

Sexual Function in Adult Life Following Passerini-Glazel Feminizing Genitoplasty in Patients with Congenital Adrenal Hyperplasia

Arianna Lesma, Aldo Bocciardi, Stefano Corti,* Giuseppe Chiumello, Patrizio Rigatti and Francesco Montorsi

From the Department of Urology (AL, SC, PR, FM) and Department of Pediatrics (GC), San Raffaele Scientific Institute, Vita-Salute University and Department of Urology, Niguarda Ca'Granda Hospital (AB), Milan, Italy

Abbreviations and Acronyms

BDI = Beck Depression Inventory

CAH = congenital adrenal hyperplasia

FSFI = Female Sexual Function Index

GSA = Genito Sensory Analyzer

SAS = Self-Rating Anxiety Scale

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Study received joint university and hospital ethics committee approval.

* Correspondence: Department of Urology, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy (telephone: 39-02-2643-7299; FAX: 39-02-2643-7298; e-mail: stefano.corti85@libero.it).

Purpose: We assessed external genitalia sensitivity and sexual function in adults with congenital adrenal hyperplasia who had undergone Passerini-Glazel feminizing genitoplasty as children, and compared them to a control group of healthy counterparts.

Materials and Methods: Inclusion criteria were congenital adrenal hyperplasia, Passerini-Glazel feminizing genitoplasty, adult age and penetrative vaginal intercourse. Thermal and vibratory sensitivity of the clitoris, vagina and labia minora were analyzed using the Genito Sensory Analyzer (Medoc Ltd., Minnetonka, Minnesota). Psychosexual outcome was assessed with the Beck Depression Inventory, Zung Self-Rating Anxiety Scale, Female Sexual Distress Scale and Female Sexual Function Index. Matched analyses were performed to compare outcomes in patients to controls (healthy medical students). All statistical tests were performed using SPSS®, version 18.0

Results: A total of 12 patients (10%) entered the study. Thermal and vibratory clitoral sensitivity was significantly decreased in all patients compared to healthy controls ($p < 0.01$). There was no difference in thermal or vibratory vaginal sensitivity between patients and controls. On the Female Sexual Distress Scale 11 patients (91.6%) and 11 controls (91.6%) described a stable satisfactory relationship. All patients reported active sexual desire, good arousal, adequate lubrication and orgasm. No significant difference in Female Sexual Function Index global score or single domain scores was observed between patients and controls.

Conclusions: Although clitoral sensitivity in sexually active patients with congenital adrenal hyperplasia treated with Passerini-Glazel feminizing genitoplasty is significantly reduced compared to controls, sexual function in those patients is not statistically or clinically significantly different from their healthy counterparts. Finally, 1-stage Passerini-Glazel feminizing genitoplasty seems to allow normal adult sexual function.

Key Words: adrenal hyperplasia, congenital; disorders of sex development; genitalia, female; surgery, plastic; urogenital surgical procedures

LONG-TERM successful feminizing genitoplasty should provide 1) a good genital appearance, 2) normal menstrual outflow and 3) satisfactory

intercourse in adult life with painless penetration and normal orgasmic sensation. Many aspects of treatment remain controversial, such as type of

surgery and timing of surgical intervention.^{1–10} At our institute we usually perform early (before age 18 months) 1-stage Passerini-Glazel feminizing genitoplasty.¹¹

Loss of clitoral sensitivity and alteration of psychosexual status are suspected in women with CAH treated with genital surgery in infancy. We evaluated sexual function with particular emphasis on the sensitivity of the external genitalia in adults with CAH who underwent 1-stage Passerini-Glazel feminizing genitoplasty as children, and compared the results with an age matched control group of healthy women.

MATERIALS AND METHODS

Patients

We reviewed the medical records of 120 patients affected with disorders of sex development referred to us between 1980 and 2010. Inclusion criteria consisted of age 18 years or older, penetrative vaginal sexual intercourse, CAH and 1-stage Passerini-Glazel feminizing genitoplasty. Exclusion criteria consisted of diabetes, multiple sclerosis, peripheral neuropathy, lumbar radiculopathy, further pelvic or retroperitoneal surgery and major depressive disorders as possible causes of genital abnormal sensitivity.

Controls

Controls consisted of healthy university students 18 years or older who had engaged in penetrative sexual intercourse and had no surgical history or chronic pathology that might alter external genitalia sensitivity.

Recruitment and Study Protocol

Eligible patients were called for an outpatient visit and asked to participate in the study. Recruitment was voluntary and informed written consent was obtained. Ethical approval was granted by the joint university and hospital ethics committee. The study protocol consisted of 1) clinical evaluation, 2) instrumental evaluation and 3) psychosexual evaluation using internationally validated questionnaires.

Clinical Evaluation

A semistructured interview was performed, which assessed gender identity, age at first sexual intercourse, heterosexual or homosexual orientation, marital status and pregnancy. Moreover, recurrent urinary tract infections and local vaginal inflammation were assessed as possible signs of gynecologic pathologies (urethrovaginal fistula, vaginal stenosis). A genital examination was performed. Patients and controls were also asked to rate the overall cosmetic appearance of the external genitalia.

Instrumental Evaluation

Thermal and vibratory sensitivity of the clitoris, vagina and labia minora was analyzed using the Genito Sensory Analyzer.¹² The GSA has 2 probes, 1 for temperature and 1 for vibratory testing. The thermal probe is a cylinder with a diameter of 2.8 cm and length of 13.5 cm, with a working temperature of 20C to 50C. The vibration probe

is 2.4 cm in diameter and 10.3 cm long, and it vibrates throughout its length at a fixed frequency of 100 Hz, with an amplitude of 0 to 130 μ m. Each probe was used externally on the clitoris and labia minora and inserted into the vagina. The probes produce stimuli in linear increments. When the patient perceives the first sensation, she stops the stimulation with a feedback patient response switch by button press. Tests were repeated 6 times each for warmth, cold and vibration at each site, and the mean of the 6 readings was calculated.

Psychosexual Evaluation

Psychosexual outcome and sexual function were assessed with internationally validated questionnaires. BDI and Zung SAS investigate depression and anxiety, respectively, which have an important role in the pathogenesis of sexual dysfunction in adult life. We investigated feelings of personal responsibility about sexual problems, level of discomfort, sadness, guilt, frustration, stress and feelings of inferiority, anxiety, inadequacy and embarrassment. To objectively analyze sexual function, we used the FSFI regarding the domains of sexual desire, arousal, vaginal lubrication, orgasm, satisfaction and pain. These questionnaires are described in detail elsewhere.^{13–16}

Statistical Analysis

Frequency and distribution characteristics were examined. A preliminary Kolmogorov-Smirnoff test proved all variables to be parametric, so independent Student t-test was used to test for differences between patients and controls. Effect sizes were evaluated with the Cohen test. All statistical tests were performed using SPSS, version 18.0.

RESULTS

Patients

Of our 120 patients with disorders of sex development 95 had CAH and underwent Passerini-Glazel feminizing genitoplasty as described by Lesma et al.¹⁷ Of these patients 64 were younger than 18 years. Of the 31 adults 14 (mean age 19 years) had not had penetrative sexual intercourse. Thus, only 17 patients met inclusion criteria. Five patients refused to enter the study and, therefore, 12 patients were enrolled. Mean patient age was 26 years (range 24 to 31).

Nine patients had undergone redo procedures elsewhere, which included reductive clitoroplasty and vaginoplasty (pull-through or cutback technique), and were subsequently referred to us due to poor outcome (residual hypertrophic clitoris, hypospadias, vaginal stenosis). These patients underwent 1-stage Passerini-Glazel feminizing genitoplasty at our institution at a mean age of 13 years, before menstruation or sexual intercourse, to avoid hematocolpos and dysfunctional intercourse. Four patients also underwent vaginal YV-plasty at a mean age of 15 years due to stenosis at the internal vaginal suture line.

Three patients had undergone 1-stage Passerini-Glazel feminizing genitoplasty as first surgery for high urogenital sinus at a mean age of 18 months (range 1 to 2 years). One of these patients underwent vaginal YV-plasty at age 12 years.

No patient underwent vaginal dilation before becoming sexually active. All patients and families were periodically followed by our multidisciplinary medical team, especially by the psychologist and the endocrinologist, throughout childhood, adolescence and adulthood. No patient was lost to followup.

Controls

A total of 24 healthy women were considered for study enrollment, of whom 4 did not meet inclusion criteria (2 did not have penetrative vaginal intercourse, 1 had diabetes and 1 had previously undergone perineal surgery). Of the remaining 20 controls only 12 agreed to participate in the study. Mean age was 26 years (range 23 to 30).

Clinical Evaluation

Mean age at menarche was 15.5 years in the patients with salt-wasting CAH and 13.5 years in patients with simple virilizing CAH. Ten patients and 12 controls were using oral contraceptives at entry into the study.

On genital examination the appearance and size of the clitoris were satisfactory in all cases.¹⁸ The urethral meatus was never located in a hypospadiac position. The vaginal introitus was always in a physiological position, and it was large and elastic in all cases with easy introduction of the GSA vibration probe (2.4 cm diameter) and the GSA thermal probe (2.8 cm). The labia majora were regular for position and dimension in all cases, while the labia minora were regular for position and dimension in 11 and hypotrophic in 1. All patients and controls were satisfied with the appearance of the external genitalia.

Instrumental Evaluation

Clitoral, vaginal and labia minora sensitivity testing was conducted. Compared to healthy controls, all redo and preliminary cases demonstrated

significant impairment of clitoral thermal sensitivity, with a higher mean threshold for warmth and a lower mean threshold for cold (table 1). All redo and preliminary cases showed a significant reduction of clitoral vibratory sensitivity with a higher mean threshold for vibration. No difference in vaginal thermal or vibratory sensitivity was observed between the 2 groups. Finally, the thermal sensitivity of the labia minora was investigated in all cases and controls, whereas vibratory sensitivity could not be evaluated because the vibratory probe vibrates throughout its length and does not allow stimulation of the labia minora without involvement of the clitoris. No difference was observed in labia minora thermal sensitivity between patients with CAH and healthy women.

Psychosexual Evaluation

Questionnaires were completed by all patients and controls. BDI revealed slight depression in only 1 patient (table 2). Zung SAS demonstrated slight anxiety in 10 patients vs 11 controls and no anxiety in 2 patients vs 1 control. On the Female Sexual Distress Scale 11 patients and 11 controls described a stable satisfactory relationship (heterosexual in 10 patients and 11 controls, homosexual in 1 patient and 0 controls). One patient and 1 control reported a stable but unsatisfactory heterosexual relationship with a feeling of frustration, discomfort and inferiority.

On the FSFI patients had either high (6) or moderate (1) sexual desire. Sexual arousal during sexual stimulation was present in all cases and was always of high intensity. Vaginal lubrication was present in all cases. Pain at penetration was described as absent by 7 patients and slight by 4, and was not evaluated in 1 homosexual patient. All 12 patients reported reaching orgasm easily, always or almost always. Compared to healthy controls, the global score and single domain scores for patients did not differ significantly (table 3).

According to the semistructured interview, first sexual intercourse was at a mean of 23 years (range 22 to 25) in patients and 18 years (16 to 19) in

Table 1. Threshold sensation of clitoris, vagina and labia minora in CAH cases and healthy controls

Threshold	Mean \pm SD CAH Cases (range)	Mean \pm SD Controls (range)	Difference (p value)*
Clitoris:			
C warmth	46.61 \pm 1.92 (42.25–48.65)	40.10 \pm 0.80 (39.50–42.20)	–10.36 (<0.01)
C cold	24.87 \pm 2.09 (22.40–30)	32.20 \pm 1.79 (29.80–34.90)	8.82 (<0.01)
μ m Vibration	6.75 \pm 3.40 (3.50–13.65)	1.85 \pm 1.05 (1.10–4.90)	–4.56 (<0.01)
Vagina:			
C warmth	44.8 \pm 1.03 (43.30–46.30)	44.50 \pm 1.48 (42.10–47.90)	–0.55 (0.58)
C cold	28.7 \pm 1.71 (27–33.50)	28.90 \pm 1.35 (27.50–32.70)	0.30 (0.76)
μ m Vibration	4.14 \pm 1.44 (2–7.75)	3.50 \pm 0.75 (1.50–4.10)	–1.29 (0.21)
Labia minora:			
C warmth	44.84 \pm 1.81 (41.50–47.80)	44.60 \pm 2.18 (40.20–47.90)	–0.27 (0.78)
C cold	25.34 \pm 1.38 (24.20–28.50)	26.30 \pm 1.53 (24.10–28.90)	1.55 (0.17)

*Independent Student t-test.

Table 2. Beck Depression Inventory, Zung Self-Rating Anxiety Scale and Female Sexual Distress Scale scores in CAH cases and healthy controls

Tool (score)	CAH Cases		Controls		Difference	
	No.	Mean \pm SD Score (range)	No.	Mean \pm SD Score (range)	(p value)*	κ (p value)†
BDI:						
Min depression (less than 14)	11	1.25 \pm 1.34 (0–3)	12	1.25 \pm 1.40 (0–4)	1.04 (0.30)	–0.04 (0.53)
Mild depression (14–19)	1	15	0	Not applicable		
Zung SAS:					0.38 (0.53)	0.02 (0.53)
No anxiety (less than 20)	2	16 \pm 1.41 (15–17)	1	18		
Mild anxiety (21–40)	10	30 \pm 4.63 (26–37)	11	28 \pm 3.46 (25–35)		
Female Sexual Distress Scale:					0.005 (0.94)	–0.004 (0.98)
No dysfunction (less than 20)	11	8.9 \pm 1.50 (7–18)	11	8.41 \pm 3.94 (6–17)		
Dysfunction (20 or greater)	1	30	1	35		

* Independent Student t-test.

† Cohen test.

controls. Mean reported number of sexual partners was 2 (range 1 to 3) for patients and 4 (1 to 6) for healthy controls. Three patients and 4 controls lived with a partner, while no patient and 2 controls were married. No patient and 1 control had children. One patient had heterosexual intercourse at the beginning of her sexual life and experienced penetrative intercourse with satisfaction. Later she switched to homosexual intercourse for personal reasons unrelated to anatomical/functional sexual problems.

DISCUSSION

In the present study thermal and vibratory clitoral sensitivity in patients with CAH appeared impaired compared to healthy controls. It is possible that innervation of the external genitalia in these cases is abnormal from birth, although this seems an unlikely explanation for our findings.⁸ Rather than an effect of CAH, the abnormal thermal sensitivity may be a result of surgery. All techniques of feminizing genitoplasty include important deconstructing surgical steps that can damage innervation. Anatomical studies show that the clitoris is the most densely innervated part of the human body, and even with careful surgical techniques, divided nerves are present in corporeal specimens obtained from women with CAH.¹⁹

The majority of our patients (9, 75%) underwent redo surgery elsewhere, consisting of reductive

clitoroplasty or vaginoplasty (pull-through or cut-back). In these cases data about the clitoral surgical technique were obtained from medical notes, where “reductive clitoroplasty” was reported without any further description. The 3 patients (25%) undergoing preliminary Passerini feminizing genitoplasty at our institution underwent repair at the beginning of the 1980s. At that time our reductive clitoroplasty technique preserved only the dorsal neurovascular bundle from the 1 o’clock to the 11 o’clock position. Beginning in 2000, after Baskin et al redefined clitoral neuroanatomy,²⁰ we started to perform a larger dissection of the neurovascular bundle by performing Buck fascia incisions at the 5 and 7 o’clock positions, as later described by Poppas et al.²¹ We believe that in this way the great majority of neural fibers are maintained, resulting in better preservation of sensitive function as described by Yang et al.²² In the future we will be able to report on a more selected population submitted to Passerini-Glazel genitoplasty as first surgery,^{11,17} and modern reductive clitoroplasty.^{20,21}

Reduced clitoral thermal and vibratory sensitivity seems to have no clinical relevance, since all patients reported reaching orgasm easily, always or almost always, even in the absence of penetration (homosexual relationship). A good functional result could be related to the absence of vaginal stenosis. The vibration probe, which has a diameter of 2.4 cm, and the thermal probe, which has a diameter of 2.8 cm, could be inserted in the vagina of all patients. At FSFI evaluation discomfort or pain during or following vaginal penetration was never or almost never present (10 patients, 83.3%), with no significant difference compared to healthy controls. No difference was observed in thermal and vibratory vaginal sensitivity between patients with CAH and healthy controls.

In addition, the vulvar epithelium has an important role in female sexual arousal and pleasure,²³ and genital tactile stimulation is regarded as

Table 3. Female Sexual Function Index scores in CAH cases and healthy controls

	Mean \pm SD CAH Cases (range)	Mean \pm SD Controls (range)	Difference (p value)*
Global score	23.31 \pm 10.78 (3.6–33.7)	23.27 \pm 9.96 (2.4–33.4)	–0.01 (0.94)
Sexual desire	4.2 \pm 0.67 (3.6–5.4)	4.31 \pm 1.19 (2.4–6)	0.25 (0.80)
Arousal	3.73 \pm 1.92 (0–6)	3.73 \pm 1.93 (0–5.7)	–0.15 (0.88)
Lubrication	3.96 \pm 2.27 (0–6)	3.57 \pm 1.89 (0–6)	–0.43 (0.67)
Orgasm	3.62 \pm 1.93 (0–6)	3.62 \pm 1.93 (0–6)	–0.11 (0.91)
Satisfaction	3.72 \pm 1.10 (0–6)	3.63 \pm 1.92 (0–5.2)	–0.09 (0.92)
No pain	4.36 \pm 2.04 (0–6)	4.40 \pm 2.22 (0–6)	0.04 (0.96)

* Independent Student t-test.

a precursor to sexual arousal and perhaps, for women, the most easily recognized initiator of central nervous system arousal.²⁴ For this reason we investigated labia minora sensitivity, and to our knowledge this is the first attempt to do so. Compared to controls, patient thermal sensitivity at the labia minora was preserved.

Regarding clitoral and vaginal sensitivity, our results are in agreement with studies by Crouch et al,^{8,10} although they could evaluate vaginal vibratory sensitivity and vaginal thermal sensitivity in only 57% and 28% of cases, respectively, because of vaginal stenosis that did not allow thermal and vibratory probe introduction. Their greater incidence of vaginal stenosis could be due to the fact that most of their patients underwent flap vaginoplasty, leaving the anterior wall of the urogenital sinus intact, whereas in the Passerini-Glazel procedure we disconnected the vagina from the urogenital sinus and created its missing distal part using a tubularized mucocutaneous flap.¹⁷ The greater incidence of vaginal stenosis in that study could explain the increased incidence of sexual dysfunction. In our population decreased sexual feeling with the partner and frustration, discomfort and feeling of inferiority with heterosexual intercourse were described in only 1 patient with moderate dyspareunia due to vaginal substenosis. These data suggest that painless vaginal penetration is a fundamental factor for satisfactory intercourse in adult life.

One limitation of the present series is the small study population. CAH is a rare congenital anomaly,^{24,25} and inclusion criteria made recruitment

selective in an already select population. Another limitation is that of the 31 adults with CAH 14 had not had penetrative sexual intercourse. In the overall study population mean age at first sexual intercourse was 23 years. Of the 14 adults who had not had penetrative intercourse 10 were younger than 20 years (mean age 19). Thus, the majority of patients who were virgins were younger than mean age at first sexual intercourse in this population. However, we cannot exclude that these patients correspond with the ones with vaginal stenosis or unsatisfactory cosmetic results, who, therefore, do not feel comfortable enough to have sexual interaction.

Selection bias could also be caused by voluntary recruitment. The study analyzes personal and private aspects of sexual life, and many patients and healthy controls may decline participation. It is possible that these individuals are the ones with sexual functional problems. Nevertheless, approval was granted by the hospital ethics committee only if recruitment was voluntary.

CONCLUSIONS

In sexually active patients treated with Passerini-Glazel feminizing genitoplasty thermal and vibratory clitoral sensitivity instrumentally evaluated with GSA is significantly decreased compared to healthy controls. However, it seems that this instrumental impairment does not affect patient sexual life, since sexual function evaluated by validated questionnaires does not differ significantly from that of healthy women.

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EDITORIAL COMMENT

The authors should be congratulated for performing an objective assessment in adult life following pediatric feminizing genitoplasty. It will be important to understand further outcomes from more of the 95 patients operated on, since the study includes only 12. A third of individuals in the primary and revision groups required an additional (minor) procedure. The data reveal a significant reduction in thermal and vibratory clitoral sensitivity but maintenance of sexual function. The authors attribute this finding to surgery, dismissing previous suggestions that CAH may underlie it (reference 8 in article). Surgery needs careful consideration at

all ages.¹ There is a question here about preemptive surgery in early puberty and whether this could be delayed. There are not enough data yet to say pediatric surgery safely avoids an impact in later life. The literature needs a study examining unoperated patients and normal controls. Current patient/parent/clinician choices avoiding early surgery may allow such a study.

Dan Wood

*Consultant in Adolescent and Reconstructive Urology
University College London Hospitals
London, United Kingdom*

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