormonal therapy.

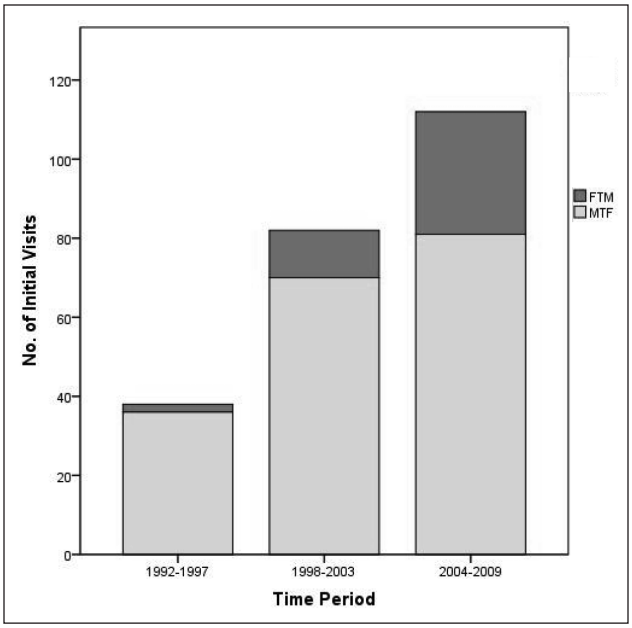

Fig. 2. Number of patients presenting for cross-sex hormonal therapy over the past 2 decades. *FTM* = female-to-male; *MTF* = male-to-female.

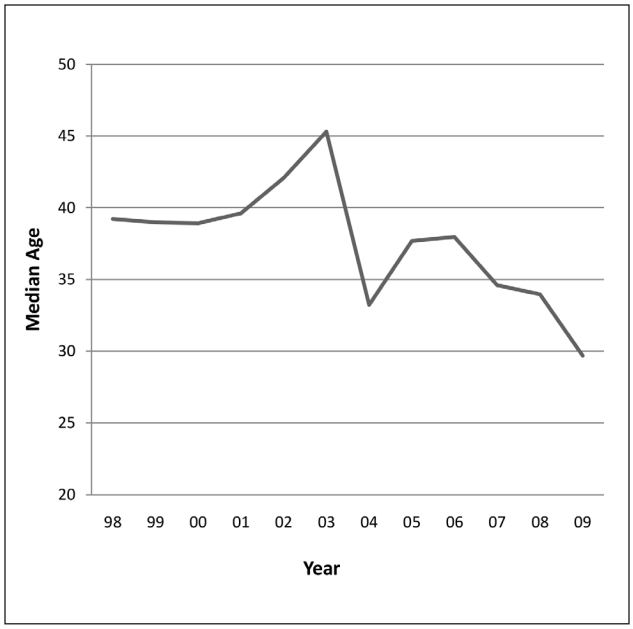

Fig. 3. Median age at presentation (rolling 2-year average) for cross-sex hormonal therapy over the past decade.

Four patients had genital cosmetic surgery ("bottom surgery;" 3 phalloplasties and 1 scrotoplasty). The average time from initiation of hormone therapy to mastectomy was 2.4 years, and the average time to hysterectomy was 4.7 years (not including 4 patients who had their hysterectomies for other medical reasons prior to initiation of hormonal therapy). None of the surgical procedures were covered by insurance, using transsexualism as the diagnosis. Among FTM patients with more than 2 years of follow-up since initiation of hormone treatment (n = 35), 9 patients did not have surgery and 18 did not have a hysterectomy (average follow-up, 6.5 years, with a maximum of 22.4 years).

Kaplan-Meier survival analysis was used to study the difference in time to surgery for the whole cohort of MTF and FTM patients, with and without mood disorders (Fig. 4). Time to surgery was significantly shorter for FTM patients (mean, 4.84 years) and was not affected by the presence of mood disorders. The average time to surgery among MTF patients was 19.4 years and was affected significantly by the presence of mood disorders (11.5 years in patients without mood disorders, 23.2 years in patients with mood disorders).

During a total of 1,380 patient years of follow-up, a total of 5 MTF patients had a deep vein thrombosis (DVT). Two patients had a confirmed pulmonary embolus (PE), 1 patient presented with respiratory symptoms, but PE could not be confirmed, and 2 patients presented with leg edema. In 2 cases, the DVT occurred prior to the patient being seen in our clinic and while they were taking nonprescribed medication (one of the patients was taking an injectable estrogen and the second patient was taking an oral contraceptive containing cyproterone). One patient was subsequently diagnosed with a genetic clotting disorder. In this patient and two others, the DVT occurred while they were being treated with Premarin (prior to most patients being switched from Premarin or ethinyl estradiol to estradiol in 2006). To our knowledge, no DVTs occurred while the patients were on estradiol.

DISCUSSION

There is a need for further data regarding the experience and treatment of transsexual persons in the United States. Over the past two decades, we have seen an increasing number of transsexual persons at our center in upstate New York. We feel this is a representative sample of patients presenting for medically supervised hormonal therapy, as we are the only center in our area providing hormonal therapy for GID (we estimate that we are caring for over 95% of those receiving medical therapy, based upon personal communications with mental health providers, endocrinologists, and other physicians).

In some ways, our experience with transsexual persons is similar to what has previously been reported outside the United States. For example, we found that the ratio of MTF to FTM patients (3.8:1) is similar to, though a little higher, than that found in recent studies in Belgium (2.4:1) (8), the Netherlands (2.5:1) (2), Singapore (2.4:1) (9), and Sweden (1.8:1) (10). Recently, our MTF to FTM ratio in

Table 2
Sex Reassignment Surgical Procedures[a]

MTF	**No. (%)**
Gender-related surgery	59 (31)
Vaginoplasty	47 (24)
Average time to vaginoplasty (years)	4.9
Orchiectomy only	8 (4)
Average time to orchiectomy (years)	5.1
Vaginoplasty and breast augmentation	14 (7)
Breast augmentation only	4 (2)
FTM	**No. (%)**
Gender-related surgery	32 (64)
Mastectomy	27 (54)
Average time to mastectomy (years)	2.4
Hysterectomy	21 (42)
Average time to hysterectomy (years)	4.7
Genital cosmetic surgery	4 (8)
Average time to genital surgery (years)	6.8

Abbreviations: FTM = female-to-male; MTF = male-to-female.
[a] Average time to surgery is measured from initiation of cross-sex hormonal therapy.

new visits has been dropping. In agreement with previous studies (9,11-14), significant differences were not observed in the level of education between MTF and FTM patients. We did find a higher percentage of FTM patients who were students (compared to MTF patients), but this may be a reflection of younger age at presentation.

There are a number of striking points in our experience. For example, we have seen a significant increase in the number of people seeking hormonal therapy (>100 new patients in the last 6 years). The age at presentation for hormonal treatment has been decreasing. This appears to be due to an increase in patients' knowledge regarding GID. We have observed that many transsexual persons presenting recently have obtained this information over the Internet. A decade ago, it was common to have patients relate long histories of unlabeled dysphoria; this is less likely today. The increase in the number of patients seeking therapy may also be a reflection of increasing social acceptance. The greater knowledge regarding GID and increased social acceptance may also explain why we have observed

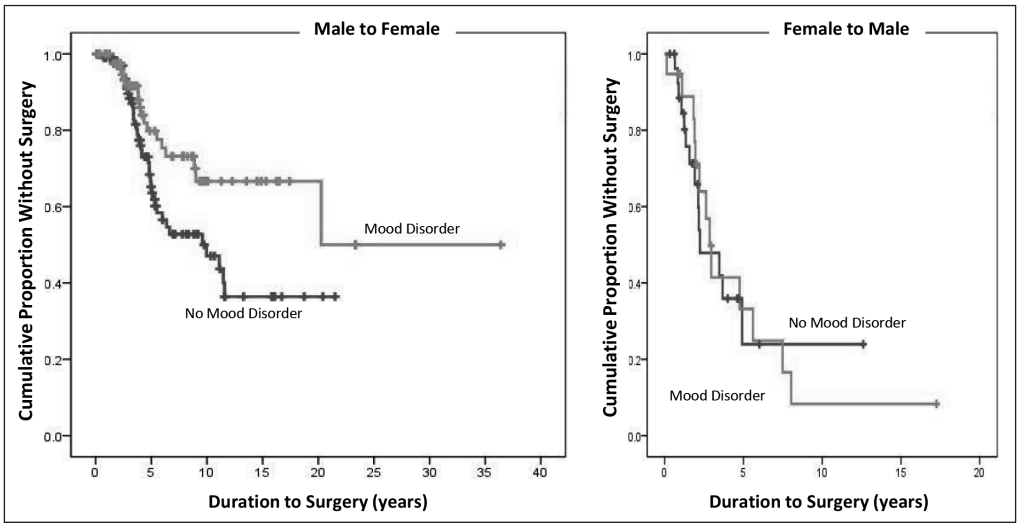

Fig. 4. Kaplan-Meier survival analysis of time to sex reassignment surgery for MTF and FTM patients. *FTM* = female-to-male; *MTF* = male-to-female.

a trend toward fewer patients taking cross-hormone therapy without a physician's supervision.

Another significant finding is the high prevalence of mental health and psychiatric problems we observed (over 50%). The most common findings were mood and adjustment disorders. The prevalence of these disorders was inversely correlated with age at presentation for therapy, and implies that earlier treatment may help alleviate these problems (15). This is perhaps not surprising. Not only is gender transition at an older age more difficult (due to establishment of families and careers that may be disrupted), prolonged dysphoria would also be expected to increase the likelihood of mental health problems (16). The high rate of disability (mostly mental health-related) and low rate of employability observed in our patients was related to mental health issues.

We found that most MTF patients did not have SRS. While not all transsexual persons seek or are appropriate for such surgery, the 31% rate for MTF patients seems low given the reported desire among this group and was not due to time needed for the "real life test." The presence of mood disorders was correlated with longer times to surgery for MTF patients. The cost of SRS is not covered by insurance or Medicaid, which for vaginoplasty can be over $20,000. Given the prevalence of mental health problems and low employability we encountered, it is not surprising that few could afford the cost out of pocket. The rate of surgery was higher in FTM patients (64%). There are a number of possible explanations for this. First, the major procedures (mastectomy and hysterectomy) are less costly than vaginoplasty. Second, there are other medical reasons that can justify hysterectomy to the satisfaction of insurance providers (and Medicaid). Finally, the higher rate of employability in our FTM population also appears to be a factor (8,13).

We encountered additional differences between our MTF and FTM patients. In agreement with other reports (8,9,12,13), the FTM patients in our study presented at a younger age and had lower rates of disability, unemployment, and substance abuse (17). This may reflect an overall lower degree of social acceptance for MTF patients. We observed that the hormonal therapy for FTM patients was generally quite effective for gender change in terms of successful masculinization, regardless of age. Hormonal therapy in older MTF patients had variable ability to induce full feminization. This may be a factor in relief of dysphoria and overall social acceptance and further underscores the need to start therapy early (18,19).

In our experience, the clinical practice guidelines of HBIGDA (now WPATH) for the management of transsexualism have been very useful, and, we believe, effective. The newly released Endocrine Society guidelines go a step further for the endocrine management of these persons. Our practice has been consistent with the bulk of these guidelines (for example, those guidelines regarding hormone type and dosing). In our experience, care provided in this manner has been both safe and effective, and we support the widespread adoption of these guidelines. One difficulty, however, concerns lack of insurance coverage for many patients for hormones (which are fortunately now available as generics), SRS, and even comprehensive laboratory follow-up.

CONCLUSION

Transsexual persons seeking hormonal therapy are being seen with increasing frequency in our clinic. Recent experience with transsexualism has led to the development of effective treatment guidelines by the WPATH and the Endocrine Society. However, there are significant barriers in the United States to implementation of these guidelines. The dysphoria present in many transsexual persons is associated with significant mood disorders that interfere with successful careers. Fortunately, it appears that starting therapy at an earlier age may lessen the negative impact on mental health and lead to improved social outcomes. With increased awareness and social acceptance, we believe long-term outcomes for transsexual persons should improve.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

ACKNOWLEDGMENT

We thank Dr. Nora Galambos for help with statistical analysis of the data.

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