

Complete Androgen Insensitivity Syndrome: Long-Term Medical, Surgical, and Psychosexual Outcome*

AMY B. WISNIEWSKI, CLAUDE J. MIGEON, HEINO F. L. MEYER-BAHLBURG, JOHN P. GEARHART, GARY D. BERKOVITZ, TERRY R. BROWN, AND JOHN MONEY

Department of Pediatrics, Division of Pediatric Endocrinology (A.B.W., C.J.M.); Department of Urology and Chief, Pediatric Urology, James Buchanan Brady Urological Institute (J.P.G.); and Department of Medical Psychology and Pediatrics (J.M.), The Johns Hopkins University School of Medicine, and Department of Biochemistry, The Johns Hopkins University School of Public Health and Hygiene (T.R.B.), Baltimore, Maryland 21287; Department of Psychiatry, Division of Child Psychiatry and Program of Developmental Psychoendocrinology, Columbia University College of Physicians and Surgeons and New York State Psychiatric Institute (H.F.L.M.-B.), New York, New York 10032; and Department of Pediatrics, Division of Pediatric Endocrinology, University of Miami School of Medicine (G.D.B.), Miami, Florida 33101

ABSTRACT

Controversy concerning the most appropriate treatment guidelines for intersex children currently exists. This is due to a lack of long-term information regarding medical, surgical, and psychosexual outcome in affected adults. We have assessed by questionnaire and medical examination the physical and psychosexual status of 14 women with documented complete androgen insensitivity syndrome (CAIS). We have also determined participant knowledge of CAIS as well as opinion of medical and surgical treatment. As a whole, secondary sexual development of these women was satisfactory, as judged by both

participants and physicians. In general, most women were satisfied with their psychosexual development and sexual function. Factors reported to contribute to dissatisfaction were sexual abuse in one case and marked obesity in another. All of the women who participated were satisfied with having been raised as females, and none desired a gender reassignment. Although not perfect, the medical, surgical, and psychosexual outcomes for women with CAIS were satisfactory; however, specific ways for improving long-term treatment of this population were identified. (*J Clin Endocrinol Metab* 85: 2664–2669, 2000)

THE RELATIVE contributions of variables such as prenatal hormones and social rearing to psychosexual development have been studied in a variety of intersex populations (1–6). These investigations have led to the wide acceptance of a multivariate conceptualization of gender development that emphasizes the importance of both nature and nurture (7–9).

Recent reports of psychosexual outcome in two penis ablation patients (10, 11) have led to reconsideration of sex assignment practices for intersexuals. One of the issues raised by these reports is the possibility that fetal androgen exposure influences the brains of such patients, resulting in male-typical psychosexual development. However, reports of psychosexual development in penis ablation patients are conflicting, and to date it remains unclear how treatment of intersex patients should be revised (12).

If androgens alone are important for male psychosexual

development, then a group of intersex patients with complete androgen insensitivity syndrome (CAIS) would not be expected to exhibit a male bias, as they have a complete end-organ resistance to androgenic effects. However, other variables related to CAIS, such as the presence of a Y-chromosome, testes and shallow vagina, have been suggested to pose obstacles to healthy psychosexual development in this group (13). Additionally, CAIS women provide an ideal opportunity to investigate potential influences of estrogens on gender development in 46,XY individuals who are unresponsive to androgens, yet respond to estrogens (14).

Subjects and Methods

The research reported here was approved by the Joint Committee of Clinical Investigations of The Johns Hopkins University School of Medicine, The Johns Hopkins Hospital (Baltimore, MD). Written, informed consent was obtained from all subjects before participation. Participants were asked to complete a written questionnaire before their physical examinations. During the physical examination, participants were asked to confirm their original questionnaire responses and also to elaborate on responses that were unclear or for which the participant desired further discussion.

Diagnostic criteria for CAIS subjects

CAIS diagnosis was based on the following: 1) presence of testes along with normal female external genitalia in a 46,XY individual, 2) identification of an androgen receptor (AR) gene mutation, 3) spontaneous feminization (but with no menses) at puberty before gonadectomy with no virilization despite normal or high male levels of testosterone,

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Address all correspondence and requests for reprints to: Dr. Amy B. Wisniewski, Department of Pediatrics, Division of Pediatric Endocrinology, The Johns Hopkins University School of Medicine, 600 North Wolfe Street, Park 211, Baltimore, Maryland 21287.

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and 4) markedly decreased or absent postpubertal axillary and pubic hair growth. The identification of an AR gene mutation is necessary for accurate diagnosis of AIS, as other syndromes of 46,XY intersex phenotypically resemble and can be reported erroneously as AIS (15). This is mostly true for partial forms of AIS.

Subjects

The total population of adult women with CAIS recorded in The Johns Hopkins Pediatric Endocrinology Clinic at the time of study consisted of 20 individuals, among whom 4 were not located, 1 did not respond to a study invitation, and 1 chose not to participate. The 14 women with CAIS who participated ranged in age from late 20s to mid-60s (mean age, 45 yr). All had been previously examined at the Johns Hopkins Pediatric Endocrinology Clinic. Nonparticipants did not differ from participants in terms of age or medical/surgical treatment received. To maintain participant anonymity age is presented in categories of 5 yr at the time of participation. Five of the 14 participants had been included in previous psychological studies when they were adolescents or young adults (16–18).

The specific AR gene mutations identified in subjects varied, as expected in light of the large number of AR gene lesions known to be associated with CAIS (19).

The only variance in the physical characteristics related to CAIS was with respect to adult sexual hair. Two women (14%) had absolutely no pubic or axillary hair, whereas the remaining 12 participants (86%) had no axillary or facial hair, but had minimal amounts of fine, silky pubic hair (early Tanner stage 2; Table 1).

Physical measurements

Physical measurements at birth. Appearance of external genitalia and weight at birth were determined from medical records. Birth weight was considered in light of previous reports of reduced birth weight associated with AIS (20).

Physical measurements in adulthood. These were obtained during an examination that took place in the Pediatric Clinical Research Unit at The Johns Hopkins Hospital as well as from medical records. Adult height was calculated as a percentile extrapolated from a growth chart for women (Serono, Norwell, MA). Weight at time of participation was determined in relation to medium build statistical norms published by Metropolitan Life Insurance Co. for women (www.indexmedico.com). Weight was documented according to the number of kilograms below or above the mean value for healthy women in relation to height. This mode of data presentation was elected to maintain the anonymity requested by participants.

The cosmetic appearance of external genitalia and breast development were evaluated independently and then agreed upon by an experienced pediatric endocrinologist (C.J.M.) and a reconstructive surgeon (J.P.G.). Vaginal depth was measured with graduated vaginal dilators and reported in centimeters. Clitoral length was measured with

a tape measure and reported in centimeters. Breast size was also measured with a tape measure and reported in centimeters, both horizontally and vertically for each breast, as conventionally performed by pediatric endocrinologists. Ages at gonadectomy and vaginoplasty were obtained from medical records. The number of surgical procedures as well as type of vaginoplasty procedure performed were obtained from medical records and were verified during physical examination.

Participants were asked first with an open-ended question and then as a review of the major body systems if they experienced medical conditions other than CAIS, to determine whether women with this syndrome were at an increased risk for additional problems. Finally, participants were asked during the physical exam to indicate their level of compliance with estrogen therapy after gonadectomy.

Psychosexual assessment

Sexual function. Participants were asked about the overall adequacy of their genitalia for sexual functioning, the estimated strength of their libido, and their ability to experience orgasms in a written questionnaire and again during the physical examination. Subjects also reported their degree of overall satisfaction with sexual functioning.

Body image. Participants were asked about their level of satisfaction with their physical appearance in a written questionnaire and again during the physical examination. When dissatisfied with their physical appearance, participants were asked which physical characteristics contributed to this dissatisfaction.

Self-perceived femininity and masculinity. Participants were asked in a written questionnaire, how masculine and feminine they considered themselves during their childhood, adolescence, and adulthood. This section of the questionnaire was based on the Sexual Behavior Assessment Schedule–adult version (Meyer-Bahlburg, H. F. L., and A. A. Ehrhardt, unpublished).

Sexual orientation. Participants were asked in a written questionnaire if they were sexually attracted to, fantasized about, or participated in sexual activity with men (female heterosexual orientation), women (female homosexual orientation), or both (female bisexual orientation) during adolescence and adulthood. This section of the questionnaire was adapted from the Sexual Behavior Assessment Schedule–adult version (Meyer-Bahlburg, H. F. L., and A. A. Ehrhardt, unpublished).

Marriage and motherhood. Frequencies of marriage and motherhood by adoption were asked for all participants in a written questionnaire.

Satisfaction with sex of rearing. Participants reported in a written questionnaire and during the physical examination on their degree of satisfaction with being a woman. Furthermore, participants were asked if at any point in their lives they had questioned their female gender or considered changing sex.

TABLE 1. Information regarding race, age, androgen receptor gene mutation, ages at surgeries, and appearance of genitalia for CAIS subjects at time of participation

ID no.	Race	Age (yr)	Androgen receptor gene mutation	Adult sexual hair	Age (yr) at gonadectomy	Age (yr) at vaginoplasty	Length of clitoris (cm)	Depth of vagina (cm)
1	Caucasian	25–30	Exon 5	Minimal	14	None	1	12
2	Caucasian	30–35	Exon 1	Minimal	2	None	1.5	8.5
3	Caucasian	36–40	Exon 3	None	16	None	1	8
4	African American	36–40	Exon 3	None	19	None	1	4.5
5	Caucasian	36–40	Deletion	Minimal	17	17, 35	0.75	14
6	African American	36–40	Exon 5	Minimal	18	None	1	13
7	African American	36–40	Exon 5	Minimal	15	None	1	13
8	Caucasian	41–45	Deletion	Minimal	18	None	1	6
9	Caucasian	41–45	Deletion	Minimal	17	None	0.2	7
10	African American	46–50	Exon 5	Minimal	16	16	1	8
11	Caucasian	46–50	Exon 7	Minimal	16	16	1	7
12	Caucasian	51–55	Not available	Minimal	13	21	0.1	4.5
13	Caucasian	56–60	Exon 7	Minimal	20	20	0.1	8
14	Caucasian	61–65	Exon 7	Minimal	21	21	1	10

Participants' opinions concerning timing of surgical treatment/third sex. Participants were asked their opinion regarding appropriate timing of gonadectomy and vaginoplasty in a written questionnaire and during the physical examination. Although the question of optimal timing for surgical treatment of intersex patients has focused on the reconstruction of ambiguous external genitalia, surgical modification of gonadal and posterior vaginal status in CAIS women also leads to permanent consequences and therefore should be considered in this patient group.

Participants were asked their opinion regarding the categorization of intersex children as a "third gender" in opposition to the more traditional categories of male or female. Although this third gender classification usually applies to individuals with ambiguous external genitalia, it can be extended to CAIS women who possess a Y-chromosome and testes. Participants were also asked if they agreed with the concept of recognizing a third intersex category within our society as an alternative to treating intersex patients as either males or females. This question was included due to suggestions that intersex patients should not be raised according to strictly male or female categories (21, 22).

Long-term psychological treatment

Participants reported in a written questionnaire and during physical examination whether they had ever received counseling concerning their condition.

Knowledge of medical history

Participants reported their level of satisfaction regarding their knowledge of AIS in a written questionnaire. Participants were also evaluated by a pediatric endocrinologist (C.J.M.) and psychologist (A.B.W.) to determine their level of understanding of AIS at the time of study participation. Specifically documented was participants' knowledge of their gonadal development, karyotype, and importance of estrogen therapy as presented in our Patients' Guide to Syndromes of Abnormal Sex Differentiation (23).

Statistical analysis

Due to the unique nature of CAIS, it is impossible to identify an appropriate control group. Additionally, the low frequency of this syndrome in the general population led to data presentation in the form of descriptive statistics and raw data.

Results

Physical measurements at birth

Mean birth weight for participants was 3.5 kg (range, 2.26–4.1 kg), which did not differ from that of the general population (3.4 kg; range, 2.5–4.6 kg) (24). External genitalia was completely female with no abnormalities at birth for all participants.

Physical measurements in adulthood

Adult height of eight subjects (57%) fell at or exceeded the 90th percentile of the range of control adult females. Adult height of the remaining women (43%) fell between the 50th and 75th percentiles. Seven participants (50%) were within ± 10 kg of their ideal weight range. The remaining seven participants exceeded their ideal weight by 15 kg or more, three of whom exceeded their ideal by 80 kg or more.

Most gonadectomies and vaginoplasties were performed on participants during their adolescence or adulthood (Table 1). Eight participants did not require vaginoplasty for peno-vaginal intercourse (one was homosexual), and one woman required vaginoplasty twice. Vaginoplasty consisted of a McIndoe partial thickness skin graft in all cases. Both examining physicians rated the appearance of the external genitalia as good for all women. Average clitoral length was 0.83

cm (range, 0.1–1.5 cm); no participant exhibited clitoral enlargement, and none required clitoroplasty. The eight women who did not experience vaginoplasty had an average vaginal length of 9 cm (range, 4.5–13 cm). The six women with a history of vaginoplasty had an average vaginal length of 8.6 cm (range, 4.5–14 cm). These measures are consistent with previous measures of mean vaginal length ranging from 7–11 cm (25–27). All women had breast development, with wide variability in breast size (range, 16 \times 14 to 41 \times 31 cm).

Regarding the occurrence of other medical conditions among CAIS women, obesity (43%) and bone loss (43%) were both reported most frequently (Table 2).

The degree of compliance with estrogen replacement therapy was determined for all participants based on information obtained from written questionnaire responses, medical charts, and discussion during the physical examination. Nine participants reported that they were compliant, whereas the remaining five women reported they had not taken estrogen replacement for most of their adult lives after gonadectomy.

Psychosexual assessment

Sexual function. Eleven of the women with CAIS studied (78%) reported satisfaction with their genitalia in terms of sexual functioning, whereas 3 others (22%) reported dissatisfaction. Ten women (71%) reported satisfaction with their sexual function overall, and four women (29%) were dissatisfied.

Despite their complete end-organ resistance to androgens, the majority of CAIS women (71%) reported a self-estimated libido of average strength or stronger, and 10 of the 13 who responded (77%) reported an ability to experience orgasms.

Body image. When provided with three response options (mainly satisfied, somewhat dissatisfied, mainly dissatisfied) regarding degree of satisfaction with physical appearance, eight women (57%) reported they were mainly satisfied, five (36%) reported being somewhat dissatisfied, and one woman reported mainly dissatisfaction with her physical appearance. Of the six women who reported being either somewhat dissatisfied or mainly dissatisfied with their physical appearance, five reported inadequate body hair, five reported looking younger than actual age, and three reported obesity as factors that contributed to this dissatisfaction.

TABLE 2. Medical and psychiatric conditions reported by CAIS women

ID no.	Medical and psychiatric conditions
1	Osteoporosis
2	Osteoporosis, breast fibroid cysts, scoliosis
3	Obesity, hypothyroid, high cholesterol
4	Obesity
5	Obesity, osteoporosis
6	Obesity, diabetes II, asthma
7	High blood pressure
8	Bulemia, osteoporosis
9	Osteoporosis
10	Depression, drug addiction, poor general health
11	Obesity, high cholesterol, asthma, high blood pressure
12	Abdominal pain
13	Obesity, hernias
14	Osteoporosis, stroke, gall stones

Self-perceived femininity and masculinity. Women with CAIS overwhelmingly reported a high degree of femininity along with a low degree of masculinity throughout development. Mean femininity rating (not feminine = 1 to highly feminine = 5) for subjects during childhood was 4.4 (range, 2–5), during adolescence was 4.2 (range, 3–5) and during adulthood was 4.6 (range, 4–5). Mean masculinity rating (not masculine = 1 to highly masculine = 5) for subjects during childhood was 1.4 (range, 1–4), during adolescence was 1.4 (range, 1–3), and during adulthood was 1.1 (range, 1–2).

Sexual orientation. A large majority of CAIS women reported female heterosexual orientation in terms of sexual attraction, fantasies, and experience during both adolescence (100%) and adulthood (93%). The one participant who reported homosexual attraction, fantasies, and experiences indicated that a lesbian orientation applied only to her adulthood. Clearly, in this case the development of female homosexuality was not associated with androgen exposure.

Marriage and motherhood. Seven women (50%) were married at the time of participation, and the mean age at first marriage was 27 yr (range, 16–38 yr). Five of these and one unmarried woman (43%) were mothers through adoption. Of the seven participants who were not married, one was engaged, one was homosexual, one was not interested in marriage, and the remaining four women expressed a desire for marriage to a man but had not yet met a satisfactory partner.

Satisfaction with sex of rearing. CAIS women unanimously reported satisfaction with being a woman (100%). Two participants (18%) questioned their physical status as women, but none reported a desire to change sex to that of a man.

Participants' opinions of timing of surgical treatment/third sex. The majority of women who responded indicated the most appropriate timing for their surgical procedures was during adolescence or adulthood (8 of 10 respondents, or 80%). Two women reported the most appropriate timing for surgery was during infancy.

The vast majority of participants (81% of the 11 who responded) did not approve of rearing intersex children according to a third gender.

Long-term psychological treatment

The majority of CAIS women studied received some form of counseling (83%) at various ages and for various lengths of time (1–15 yr) concerning aspects of their syndrome.

Knowledge of medical history

Eight CAIS women (57%) exhibited no understanding of CAIS (*i.e.* were unaware of their karyotype, gonadal characteristics, or the importance of estrogen replacement) at the time of participation, and only 64% indicated that they were satisfied with their level of knowledge regarding their condition. It could not be determined if participants ever received information about their syndrome or if they were previously informed but did not recall the information. Nevertheless, this finding emphasizes the importance of following CAIS patients into adulthood and subsequently offering them adult education about their syndrome.

Discussion

To determine the natural history of CAIS and long-term outcome of treatment intervention, it is necessary to follow affected individuals over time. Previous knowledge of CAIS has been based on studies of relatively young patients. Such young CAIS women overwhelmingly report contentment with being female, a desire for marriage and motherhood, sexual attraction and practice exclusively oriented toward men, as well as the ability to experience orgasms (16–18, 28). However, it is likely that older women have the benefit of greater experience with their gender and sexuality compared to younger women and girls. The present study extends our knowledge of CAIS to an older cohort of women.

Furthermore, quality of sexual function and appearance of genitalia and secondary sexual characteristics were considered in conjunction with our psychosexual evaluation. Previous psychosexual studies of intersex patients have not consistently assessed outcome of medical and surgical treatment in terms of sexual function and appearance. It is likely that factors such as an individual's cosmetic appearance and quality of sexual function influence gender and sexuality, and therefore should be considered in psychosexual outcome research concerning intersex populations.

Physical

CAIS babies appeared no different from unaffected infants in terms of birth weight or genital appearance. Consistent with previous reports, CAIS women tend to be tall (29, 30) and experience normal feminization of secondary sexual characteristics, with the exception of lacking female-typical amounts of axillary and pubic hair in adulthood (31). Interestingly, 12 participants had a minimal amount of fine, soft pubic hair but no axillary hair. This is consistent with previous observations in this group of vellus down on the body that is not androgen dependent (32). Aside from lacking sexual hair, the external genitalia of all participants appeared normal. Six women (43%) had undergone vaginoplasty, but none required or had clitoroplasty.

Psychosexual

Most CAIS women were satisfied with their sexual functioning. However, three (21%) were dissatisfied. Of these, one did not receive any genital reconstructive surgery despite a shallow vaginal depth and thinks she would be unable to participate in peno-vaginal intercourse. Although this woman has never attempted peno-vaginal intercourse, she has discovered great satisfaction from homosexual sexual activity. The remaining two had undergone vaginoplasties that resulted in sufficient vaginal length for peno-vaginal intercourse. Their dissatisfaction may be related to other variables. One woman was a victim of sexual abuse early in life and is presently in poor health resulting from substance abuse; the other reported severe dissatisfaction with her body image.

Libido and ability to experience orgasms were not a problem for the CAIS women in this study. This illustrates that although androgens may contribute to libido and orgasmic potential in non-CAIS women (33–35), libido and orgasm can

be experienced by women who exhibit complete end-organ insensitivity to androgens. Furthermore, there were no differences in self-reported libido based on compliance with estrogen therapy. Vaginal lubrication is another characteristic of sexual functioning thought to be related to estrogen levels. No participant reported difficulty with vaginal lubrication on the written questionnaire or during the physical examination.

Despite some of the unhappiness with physical attributes, the majority of women with CAIS were mainly satisfied with their physical appearance.

CAIS women overwhelmingly perceive themselves as highly feminine and not masculine throughout development. Additionally, CAIS women largely report their sexual attraction, fantasies, and experiences were best described as female heterosexual. Concerning the one woman who reported heterosexual attraction and fantasies in adolescence followed by homosexual thoughts and actions in adulthood, perhaps a short vagina coupled with fear of vaginoplasty contributed to this change. Several women were married and/or mothers. All participants reported being mainly satisfied when asked their degree of satisfaction in being a woman. Of the two women who stated that they questioned their physical status as women, one responded that this was due to her inability to menstruate and become pregnant, and the other reported that this was in response to media articles she encountered regarding intersexuality.

Treatment

Several issues of long-term health status are of concern in our CAIS participants. First, long-term compliance with estrogen replacement is less than optimal in this group. Second, older CAIS women as a group are obese. However, obesity among women with CAIS mirrors rates observed in the population of American women at large and does not appear to be directly related to this condition (36, 37). Lastly, women with CAIS appear to be at risk for bone-related disease. It is unclear at this time, however, if this is a result of androgen insensitivity *per se*, a consequence of inadequate estrogen replacement, or both (38).

Most women (80% who responded) sought psychological counseling at some point in development, as indicated by the written questionnaire. The majority of participants did not believe a third gender category was appropriate for intersex patients. These points stress the importance of providing well rounded care to these patients that includes counseling services as well as medical and surgical care.

The great majority of these CAIS women (78%) reported that the most appropriate timing of gonadectomy and vaginoplasty procedures was during adolescence or adulthood. More than half (64%) did not fully understand their diagnosis in adulthood, and the majority indicated a desire to better understand their condition. However, all women stressed the importance of confidentiality regarding their condition. These results support the concerns of CAIS patient advocacy groups regarding the disclosure of medical information to patients and the postponement of vaginoplasty to late adolescence or adulthood for CAIS patients (8, 39).

Complete insensitivity to androgen action is clearly an

extreme in the spectrum of congenital malformations of sex organs. Additional studies of long-range outcome of subjects with partial AIS and other conditions associated with ambiguous genital development are in progress.

References

1. Money JM, Hampson JG, Hampson JL. 1957 Imprinting and the establishment of gender role. *Arch Neurol Psychol.* 77:333–336.
2. Money J, Dalery J. 1976 Iatrogenic homosexuality: Gender identity in seven 46,XX chromosomal females with hyperadrenocortical hermaphroditism born with a penis, three reared as boys, four reared as girls. *J Homosexuality.* 1:357–371.
3. Money J, Schwartz M, Lewis VG. 1984 Adult erotosexual status and fetal hormonal masculinization and demasculinization: 46,XX congenital virilizing adrenal hyperplasia and 46,XY androgen-insensitivity syndrome compared. *Psychoneuroendocrinology.* 9:405–414.
4. Money J, Lehne GK, Pierre-Jerome F. 1985 Micropenis: gender, erotosexual coping strategy and behavioral health in nine pediatric cases followed to adulthood. *Comp Psychol.* 26:29–42.
5. Money J, Devore H, Norman BF. 1986 Gender identity and gender transposition: longitudinal outcome study of 32 male hermaphrodites assigned as girls. *J Sex Mar Ther.* 12:165–181.
6. Money J, Norman BF. 1987 Gender identity and gender transposition: longitudinal outcome study of 24 male hermaphrodites assigned as boys. *J Sex Mar Ther.* 13:75–79.
7. Money J. 1994 Hormones, hormonal anomalies, and psychologic health care. In: Kappy MS, Blizzard RM, Migeon CJ, eds. *Wilkins' the diagnosis and treatment of endocrine disorders in childhood and adolescence*, 4th Ed. Springfield: Thomas; 1141–1178.
8. Money J. 1994 *Sex errors of the body and related syndromes: a guide to counseling children, adolescents and their families*, 2nd Ed. Baltimore: Brookes.
9. Money J, Ehrhardt A. 1972 *Man and woman, boy and girl: differentiation and dimorphism of gender identity from conception to maturity*. Baltimore: Johns Hopkins University Press.
10. Bradley SJ, Oliver GD, Chernick AB, Zucker KJ. 1982 Experiment of nurture: ablation penis at 2 months, sex reassignment at 7 months, and a psychosexual follow-up in young adulthood. *Pediatrics.* 102:E91–E95 (<http://www.pediatrics.org/cgi/content/full/102/1/e9>).
11. Diamond M, Sigmundson HK. 1997 Sex reassignment at birth: long-term review and clinical implications. *Arch Pediatr Adolesc Med.* 151:298–304.
12. Zucker KJ. 2000 Intersexuality, and gender identity differentiation. *Annu Rev Sex Res.* 10:1–69.
13. Migeon CJ, Wisniewski AB. 1998 Sex differentiation: from genes to gender. *Horm Res.* 50:245–251.
14. Meyer-Bahlburg HFL. 1997 The role of prenatal estrogens in sexual orientation. In: Ellis L, Ebertz L, eds. *Sexual orientation: toward biological understanding*. Westport: Praeger.
15. Boehmer ALM, Brinkmann AO, Sandkuijl LA, et al. 17 β -Hydroxysteroid dehydrogenase 3 deficiency: diagnosis, phenotypic variability, population genetics, and world-wide distribution of ancient and *de novo* mutations. *J Clin Endocrinol Metab.* In press.
16. Money J, Ehrhardt AA, Masica DN. 1968 Fetal feminization induced by androgen insensitivity in the testicular feminizing syndrome: effect on marriage and maternalism. *Johns Hopkins Med J.* 123:105–114.
17. Masica DN, Money J, Ehrhardt AA. 1971 Fetal feminization and female gender identity in the testicular feminizing syndrome of androgen insensitivity. *Arch Sex Behav.* 1:131–142.
18. Lewis VG, Money J. 1983 Gender-identity/role: G-I/R. A. XY (androgen-insensitive) syndrome and XX (Rokitansky) syndrome of vaginal atresia. In: Dennerstein L, Burrows G, eds. *Handbook of psychosomatic obstetrics and gynaecology*. Amsterdam: Elsevier.
19. Gottlieb B, Trifiro M, Lumbroso R, Pinsky L. 1997 The androgen receptor gene mutation database. *Nucleic Acids Res.* 25:158–162 (www.mcgill.ca/androgendb).
20. de Zegher F, Francois I, Ibanez L. 1999 Pediatric endocrinopathies related to reduced fetal growth. *Growth Genet Horm.* 15:1–6.
21. Fausto-Sterling A. 1993 The five sexes: why male, and female are not enough. *The Sciences.* 33:20–25.
22. Diamond M, HK Sigmundson. 1997 Management of intersexuality: guidelines for dealing with persons with ambiguous genitalia. *Arch Pediatr Adolesc Med.* 151:1046–1050.
23. Migeon CJ, Wisniewski AB, Gearhart JP. 1999 Syndromes of abnormal sex differentiation: a guide for patients and their families, <http://www.med.jhu.edu/pedendo/intersex/>.
24. Kaplan SL. 1987 Growth: normal and abnormal. In: Rudolph AM, Hoffman JIE, eds. *Pediatrics*, 18th Ed. Norwalk: Appleton & Lange; 75–91.

25. **Dickinson RL.** 1949 The vagina. In: Human sex anatomy, 2nd Ed. Baltimore: Williams & Wilkins; 34–35.
26. **Masters WH, Johnson VE.** 1966 The vagina. In: Human sexual response. Boston: Little Brown; 73–75.
27. **Given FT, Muhlendorf IK, Browning GM.** 1993 Vaginal length and sexual function after colopexy for complete uterovaginal eversion. *Am J Obstet Gynecol.* 169:284–287.
28. **Slijper FME, Drop SLS, Molenaar JC, de Muinck Keizer-Schrama MPF.** 1998 Long-term psychological evaluation of intersex children. *Arch Sex Behav.* 27:125–144.
29. **Polani PE.** 1970 Hormonal, and clinical aspects of hermaphroditism and the testicular feminizing syndrome in man. *Phil Trans R. Soc.* 259:187–204.
30. **Migeon CJ, Brown TR, Fichman KR.** 1981 Androgen insensitivity syndrome. In: Josso N, ed. The intersex child. *Pediatric and adolescent endocrinology.* Basel: Karger; 171–202.
31. **Migeon CJM, Berkovitz G, Brown TR.** 1994 Sexual differentiation and ambiguity. In: Kappy MS, Blizzard RM, Migeon CJ, eds. *Wilkins' the diagnosis and treatment of endocrine disorders in childhood and adolescence*, 4th Ed. Springfield; Thomas; 573–715.
32. **Quigley CA, De Bellis A, Marschke KB, El-Awady MK, Wilson EM, French FS.** 1995 Androgen receptor defects: historical, clinical and molecular perspectives. *Endocr Rev.* 16:271–321.
33. **Money J.** 1965 Influence of hormones on sexual behavior. *Annu Rev Med.* 16:67–82.
34. **Sherwin BB.** 1988 A comparative analysis of the role of androgen in human male, and female sexual behavior. *Psychobiology.* 16:416–425.
35. **Wiebke A, Callies F, Van Vlijmen JC, et al.** 1999 Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med.* 341:1013–1020.
36. **Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath Jr CW.** 1999 Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med.* 341:1097–1105.
37. **Sichieri R, Everhart JE, Hubbard VS.** 1991 Relative weight classifications in the assessment of underweight and overweight in the United States. *Int J Obesity.* 16:303–312.
38. **Marcus R, Leary D, Schneider DL, Shane E, Favus M, Quigley CA.** 2000 The contributions of testosterone to skeletal development and maintenance: lessons from the androgen insensitivity syndrome. *J Clin Endocrinol Metab.* 85:1032–1037.
39. **Medhelp.** 1999. <http://www.medhelp.org/www/ais>.