Ambiguous Genitalia With Perineoscrotal Hypospadias in 46,XY Individuals: Long-Term Medical, Surgical, and Psychosexual Outcome

Claude J. Migeon, MD*; Amy B. Wisniewski, PhD*; John P. Gearhart, MD†;
Heino F.L. Meyer-Bahlburg, Dr. rer. nat.§; John A. Rock, MD∥; Terry R. Brown, PhD‡‡;
Samuel J. Casella, MD‡; Alexander Maret, MD*; Ka Ming Ngai‡; John Money, PhD**; and
Gary D. Berkovitz, MD‡‡

ABSTRACT. Objectives. To identify and study adults (21 years or older) who have a 46,XY karyotype and presented as infants or children with genital ambiguity, including a small phallus and perineoscrotal hypospadias, reared male or female.

Methods. Participants were classified according to the cause underlying their intersex condition based on review of medical and surgical records. Long-term medical and surgical outcome was assessed with a written questionnaire and physical examination. Long-term psychosexual development was assessed with a written questionnaire and semistructured interview.

Results. Thirty-nine (72%) of 54 eligible patients participated. The cause underlying genital ambiguity of participants included partial androgen insensitivity syndrome (n = 14; 5 men and 9 women), partial gonadal dysgenesis (n = 11; 7 men and 4 women), and other intersex conditions. Men had significantly more genital surgeries (mean: 5.8) than women (mean: 2.1), and physician-rated cosmetic appearance of the genitalia was significantly worse for men than for women. The majority of participants were satisfied with their body image, and men and women did not differ on this measure. Most men (90%) and women (83%) had sexual experience with a partner. Men and women did not differ in their satisfaction with their sexual function. The majority of participants were exclusively heterosexual, and men considered themselves to be masculine and women considered themselves to be feminine. Finally, 23% of participants (5 men and 4 women) were dissatisfied with their sex of rearing determined by their parents and physicians.

Conclusions. Either male or female sex of rearing can lead to successful long-term outcome for the majority of cases of severe genital ambiguity in 46,XY individuals.

We discuss factors that should be considered by parents and physicians when deciding on a sex of rearing for such infants. Pediatrics 2002;110(3). URL: http://www.pediatrics.org/cgi/content/full/110/3/e31; intersex, sex assignment, gender, androgen insensitivity, gonadal dysgenesis, psychosexual, genital reconstruction, hormone replacement.

ABBREVIATIONS. PAIS, partial androgen insensitivity syndrome; PGD, partial gonadal dysgenesis.

During fetal sex differentiation, genetic males who are unable to masculinize their sex ducts and external genitalia can be classified into 2 major etiologic groups: 1) the inability of the fetus to produce sufficient amounts of testosterone and dihydrotestosterone or 2) the inability of the fetus to respond to androgens that are present in normal amounts.1 We previously described a population of 46,XY subjects who presented to the Pediatric Endocrinology Clinic of Johns Hopkins Hospital with varying degrees of undermasculinized genitalia.2 In this population, the most difficult group to treat in terms of gender assignment is that of individuals who were born with ambiguous genitalia that includes a small phallus and perineoscrotal hypospadias.3 For this group of patients, there is a lack of agreement about optimal sex assignment (in terms of the child developing a gender identity that is congruent with his or her rearing) and types of genital surgery associated with the best cosmetic and functional outcome.

The dominant view has been that female sex assignment by physicians and parents is optimal in severely undermasculinized cases because feminization with surgical4 and endocrine5 treatment was considered more successful than masculinization. The appropriateness of this type of sex assignment in 46,XY individuals with a small phallus and perineoscrotal hypospadias has been questioned in response to accounts of individuals who were raised female and report dissatisfaction in adolescence or later with their female rearing. Some investigations do not provide precise physical descriptions of subjects to determine either cause underlying genital ambiguity or extent of androgen exposure during fetal development.6 Other reports relate to subjects with 5α-reductase deficiency7,8 and 17β-hydroxysteroid dehydro-
genase deficiency. In both of these conditions, the external genitalia are severely undermasculinized at birth but present partial virilization at puberty if the gonads remain in situ. In mid-adolescence or later, some of these subjects have developed a male gender identity despite their female rearing. Single case reports of similar outcomes associated with fetal pheno- type10 and mixed gonadal dysgenesis11,12 also exist.

Larger long-term outcome studies of gender development in male pseudohermaphrodites report acceptance of sex assignment established by parents and physicians by the majority of participants, regardless of female or male rearing.13,14 The common predictor of gender transposition, defined in these studies as gender identity change and/or homosexuality, in subjects who were reared male or female was stigmatization related to having an intersex condition.

In addition to the question of acceptance of female sex assignment by 46,XY intersex patients, one needs to ask whether surgical feminization is easier and preferable to surgical masculinization. Feminizing surgeries can include procedures to reduce the size of an enlarged clitoris by amputation (historical only in the United States) or resection/recession, to create a vagina (McIndoe and/or bowel segment procedure), and to remove the gonads.

Results of clitoral surgery are mixed. For example, preservation of nerve conduction in the neurovascular bundle of the phallus was reported after excision of the corporeal bodies in infants with ambiguous genitalia, although long-term sexual function remains to be investigated in these patients. A second article reported excellent cosmetic and functional outcome after clitoral recession16; however, an unwanted outcome of clitoral necrosis can occur.17

When cosmetic outcomes of several types of clitoral surgeries were considered together (resection, resection, and amputation), the postsurgical appearance of the genitalia were considered to be poor by Creighton et al.18 The young age of some of the participants in these studies makes it difficult to interpret the functional significance of the findings. In addition, some of the above-mentioned studies used measures of cosmetic outcome that were determined by the investigators, not by the patients themselves.

Follow-up studies of vaginoplasty are also limited in number. A large study was conducted in women with mullerian agenesis or Mayer-Rokitansky-Küster-Hauser syndrome (also referred to as Rokitansky syndrome) by Rock et al.19 In this group of patients, the McIndoe vaginoplasty procedure was rated to be successful in terms of postsurgical vaginal depth for sexual activity by all women. Women who had congenital adrenal hyperplasia as a result of 21-hydroxylase deficiency and underwent a McIndoe procedure reported a lower success rate (62%) in terms of comfortable penovaginal intercourse.20 Outcome studies of the McIndoe procedure in women with complete androgen insensitivity syndrome reported satisfactory intercourse postoperatively in 72% of patients21 and orgasm in 78%.22 In a similar group of patients with complete androgen insensitivity syndrome, good sexual function in terms of patients’ satisfaction with their genitalia (78%), satisfactory libido (71%) and orgasm (77%) were reported by study participants.23 Creighton et al.24 reported the results of several vaginoplasty procedures in girls and young women who were affected by a variety of urogenital abnormalities resulting in ambiguous genitalia. In these patients, the vaginal introitus was absent or small in 82%, vaginal length was inadequate in 27%, and additional vaginal procedures were required in 75%.

Investigations of masculinizing surgeries, like feminizing surgeries, in 46,XY intersex individuals with perineoscrotal hypospadias are limited. The only study to have evaluated exclusively the surgical outcome of the most severe cases of hypospadias reported on 19 men, approximately half of whom experienced difficulties with micturition, urologic function, and ejaculation.24 Roughly one third of patients were affected by marked impairment in quality of life resulting from their ambiguous genitalia, ranging from mild depression to severe psychiatric impairment. Another follow-up assessment of hypospadias repair in adults included 8 men with perin- eoscrotal hypospadias.25 In all cases, multiple hypospadias repairs were attempted with a postoperative complication rate of 64%. Repeated surgical procedures and complications are of particular concern because of scarring and loss of tissue associated with each surgery,26 as well as the presumed negative impact on sexual function.

In light of discrepant reports of long-term gender development and surgical outcome of 46,XY intersex individuals who were born with a small phallus and perineoscrotal hypospadias, the current study was designed to assess these variables in such patients treated at the Johns Hopkins Pediatric Endocrine Clinic. The specific goals of our investigation were to document long-term satisfaction with the gender assignment given by parents and physicians and with medical/surgical outcome in a group of patients who presented with the same degree of severe genital ambiguity at birth.

METHODS

The present research was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins University School of Medicine (Baltimore, MD). Written, informed consent was obtained from all participants before participation. Participants were asked to complete a written questionnaire and to visit the Johns Hopkins Clinical Research Center for the purpose of completing a physical examination, at which time a discussion regarding their health status was offered. Participants were asked to confirm their questionnaire responses and to elaborate on unclear or incomplete responses.

Participants

A total of 183 adults with a 46,XY karyotype and intersex condition had been cared for at the Pediatric Endocrine Clinic of the Johns Hopkins Hospital from 1950 to the present. Among these, 54 presented with ambiguous genitalia, including perin- eoscrotal hypospadias, and thus were eligible for study recruitment.2 Written, informed consent and completed the study. Participants ranged in age from early 20s to early 50s (mean age: 34 years). For maintaining participant ano-
nymity, age is presented in categories of 5 years at the time of participation (Tables 1 and 2).

Fourteen participants, 5 currently living as men (1–5) and 9 currently living as women (22–30), were classified as having partial androgen insensitivity syndrome (PAIS) on the basis of androgen receptor studies in cultured genital skin fibroblasts. These participants had either a low number of receptor binding sites for dihydrotestosterone or a low binding affinity. However, a mutation in exons 2 through 8 of the androgen receptor gene was detected in only 6 of these participants. In addition, for participants in whom no androgen receptor mutations were identified, no mutations of the 17β-hydroxysteroid dehydrogenase gene, as reported by Boehmer et al,27 were observed.

Eleven participants, 7 currently living as men (6–12) and 4 currently living as women (31–34), were classified as having partial gonadal dysgenesis (PGD) on the basis of the presence of well-defined müllerian duct remnants. Indeed, all participants in the PGD group presented with a uterus initially.

Fourteen participants, 9 currently living as men (13–21) and 5 currently living as women (35–39), were considered to have a poorly defined cause underlying their genital ambiguity. Four participants (13, 19, 20, and 38) were believed to be affected by a typical gonadal dysgenesis (PGD) on the basis of the presence of well-defined müllerian duct remnants. Indeed, all participants in the PGD group presented with a uterus initially.

For participants who were living as men, evaluation of the cosmetic appearance of the external genitalia included vaginal depth measured with graduated vaginal dilators (cm) and placement of the vaginal introitus on the perineum. Clitoral length was also measured (cm). As in the case of the men, cosmetic appearance of the genitalia was rated as good when all 3 measures were normal, fair when any 1 measure was abnormal, and poor when 2 or more measures were abnormal.

Physical Measurements

Physical Measurements at Birth

Appearance of the external genitalia was determined from medical records and was agreed on by 2 of the authors (C.J.M. and A.B.W.). The grading scheme described by Quigley et al28 was used to classify the degree of undermasculinization of 46,XY individuals with ambiguous external genitalia using a 7-point scale (1 = male phenotype to 7 = female phenotype).

Physical Measurements in Adulthood

Physical measurements in adulthood were obtained during an examination that took place in the Clinical Research Unit at the Johns Hopkins Hospital and also from medical records and was agreed on by 2 physicians (C.J.M. and A.B.W.). The grading scheme described by Quigley et al was used to classify the degree of undermasculinization of 46,XY individuals with ambiguous external genitalia using a 7-point scale (1 = male phenotype to 7 = female phenotype).

For participants who were living as men, rating of cosmetic appearance of the external genitalia (stretched penile length [cm], size of testes [cm], and quality of corporal bodies) were evaluated independently and then agreed on by 2 physicians (C.J.M. and J.P.G.). When all 3 genital measures were within the normal range, cosmetic appearance of the genitalia was rated as good. When 1 of the 3 measures was abnormal, a rating of fair was given; and when 2 or more measures were abnormal, the cosmetic appearance of the genitalia was rated to be poor.

When breast enlargement was present, breast size was measured (cm) both horizontally and vertically (pediatric endocrine technique) for each breast. Measurement did not differentiate between glandular and adipose tissue. Type and timing of surgeries used to masculinize the external genitalia were obtained from surgical records and then verified during the physical examination. The existence and size of the prostate gland were recorded. Pubic hair growth was rated according to male-typical Tanner stage ratings.29

For participants who were living as women, evaluation of the cosmetic appearance of the external genitalia included vaginal depth measured with graduated vaginal dilators (cm) and placement of the vaginal introitus on the perineum. Clitoral length was also measured (cm). As in the case of the men, cosmetic appearance of the genitalia was rated as good when all 3 measures were normal, fair when any 1 measure was abnormal, and poor when 2 or more measures were abnormal. Breast size was measured as reported for men. Type and timing of surgeries to feminize the external genitalia were obtained from surgical records and then verified during the physical examination. Pubic hair growth was rated according to female-typical Tanner stage ratings.29

Physical Measurements

Psychosexual Assessment

Genitosexual Function

Participants were asked about the adequacy of their genitalia for sexual functioning (scale: 1 = adequate, 3 = somewhat inadequate, to 5 = totally inadequate), self-estimated strength of libido (scale: 0 = none, 3 = average, to 7 = very high), and experience of orgasm (yes/no).

TABLE 1. Number of Genital Surgeries, Physician-Rated Appearance of the Genitalia, Self-Reported Body Image, Final Stretched Penile Length, and Self-Reported Satisfaction With Sexual Function in Adult 46,XY Patients Who Were Born With a Small Phallus and Perineoscrotal Hypospadias and Were Living as Men at the Time of Study Participation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age of Final Male Gender Assignment (Years)</th>
<th>Total No. of Male Genital Surgeries</th>
<th>Physician-Rated Appearance of Adult Genitalia (Good 1…5 Poor)</th>
<th>Self-Reported Body Image (Satisfied 1…5 Dissatisfied)</th>
<th>Final Stretched Penile Length (cm) ± Z Score (Satisfied 1…5 Dissatisfied)</th>
<th>Self-Reported Sexual Function (Satisfied 1…5 Dissatisfied)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>First week 35–39</td>
<td>≥10</td>
<td>2</td>
<td>3</td>
<td>12/−0.8</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>First week 20–24</td>
<td>0</td>
<td>NA</td>
<td>3</td>
<td>NA</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>First week 25–29</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>7/−3.9</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>First week 45–49</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>6/−4.5</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>First week 40–44</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>5/−5.1</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>First week 30–34</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>6/−4.5</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>First week 40–44</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>7/−3.9</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>First week 30–34</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>10/−2.0</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>First week 40–44</td>
<td>NA</td>
<td>4</td>
<td>1</td>
<td>8/−3.3</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>First week 20–24</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>11/−1.4</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>Fourth month 35–39</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>14/0.4</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>First week 35–39</td>
<td>≥10</td>
<td>3</td>
<td>1</td>
<td>9/−2.7</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>Fourth month 40–44</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>6/−4.5</td>
<td>3</td>
</tr>
<tr>
<td>14</td>
<td>First week 30–34</td>
<td>≥10</td>
<td>10</td>
<td>1</td>
<td>10/−2.0</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>First week 40–44</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>11.5/−1.1</td>
<td>3</td>
</tr>
<tr>
<td>16</td>
<td>First week 30–34</td>
<td>NA</td>
<td>3</td>
<td>5</td>
<td>11/−1.4</td>
<td>5</td>
</tr>
<tr>
<td>17</td>
<td>First week 25–29</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>5/−5.1</td>
<td>5</td>
</tr>
<tr>
<td>18</td>
<td>Second week 25–29</td>
<td>2</td>
<td>NA</td>
<td>3</td>
<td>NA</td>
<td>3</td>
</tr>
<tr>
<td>19</td>
<td>Third week 30–34</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>14/0.4</td>
<td>3</td>
</tr>
<tr>
<td>20</td>
<td>23 y</td>
<td>40–44</td>
<td>NA</td>
<td>3</td>
<td>6/−4.5</td>
<td>3</td>
</tr>
<tr>
<td>21</td>
<td>First week 30–34</td>
<td>3</td>
<td>NA</td>
<td>3</td>
<td>NA</td>
<td>1</td>
</tr>
</tbody>
</table>

NA indicates not applicable.
TABLE 2. Number of Genital Surgeries, Physician-Rated Appearance of the Genitalia, Self-Reported Body Image, Final Clitoral Length and Vaginal Depth, and Self-Reported Satisfaction With Sexual Function in Adult 46,XY Patients Who Were Born With a Small Phallus and Perineoscrotal Hypospadias and Were Living as Women at the Time of Study Participation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age of Final Gender Assignment</th>
<th>Age at Study Participation (Years)</th>
<th>Total No. of Female Genital Surgeries</th>
<th>Physician-Rated Appearance of Adult Genitalia (Good 1...5 Poor)</th>
<th>Self-Reported Body Image (Satisfied 1...5 Dissatisfied)</th>
<th>Final Clitoral Length (cm) and Vaginal Depth (cm)</th>
<th>Self-Reported Sexual Function (Satisfied 1...5 Dissatisfied)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>28 mo</td>
<td>35–39</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0/11</td>
<td>3</td>
</tr>
<tr>
<td>23</td>
<td>First month</td>
<td>25–29</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>1/11</td>
<td>3</td>
</tr>
<tr>
<td>24</td>
<td>17 mo</td>
<td>30–34</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0/8</td>
<td>5</td>
</tr>
<tr>
<td>25</td>
<td>Third month</td>
<td>20–24</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1.5/15</td>
<td>3</td>
</tr>
<tr>
<td>26</td>
<td>First week</td>
<td>20–24</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1.5/15</td>
<td>3</td>
</tr>
<tr>
<td>27</td>
<td>First week</td>
<td>40–44</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0/9.5</td>
<td>3</td>
</tr>
<tr>
<td>28</td>
<td>First week</td>
<td>35–39</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>0.5/12</td>
<td>5</td>
</tr>
<tr>
<td>29</td>
<td>First month</td>
<td>25–29</td>
<td>2</td>
<td>NA</td>
<td>1</td>
<td>1/10</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>22 y</td>
<td>45–49</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0/10</td>
<td>5</td>
</tr>
<tr>
<td>31</td>
<td>Fourth month</td>
<td>20–24</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1/10</td>
<td>3</td>
</tr>
<tr>
<td>32</td>
<td>First week</td>
<td>20–24</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>0.5/9</td>
<td>1</td>
</tr>
<tr>
<td>33</td>
<td>14 mo</td>
<td>20–24</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2.5/13</td>
<td>1</td>
</tr>
<tr>
<td>34</td>
<td>First week</td>
<td>30–34</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>0/8</td>
<td>1</td>
</tr>
<tr>
<td>35</td>
<td>First week</td>
<td>25–29</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0/12</td>
<td>3</td>
</tr>
<tr>
<td>36</td>
<td>First month</td>
<td>50–54</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>0/6</td>
<td>3</td>
</tr>
<tr>
<td>37</td>
<td>First week</td>
<td>25–29</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0/12</td>
<td>1</td>
</tr>
<tr>
<td>38</td>
<td>Fourth month</td>
<td>30–34</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.75/12</td>
<td>1</td>
</tr>
<tr>
<td>39</td>
<td>First week</td>
<td>20–24</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0/14</td>
<td>2</td>
</tr>
</tbody>
</table>

NA indicates not applicable.

**Body Image**

Participants were asked about satisfaction with their appearance (scale: 1 = mainly satisfied, 3 = somewhat dissatisfied, to 5 = mainly dissatisfied) and to indicate which physical characteristics contributed to dissatisfaction, if any.

**Femininity and Masculinity**

Participants were asked to rate their degree of masculinity (scale: 1 = not at all masculine, 3 = somewhat masculine, to 5 = highly masculine) and femininity (scale: 1 = not at all feminine, 3 = somewhat feminine, to 5 = highly feminine) at the time of study participation.

**Sexual Orientation**

Participants were asked to rate on a 7-point scale whether they were sexually attracted to, fantasized about, or participated in sexual activity with women and/or men (0 = women only; 1 = mostly women, rarely men; 2 = both, but women more than men; 3 = women and men about equal; 4 = both, but men more than women; 5 = mostly men; 6 = men only).30

**Long-Term Romantic Relationships and Parenthood**

Frequency of long-term romantic relationships (marriage and domestic partnership) and parenthood was asked of all participants.

**Satisfaction With Physician/Parent-Assigned Sex**

Participants were asked about their satisfaction with their physician/parent-assigned sex of rearing and whether at any point in development they had considered changing their assigned sex of rearing.

**Long-Term Counseling**

Participants were asked whether they had received psychological or psychiatric counseling for issues related to their medical condition.

**Statistical Analysis**

Descriptive statistics were used for the physical and psychosocial measures. Comparisons between responses from participants who were living as men and women were analyzed with 2-tailed t tests. Mean differences were considered statistically significant at P < .05.

**RESULTS**

Participants Currently Living as Men

**Physical Appearance at Birth**

Classification of the appearance of the external genitalia ranged from Quigley grade 2 to 4 (mean: 3.4). One set of siblings with PAIS exhibited different degrees of undermasculinization of their genitalia at birth, consistent with previous reports of phenotypic diversity among patients with PAIS.31–33 Age at final male sex assignment occurred in the first few weeks of life (parent/physician assigned) in all but the 1 participant who elected to be reassigned to the male sex in early adulthood (Table 1).

**Physical Appearance in Adulthood**

Physician-rated cosmetic appearance of the adult external genitalia ranged from 2 to 5 (mean: 3.3; scale: 1 = good, 3 = fair, to 5 = poor). Final stretched penile length ranged from 5 to 14 cm (mean: 8.8; Table 1). Ten of the 18 men who consented to a physical examination (56%) attained a final penile length at or below 2.5 standard deviations of the mean established by Schonfeld and Beebe.34 It should be noted that variation exists in what is considered to be a normal distribution of penile length.35,36 For the sake of comparing the present set of data with those in other reports, we used Schonfeld and Beebe’s34 norms as a comparison.

Size of the testes varied for participants: some were considered within normal limits, whereas others were small and replaced with prostheses earlier in life. Size of the prostate gland was small or not palpable for the 18 men who consented to this portion of the physical examination. Genital reconstructive surgeries ranged in number from 0 to >10 (mean: 5.8) from early infancy through adulthood (Table 1). Surgical procedures included release of chordee, multiple-stage hypospadias repair with postoperative complications, removal of Müllerian remnants, orchiopexy, and implantation of prosthetic testes.

Development of secondary sexual characteristics varied among participants. Five men (24%) developed gynecomastia, 3 of whom underwent a mastectomy. Two of these men developed additional gy-
necomastia after their first breast removal. Pubic hair development ranged from male Tanner stage 3 to 5 (mean: 4.1). Ten men did not require testosterone replacement because they had sufficient endogenous production in adulthood. Among the remaining 11 who required testosterone replacement therapy to treat their hypogonadism, 5 (45%) were compliant with their replacement and 6 (55%) were noncompliant as reported during the physical examination. The remaining 8 men did not treat their hypogonadism at the time of participation despite their opportunity for obtaining prescriptions for testosterone replacement.

Body Image

Scores for body image ranged from 1 to 5 (scale: 1 = mainly satisfied, 3 = somewhat dissatisfied, to 5 = mainly dissatisfied; mean score: 2.2; Table 1). Dissatisfaction with body image was attributed to the following characteristics: unusual appearing genitalia ($n = 15$ [71%]), a small penis ($n = 16$ [76%]), gynecomastia ($n = 5$ [24%]), abnormal patterns of body hair ($n = 3$ [14%]), and short stature ($n = 5$ [24%]). Self-rated body image scores were significantly better for men than the physician-rated scores (mean score: 3.3) regarding the appearance of their genitalia ($t(36) = 3.1, P < .005$).

Genitosexual Function

Satisfaction with sexual function ranged from 1 to 5 (mean: 2.7) using the following scale: 1 = mainly satisfied, 3 = somewhat dissatisfied, to 5 = mainly dissatisfied. Three men (14%) were mainly dissatisfied with their sexual function (Table 1). Self-reported libido was above average for 7 men (33.3%), average for 7 men (33.3%), and lower than average for 7 men (33.3%). All of the men who answered ($n = 17$) reported the ability to have erections. Four men were unwilling to answer this question. Contributing to dissatisfaction with genitosexual function were surgical complications including penile fistulas and strictures, chronic urinary tract infections, urethral dilations, testicular pain, and discomfort resulting from hair growth in the skin graft of the urethra. Despite these difficulties, 19 men (90%) reported having had previous sexual experience with others and 17 (81%) reported an experience with a sex partner in the past year.

Long-Term Romantic Relationships and Parenthood

Eleven men (52%) were married or in long-term relationships, and 2 (10%) were parents via adoption or sperm donation. One man whose genital ambiguity was attributed to a timing defect had a low sperm count and is currently attempting in vitro fertilization with his wife.

Psychological Treatment

Thirteen men (62%) received counseling for issues related to their diagnosis. Reasons listed included concerns about romance and dating ($n = 7$ [33.3%]), sexual function ($n = 7$ [33.3%]), problems with family members ($n = 5$ [24%]), depression ($n = 8$ [38%]), substance abuse ($n = 5$ [24%]), and teasing ($n = 6$ [29%]).

Participants Currently Living as Women

Physical Appearance at Birth

Classification of the appearance of the external genitalia ranged from Quigley grade 3 to 4 (mean: 3.6). There was no significant difference in the Quigley rating of the genitalia at birth between participants who were reared male or female ($t(36) = 0.92, P > .05$). Similar to participants who are living as men, 1 pair of siblings who were reared female exhibited different degrees of ambiguity of their genitalia at birth. All participants exhibited perineal hypospadias, a small phallus with chordee, urogenital sinus, and bifid scrotum at initial presentation.

Final female gender assignment was established at various ages for the group. For 11 participants, parents and physicians established a female sex assignment in the first month of life. For 6 participants, physicians and parents established a female sex assignment between 3 and 8 months. Two participants had their gender reassigned by their parents and physicians twice (F→M→F) during early childhood. One participant initiated a male-to-female sex reassignment in early adulthood (Table 2). Genital reconstructive surgeries ranged in number from 1 to 3 (mean: 2.1) from early infancy through adulthood and included feminization of the external genitalia and vaginoplasty (Table 2). Overall, participants who are currently living as women required fewer genital surgical procedures than those who are currently living as men ($t(17) = 3.11, P < .05$).

Physical Appearance in Adulthood

Physician-rated cosmetic appearance of the adult external genitalia ranged from 1 to 2 (mean: 1.5; scale: 1 = good, 3 = fair, to 5 = poor; Table 2). Women were considered to have a better cosmetic outcome of their genital reconstruction, as rated by physicians, than men ($t(25) = 7.14, P < .05$). Clitoral length ranged from 0 to 2.5 cm (mean: 0.6). Nine (50%) women had complete clitoral amputation, 5 (28%) had clitoral reduction, and 4 (22%) had clitoral recession. Vaginal depth ranged from 6 to 15 cm (mean: 9.4). Seventeen women (94%) had a vaginal depth within the normal range (>7 cm) after vaginoplasty. Vaginoplasty consisted of the McIndoe procedure for 11 women (61%), a colonic sigmoid procedure for 6 women (33%), and 1 woman (6%) did not receive any type of vaginal construction. Two women who underwent a McIndoe vaginoplasty subsequently elected to have a colonic sigmoid procedure.

Development of secondary sexual characteristics was variable in this group. Two women had breast implants in early adulthood. However, each has since had the implants removed (an implant rupture was cited by 1 woman as reason for removal, and the other woman considered her implants to be too large). Breast size for the group was variable (range: 12 × 9 to 20 × 24 cm). Pubic hair development ranged from female Tanner stage 1 to 5 (mean: 2.6).
None of the women exhibited facial hair. All women required hormone replacement therapy after gonadectomy, and 14 (78%) were compliant with this treatment.

Body Image

Scores for body image ranged from 1 to 5 (scale: 1 = mainly satisfied, 3 = somewhat dissatisfied, to 5 = mainly dissatisfied; mean: 1.8). When dissatisfaction occurred, it was attributed to inadequate sexual hair (n = 5 [28%]), unusual-appearing genitalia (n = 4 [22%]), small breasts (n = 3 [16.5%]), tall or short stature (n = 3 [16.5%]), and poor muscle development (n = 2 [11%]). Self-rated scores by the women did not differ from their physician-rated scores regarding the appearance of their genitalia (t(23) = 0.8, P > .05). Participants who are living as either men or women did not differ overall in their degree of satisfaction with their body image (t(36) = 1.19, P > .05), and the majority of participants were more satisfied than dissatisfied with their physical appearance.

Genitosexual Function

Satisfaction with sexual function ranged from 1 to 5 (mean: 2.5; scale: 1 = mainly satisfied, 3 = somewhat dissatisfied, to 5 = mainly dissatisfied). Women who had undergone clitoral amputation were more dissatisfied with their sexual function (mean: 2.9) than women who had other types of clitoral surgery (mean: 2.3). However, this difference was not statistically significant (t(16) = 0.82, P > .05). Men and women did not differ according to their degree of satisfaction with their sexual function (t(34) = 0.47, P > .05).

Self-reported libido was above average for 2 women (11%), average for 6 women (33%), and lower than average for the remaining 10 women (56%). Twelve women (67%) reported the ability to experience orgasm, 3 (16.5%) were unsure, and 3 (16.5%) reported never having experienced orgasm. Contributing to dissatisfaction with genitosexual function was an introitus placed too posterior, a small vagina, pain during intercourse, low libido, and lack of self-lubrication. Despite these problems, 15 women (83%) reported ever having had a sexual experience with a partner, and 10 women (56%) reported a sexual experience with a partner in the past year.

Long-Term Romantic Relationships and Parenthood

Similar to the men, 7 women (39%) were married or had established long-term romantic relationships. One woman was an adoptive parent.

Psychological Treatment

The majority of women who participated (n = 12 [67%]) received counseling for issues concerning their diagnosis. Reasons listed for receiving counseling included concerns about romance and dating (n = 5 [28%]), sexual function (n = 9 [50%]), problems with family members (n = 3 [16.5%]), depression (n = 5 [28%]), and teasing (n = 2 [11%]).

Comparison of Men’s and Women’s Responses

Satisfaction With Parent/Physician-Assigned Gender

Sixteen participants (76%) were mainly satisfied with their male sex of rearing established by physicians and parents. Five participants (24%) reported dissatisfaction with their male sex of rearing, 1 of whom preferred to think of himself as intersex and 1 reassigned her gender to that of a woman in early adulthood. Fourteen participants (78%) were mainly satisfied with their physician/parent-established female sex of rearing. Four participants (22%) reported dissatisfaction with their female sex of rearing. Among the dissatisfied women, 1 reported that her female homosexual orientation was an obstacle and as a result she would have preferred a male sex of rearing, and 1 subject reassigned his sex to that of an intersexed man in early adulthood. Satisfaction with physician/parent-established sex of rearing did not differ between men and women (t(37) = 0.57, P > .05; Fig 1).

Self-Rated Masculinity and Femininity

Mean self-rated masculinity score at the time of participation for men was 3.9 (range: 3–5). However, 2 men (10%) did not respond to this question. Mean self-rated femininity score was 1.5 (range: 1–3). However, 5 men (24%) did not respond to this question.

Mean self-rated masculinity score at the time of participation for women was 1.9 (range: 1–3), and mean self-rated femininity score was 3.3 (range: 1–5). Men were significantly more masculine than women (t(35) = 7.8, P < .05), and women were significantly more feminine than men (t(30) = 5.64, P < .05; Fig 2).

Sexual Orientation

Most men rated themselves at the extreme male heterosexual end of the scale adapted from Kinsey et al,30 and the majority of women rated themselves at the extreme female end of the scale (t(28) = 6.77, P < .05). More women than men indicated an intermediate response (Fig 3).
DISCUSSION

Limitations of the Present Study

Our purpose for studying long-range outcome of patients affected by intersex conditions was to determine the success of female versus male sex of rearing in these individuals. The corollary is that results from this type of study will allow for better therapeutic decisions concerning sex of rearing for future patients.

Regrettably, long-term outcome studies are inherently limited by the amount of time needed for intersex patients to become adults, thus allowing for the "real-life" test of living as a sexually mature man or woman. Some of our patients died before the start of the present investigation, some had mental retardation, some could not be located for study, and others were located but refused to participate. It is possible that those who refused to participate were particularly dissatisfied with their sex assignment established by parents and physicians and their medical or surgical treatment; in addition, some preferred not to discuss their intersex condition. Finally, establishing a cause underlying the genital ambiguity of participants in the present study also proved difficult, particularly in cases of PAIS.

Physical Appearance and Choice of Gender at Birth

That the degree of sexual ambiguity at birth was the same for participants who were reared male (Quigley scale 3.4) or female (Quigley scale 3.6) was an artifact of our sampling method to include only those patients who presented with a small phallus and perineoscrotal hypospadias. It is interesting that half of these were raised male and the other half were raised female. It was not clear from the chart review which factors contributed to the decision by parents and physicians to choose a particular gender for infants with severe genital ambiguity. Future studies should investigate this decision-making process.

Physical Outcome

More than half of participants who are currently living as men had a stretched penile length below 2.5 standard deviations of the mean compared with only 6% of participants who are currently living as women and presented with a short vagina in adulthood. Women received fewer genital surgeries (mean: 2.1 vs 5.8) and had a better cosmetic appearance of their genitalia, as rated by physicians (mean: 1.5 vs 3.3), than men. Despite these seeming advantages to feminizing surgery, women and men did not differ in their degree of satisfaction with their sexual functioning (mean: 2.5 vs 2.7) or body image (mean: 1.8 vs 2.2) at the time of study participation (Table 3). Both groups cited the appearance of their genitalia as being the greatest contributing factor to their dissatisfaction with their body image. Finally, the number of clitoral amputations in the group of women re-
TABLE 3. Summary of Outcome Data for 46,XY Individuals Who Were Born With Ambiguous Genitalia Including Perineoscrotal Hypospadias

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Gender at Participation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21 Men 18 Women</td>
<td></td>
</tr>
<tr>
<td>PAIS</td>
<td>5 9</td>
<td></td>
</tr>
<tr>
<td>PGD</td>
<td>7 4</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 5</td>
<td></td>
</tr>
<tr>
<td>Mean no. of genital surgeries</td>
<td>5.8 2.1 &lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Physician-rated surgical outcome</td>
<td>3.3 1.5 &lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Participant-rated body image</td>
<td>2.2 1.8 NS</td>
<td></td>
</tr>
<tr>
<td>Participant-rated genital function</td>
<td>2.7 2.5 NS</td>
<td></td>
</tr>
<tr>
<td>% Satisfied with sex of rearing</td>
<td>76 78 NS</td>
<td></td>
</tr>
</tbody>
</table>

NS indicates not significant. Female sex of rearing resulted in fewer genital surgical procedures overall and better cosmetic appearance of the external genitalia as rated by physicians, compared with patients who were reared male. Despite these seeming advantages to female sex of rearing, men and women did not differ according to their degree of satisfaction with their physical appearance, genital function, and sex of rearing.

Sexual Orientation

Exclusive heterosexual orientation was observed in the majority of men and women, indicating that a 46,XY chromosome complement with weak prenatal androgen exposure is not sufficient to determine sexual orientation in this group of patients. These results are consistent with the hypothesis stating that gender assignment and sex of rearing contribute, at least in part, to the development of sexual orientation.

Women reported intermediate ratings of sexual orientation more often than men. One could speculate that women in general, whether affected by an intersex condition or not, report greater variability on scales of sexual orientation compared with men. However, this speculation is not always supported by data. Exposure to an abnormal endocrine milieu in early development and/or the effects of genital surgery may predispose these women to a wider range of expression of their sexual orientation than their male counterparts. Alternatively, participants who have genital malformations and were reared male may feel obliged to report exclusive heterosexuality. These hypotheses deserve additional investigation.

The majority of participants (62% men and 67% women) sought counseling for problems that they attributed to their diagnostic condition. Concerns about dating and sexual function, as well as feelings of depression, were evident in both groups. Clearly, patients who were born with ambiguous genitalia face psychological obstacles regardless of their sex of rearing. Information pertaining to membership of intersex patient advocacy and support groups was not elicited from study participants. Future studies should assess cohort effects in terms of medical, surgical, and psychosocial outcome of individuals who belong to such groups compared with those who do not.

Sex of Rearing

Our previous study of 46,XY individuals who were born with female genitalia indicated that female sex of rearing was successful in terms of gender identity. For 46,XY patients with congenital microphallus and no hypospadias, male sex of rearing was found to be optimal despite the success of some patients who were raised female.

Concerning patients with markedly ambiguous genitalia of the degree studied in the current investigation, establishing an optimal sex of rearing requires the consideration of several variables. Participants in the present study were reared according to the sex decided on by their parents and physicians. The majority of men (76%) and women (78%) were satisfied with their assigned sex (Table 3). However, some dissatisfied participants were identified, regardless of male or female rearing, indicating that general predictions cannot guarantee future gender development for any single case. In our sample, 2 participants (1 reared male and the other reared female) chose to reassign their sex in early adulthood.

To understand better why some patients who are affected by intersex conditions reject their parent/physician-assigned gender, future studies could investigate the impact of parents, siblings, partners, and spouses on long-term psychosexual development in this group. In addition, the impact of variables such as infertility, sexual dysfunction, and poor body image on gender development could be studied in populations that are not affected by intersex conditions. Although it is gratifying to observe satisfaction with gender assignment in the majority of patients studied, the rate of dissatisfaction reported here is problematic and illustrates the importance of additional studies.

An important consideration for deciding on female or male gender assignment in 46,XY infants with markedly ambiguous genitalia is the underlying cause of the intersex condition. The present study illustrates the difficulty in establishing such diagnoses. Despite this difficulty, some intersex conditions are life-threatening, thus requiring prompt identification and treatment.

The birth of an intersex infant is often viewed as a major crisis by parents and other family members. In these instances, pediatric endocrinologists can offer valuable support by helping the parents to understand sex differentiation and medical/surgical options that are available for their child. Specifically, physicians should inform parents about 1) long-term cosmetic and functional outcomes associated with genital reconstruction, 2) the need for long-term sex hormone replacement, and 3) possibilities for reproduction.

Physician-rated appearance of the external genitalia is better in women than in men, and women required fewer genital surgeries than did men (Table 3). Despite these seeming advantages for women, neither satisfaction with body image nor sexual function differed significantly between women and men.

In the most ambiguous cases, such as those in-
cluded in the current study, it is important to consider complications and outcomes of genital surgery. Men required more surgeries than women, but neither obtained an end result that was entirely satisfactory: approximately half of all participants reported dissatisfaction with their body image, and two thirds were dissatisfied to some degree with their sexual function.

All 46,XY intersex patients who were reared female will require life-long hormone replacement therapy. Excluding cases of 5α-reductase deficiency, 17-ketosteroid reductase deficiency, timing defect, and PAIS, patients who were reared male will also require hormone replacement.

Finally, the consideration of fertility should enter the equation when deciding on an optimal sex of rearing for infants with a small phallus and perineoscrotal hypospadias. For example, patients who have PGD and were born with a uterus may find it advantageous to be raised female, whereas those with the potential for spermatogenesis (5α-reductase deficiency and timing defect) may find it advantageous to be raised male.

CONCLUSION

For infants with markedly ambiguous genitalia, including a small phallus and perineoscrotal hypospadias, sex of rearing should be decided by parents who have been thoroughly informed about their child’s medical and surgical options and have also been informed of available outcome data. Advances in medical and surgical procedures used to treat intersex conditions, along with better education and support provided to patients and their families, may further improve the quality of life experienced by individuals who are affected by syndromes of abnormal sex differentiation.

ACKNOWLEDGMENTS

This work was supported by a grant from the Genentech Foundation for Growth and Development (98-33C); National Institutes of Health National Research Service Award F32HD08544; National Institutes of Child Health, National Center for Research Resources, General Clinical Research Center grant RR-00052; and an Endocrine Society 2001 Summer Research Fellowship. Many of the studies obtained on the patients in this article were made possible by National Institutes of Health grant 5-ROI-DK-00180 (1953–1997).

REFERENCES

33. Wilson JD, Harrod MJ, Goldstein JL, Hemsell DL, MacDonald PC. Familial incomplete male pseudohypoparathyroidism, type 1. Evidence for

34. Schonfeld WA, Beebe GW. Normal growth and variation in male genitalia from birth to maturity. J Urol. 1942;64:759–777


37. Dickinson RL. The Vagina. Baltimore, MD: Williams & Wilkins; 1949


Ambiguous Genitalia With Perineoscrotal Hypospadias in 46,XY Individuals: Long-Term Medical, Surgical, and Psychosexual Outcome


*Pediatrics* 2002;110;e31
DOI: 10.1542/peds.110.3.e31

Updated Information & Services

including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/110/3/e31

References

This article cites 31 articles, 2 of which you can access for free at:
http://pediatrics.aappublications.org/content/110/3/e31.full#ref-list-1

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):

- Genetics
  http://classic.pediatrics.aappublications.org/cgi/collection/genetics_sub
- Dysmorphology
  http://classic.pediatrics.aappublications.org/cgi/collection/dysmorphology_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints

Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2002 by the American Academy of Pediatrics. All rights reserved. Print ISSN: .
Ambiguous Genitalia With Perineoscrotal Hypospadias in 46,XY Individuals: Long-Term Medical, Surgical, and Psychosexual Outcome

*Pediatrics* 2002;110:e31
DOI: 10.1542/peds.110.3.e31

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/110/3/e31