



Lower Urinary Tract Symptoms in Adult Females after Feminizing Genitoplasty for Congenital Adrenal Hyperplasia

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Purpose: We investigated quality of life, long-term lower urinary tract symptoms, sexual function and subjective attitudes toward surgery in adult women after feminizing genitoplasty for congenital adrenal hyperplasia.

Materials and Methods: We retrospectively reviewed the medical files of all patients with congenital adrenal hyperplasia who underwent feminizing genitoplasty from 1996 to 2018 in our tertiary center. Of those, patients older than 16 years of age were asked to answer 1 nonvalidated and 3 standardized and validated questionnaires evaluating their current mental well-being (WHO-5 Well-Being Index), lower urinary tract symptoms (ICIQ-FLUTS) and sexual function (GRISS). The anonymized answers of this cross-sectional study were compared to a control group of 50 healthy females. Student's t-test, Pearson's χ^2 test, Fisher's exact test and Spearman's rank correlation coefficient were performed. A p-value less than 0.05 was considered significant.

Results: Out of 106 patients who underwent feminizing genitoplasty, 64 patients were included and 32 patients, aged 17 to 40 years (median 25.5 years), answered the questionnaires (50% response rate). The difference between congenital adrenal hyperplasia and control group mental well-being was not statistically significant (WHO-5 median score 60 and 64, respectively; $p=0.82$). We found no significant difference in the lower urinary tract symptoms subscales of filling, voiding or incontinence, nor in the overall lower urinary tract symptoms score (ICIQ-FLUTS overall median score 3.5 and 3, respectively; $p=0.43$).

Conclusions: We found in our group no abnormal mental well-being or prevalence of long-term symptoms of lower urinary tract dysfunction in adult female patients with congenital adrenal hyperplasia following feminizing genitoplasty.

Abbreviations and Acronyms

CAH = congenital adrenal hyperplasia

CE = clitorrectomy

DSD = disorders of sex development

FG = feminizing genitoplasty

ICIQ-FLUTS = International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms

LUTS = lower urinary tract symptoms

VPPT = vaginoplasty pull-through

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THE need for surgery in patients with disorders of sex development has been controversial. Despite the establishment of multidisciplinary teams for DSD in many tertiary centers, parents are still often traumatized by the uncertainty about their child's future development.¹ Quality of life in general, mental well-being, sexual dysfunction and long-term lower urinary tract

dysfunction and its symptoms (LUTS) have been underreported by clinical researchers in patients with DSD according to several recently published review articles from expert panels.²⁻⁸

Congenital adrenal hyperplasia accounts for the most frequent type of DSD, and feminizing genitoplasty, as the standard operation offered to parents of children with CAH, has

been performed to create a feminine appearance, allow passage of menses, preserve sexual function, and prevent subsequent urinary tract complications.⁹ It is not clear if, compared to healthy controls, there is a higher prevalence of LUTS in this group of patients.^{9–15} In this article we report the prevalence of LUTS as well as mental well-being in adult women with CAH who underwent FG in their childhood at our tertiary center. The quality of sexual life and subjective attitude towards surgery will be reported separately.

MATERIALS AND METHODS

Between March 2018 and September 2019, we carried out a cross-sectional study to which we recruited individuals 16 years or older with CAH, 46XX karyotype, and living as females who underwent FG in early childhood plus any subsequent related operations. We retrospectively reviewed their medical records to confirm the diagnosis and the type of surgical procedures performed.

All patients with DSD who underwent FG and who were not females with CAH and a 46XX karyotype were excluded. A control group of healthy females of similar age and education who came to see their gynecologist for a regular check-up was recruited in 3 gynecological outpatient clinics. The study was approved by the Ethical Committee on Clinical Trials of the Motol University Hospital and 2nd Medical Faculty, Charles University (ID No. EK-137/18). The study inclusion consent form was prepared by the hospital's Legal Department.

All females over 16 years of age were contacted with an explanation letter, email or telephone call and asked to complete 3 validated standardized and one nonvalidated online questionnaires. If the patients had not answered within 3 months, they were contacted again. To be able to start to fill in online anonymized and secured answers, all participants had to agree with the conditions and guarantees described in the consent form.

To assess subjective psychological well-being, we chose the WHO-5 Well-Being Index (supplementary Appendix 1, <https://www.jurology.com>), which is available in more than 30 languages, including Czech. This questionnaire consists of 5 simple and noninvasive questions. It has high clinimetric validity, serves as a sensitive and specific screening tool for depression and its applicability across study fields is very high.¹⁶ The respondent is asked to rate how well each of the 5 statements describing mental well-being applies to him or her when considering the last 14 days. Each of the 5 items is scored from 5 (all of the time) to 0 (none of the time). Therefore, the raw score theoretically ranges from 0 (absence of well-being) to 25 (maximal well-being). Because scales measuring health-related quality of life are conventionally translated to a percentage scale from 0 (absent) to 100 (maximal), the raw score is multiplied by 4.

To assess urinary outcomes, the International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) was used (supplementary Appendix 2, <https://www.jurology.com>). The ICIQ-FLUTS is a brief and psychometrically robust

patient-completed questionnaire for evaluating female LUTS and impact on quality of life in research and clinical practice across the world.¹⁷ It is scored on a scale of 0–16 for symptoms of filling, 0–12 for voiding symptoms and 0–20 for incontinence symptoms. The original English version of the ICIQ-FLUTS was translated into Czech by a professional agency specializing in medical translations.

The complex questionnaires were analyzed by 1 researcher (JT), who was blinded to the respondent's identity and the type of surgery they underwent. Statistical analysis was done with R software, version 3.4.4, with Student's *t*-test, Pearson's χ^2 test, Fisher's exact test and Spearman's rank correlation coefficient. We judged a *p*-value less than 0.05 to be statistically significant.

RESULTS

We identified 106 patients who underwent FG between 1996 and 2018. Besides the patients with CAH who were 46XX, there were 7 patients who were 46XY with complete androgen insensitivity syndrome, 6 patients who were 46XY/45X0 with mixed gonadal dysgenesis and 1 patient who was 46XX with ovotesticular DSD who were excluded. From the 92 remaining patients with CAH who were 46XX, 1 lived as a man with a female partner and was excluded. A total of 27 patients younger than 16 years old were also excluded.

The remaining 64 patients were included and contacted via contact details in our hospital database. Twenty-seven patients were sent a written letter. Six patients were lost to followup with no valid contact details. Three parents refused to give us any contact information for their grownup children during the phone call, as they claimed to be traumatized by the hospital stays or wanted to forget all related memories. For similar reasons, 2 of the contacted patients explicitly refused to fill in the questionnaire. Despite our reminders, only 32 patients participated, making the response rate 50% (32 out of 64). The age of respondents with CAH was 17 to 40 years old (median 25.5).

The inclusion criteria for the control group were age 16 to 40 years and no history of chronic disease that could influence their mental status, quality of life, lower urinary tract or sexual function. Out of 83 completed questionnaires, we included 50 that fulfilled the abovementioned criteria. The age of the controls was 18 to 40 years old (median 29).

Concerning the surgeries performed on our respondents with CAH, 11 patients underwent complete clitorrectomy (amputation of the clitoris) by a pediatric gynecologist at the age of 3 to 6 years (current age of the respondents is 29 to 40 years old), and then later at puberty at the age of 12 to 15 years, most of them (9 out of 11) underwent pull-through vaginoplasty as described by Hendren.¹⁸ The principle of Hendren's operation was to invert 2

Table 1. Baseline characteristics of CAH patients, type of operation and scores

Pt No.	Date of Birth (mo/day/yr)	Age	Type of Surgery	Current Treatment for Any Other Disorders Except CAH	WHO-5 Well-Being Index Question					WHO-5 Well-Being Index Score		ISIQ-FLUTS Score			
					1. I have felt cheerful and in good spirits	2. I have felt calm and relaxed	3. I have felt active and vigorous	4. I woke up feeling fresh and rested	5. My daily life has been filled with things that interest me	Raw	%	Filling	Voiding	Incontinence	Overall
1	10/25/1979	40	CE+VPPT		5	5	5	3	4	22	88	5	1	2	8
2	11/14/1980	39	FG+VPPT	Recurrent headaches, thyroid gland dysfunction, psychiatric disorders	1	1	1	1	1	5	20	10	1	1	12
3	6/26/1982	37	CE+VPPT	Tendinitis	3	3	2	2	3	13	52	0	0	0	0
4	6/8/1983	36	FG	Thyroid gland dysfunction	3	2	1	2	3	11	44	4	2	3	9
5	7/7/1983	36	CE+VPPT		3	3	3	4	4	17	68	1	2	0	3
6	4/4/1984	35	CE+VPPT	Mixed depressive + anxiety disorder	3	3	4	4	4	18	72	2	1	1	4
7	7/30/1984	35	CE+VPPT		4	4	4	4	5	21	84	0	0	1	1
8	8/27/1984	35	CE+VPPT		5	5	3	4	5	22	88	0	0	0	0
9	5/4/1985	34	CE+VPPT	Anxiety disorder	4	4	4	4	5	21	84	2	1	6	9
10	10/5/1985	34	CE+FG	Glaucoma, osteoporosis, pollen allergy	3	3	2	3	3	14	56	1	2	0	3
11	1/31/1988	31	CE+VPPT		3	4	3	4	4	18	72	0	0	0	0
12	8/25/1990	29	CE+VPPT		5	4	5	4	3	21	84	2	0	2	4
13	4/10/1991	28	CE+FG	Panic disorder	3	3	3	3	4	16	64	5	0	0	5
14	4/14/1992	27	FG		3	3	2	0	3	11	44	4	0	0	4
15	7/11/1994	25	FG		4	4	4	4	4	20	80	2	0	0	2
16	5/22/1993	26	FG+VPPT	Mixed depressive + anxiety disorder	1	1	1	1	2	6	24	1	0	0	1
17	11/1/1993	26	FG+VPPT		4	5	5	5	4	23	92	2	0	4	6
18	1/25/1994	25	FG		4	4	3	1	4	16	64	1	1	0	2
19	7/11/1995	24	FG		5	5	1	4	4	19	76	1	0	1	2
20	7/17/1996	23	FG		2	2	3	4	4	15	60	3	4	2	9
21	6/3/1998	21	FG		4	4	3	2	1	14	56	1	0	0	1
22	9/9/1998	21	FG		4	2	1	2	1	10	40	3	0	1	4
23	6/11/1999	20	FG		3	3	4	1	2	13	52	1	0	1	2
24	8/12/1999	20	FG+VPPT		4	4	3	5	4	20	80	2	0	0	2
25	10/1/1999	20	FG+VPPT		4	5	4	4	4	21	84	1	0	0	1
26	10/18/1999	20	FG		3	2	4	1	4	14	56	1	1	6	8
27	4/22/2000	19	FG		3	2	2	1	3	11	44	3	6	10	19
28	10/1/2000	19	FG		4	2	2	2	4	14	56	3	0	0	3
29	1/21/2001	18	FG		3	3	2	3	4	15	60	2	3	1	6
30	4/3/2002	17	FG		3	3	2	2	2	12	48	0	1	0	1
31	4/30/2002	17	FG		3	2	2	2	2	11	44	2	1	1	4
32	6/22/2002	17	FG		4	2	3	4	2	15	60	2	0	2	4

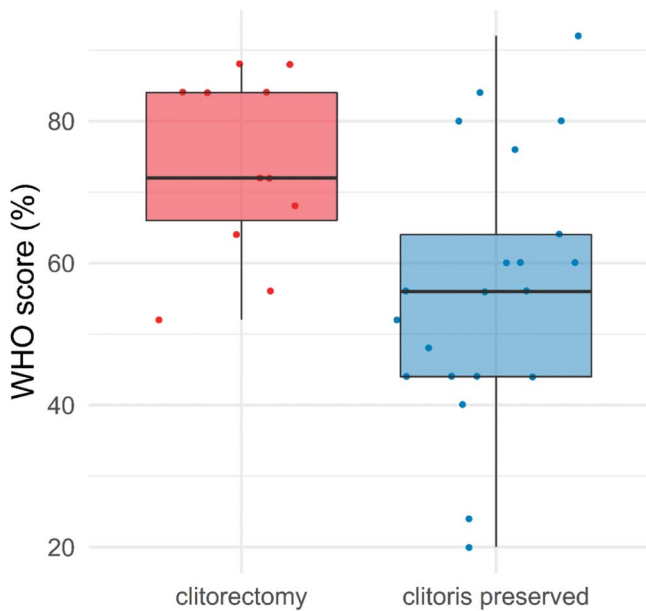


Figure 1. Comparison of WHO-5 Well-Being Index scores within operated group between females after clitorrectomy and females with preserved clitoris.

perineal flaps, dorsal and ventral, to pull the vagina disconnected from urethra onto the perineum. The remaining patients with preserved clitoris underwent modern FG, including reduction clitoroplasty with neurovascular bundle preservation, wedge glanuloplasty to reduce the size of the glans, minor plus major labioplasty and perineal skin flap introitoplasty for low type of CAH or pull-through vaginoplasty for high type of CAH as described further down.

FG was performed in 1 stage for all patients with low type of CAH, where the confluence of the urethra and vagina was found distal to the external urethral sphincter on preoperative cystoscopy. For all patients with high type of CAH, where the

confluence was proximal to the urethral sphincter and more extensive mobilization of the vagina was needed, FG was done in 2 stages: clitoroplasty and labioplasty first and pull-through vaginoplasty after estrogenization at puberty when the blood supply and strength of mobilized tissue improved.

One-stage FG was performed in 16 patients at the ages of 1 to 6 years old. Two-stage FG was performed in 5 patients at the ages of 1 to 6 years old (first stage) and at 12 to 15 years old (second stage). Nine patients out of 21 who had previous sexual intercourse performed regular vaginal dilatation. Except for all clitorrectomies, all other operations were performed by a single pediatric surgeon (RS).

The subjective psychological well-being of the CAH and control groups on the scale of 0 to 100 (100% feeling great) was not statistically different (WHO-5 median score 60 and 64, respectively; $p=0.82$). Among patients with CAH there were 5 followed up by a psychiatrist: 2 for mixed depressive and anxiety disorder, 1 for anxiety disorder, 1 for panic disorder and 1 for nonspecified complaints (WHO-5 scores 72, 24, 84, 64 and 20, respectively). When WHO-5 scores were compared within the operated group between the patients after clitorrectomy and with the clitoris preserved, there was a statistically significant difference (WHO-5 median score 84 and 56, respectively; $p=0.0096$) (table 1 and fig. 1).

LUTS assessment showed no significant difference in all 3 subscales between the CAH and control groups (median filling score 2 and 2, respectively, $p=0.63$; median voiding score 0 and 0, respectively, $p=0.82$; median incontinence score 1 and 0, respectively, $p=0.24$). The overall LUTS score was also similar in both groups (ICIQ-FLUTS overall median score 3.5 and 3, respectively; $p=0.43$) (fig. 2). In particular, 3 of the most frequent complaints in both

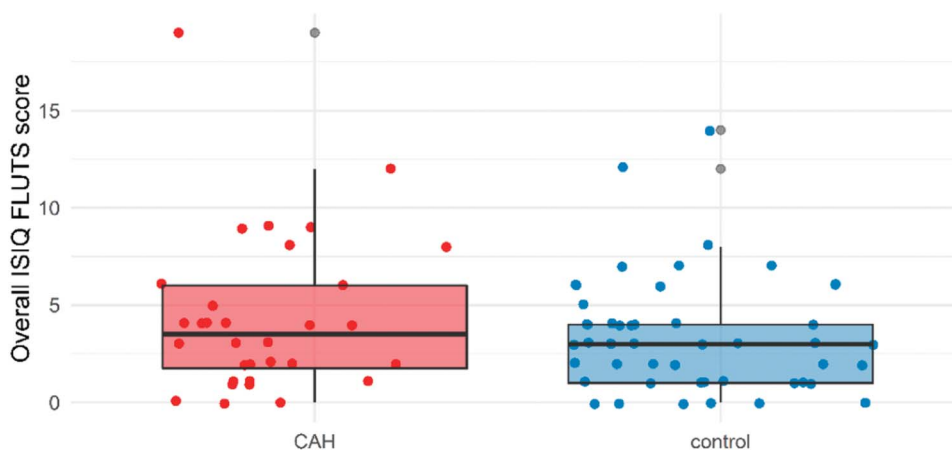


Figure 2. Overall ISIQ-FLUTS scores in CAH and healthy control groups

Table 2. Number of reported LUTS in patients with CAH and controls in studies by Davies et al⁹ and Bogdanska et al¹⁴ as well as our study

	No. CAH (%)			No. Controls (%)			p Value		
	Davies	Bogdanska	Trachta	Davies	Bogdanska	Trachta	Davies	Bogdanska	Trachta
Pts	19	17–21	32	19	20	50			
Urgency	13 (68)	12 (57)	18 (56)	8 (42)	4 (20)	18 (36)	0.19	0.015	0.07
Urge incontinence	13 (68)	10 (59)	9 (28)	3 (16)	1 (5)	9 (18)	0.003	0.001	0.28
Stress incontinence	9 (47)	7 (41)	10 (31)	5 (26)	5 (25)	16 (32)	0.31	0.48	0.94
Unexplained incontinence	13 (68)	8 (47)	4 (13)	0 (0)	1 (5)	3 (6)	<0.001	0.005	0.31
Dysuria/bladder pain	10 (53)	5 (24)	5 (16)	5 (26)	2 (10)	8 (16)	0.18	0.240	0.96
Hesitancy	11 (58)	10 (48)	5 (16)	4 (21)	5 (25)	11 (22)	0.045	0.133	0.47
Incomplete emptying	13 (68)			7 (37)			0.10		
Intermittent stream		8 (38)	13 (41)		6 (30)	17 (34)		0.59	0.54
Frequency of incontinence episodes		10 (59)	8 (25)		3 (15)	9 (18)		0.008	0.45
Higher frequency		5 (24)	18 (56)		0 (0)	30 (60)		0.020	0.74
Straining		3 (14)	4 (13)		0 (0)	8 (16)		0.079	0.66
Nocturia		2 (14)	3 (9)		1 (5)	14 (28)		0.317	0.03
Enuresis		5 (29)	5 (16)		0 (0)	0 (0)		0.014	0(0)

Statistically significant differences are in bold fonts.

the CAH and control groups were urgency in 18/32 (56%) patients and 18/50 (36%) patients, respectively; higher frequency in 18/32 (56%) patients and 30/50 (60%) patients, respectively; and intermittent stream in 13/32 (41%) patients and 17/50 (34%) patients, respectively (table 2). However, this needs to be interpreted according to the severity of symptoms (table 2 and fig. 3).

DISCUSSION

In this study, we have investigated in detail the impact of FG (and clitorrectomy) in patients with CAH on their quality of life in general, lower urinary tract function, quality of sexual life, subjective assessment of the outcomes and patient’s attitude towards the need and timing of such surgery. Compared to healthy controls, we have found no significant impact neither on the current mental

well-being nor on lower urinary tract function. The findings of the latter 2 research goals will be published separately.

Among patients with CAH, there were 5 who were followed by a psychiatrist for different disorders, with WHO-5 scores ranging broadly from 20 to 84. This might reflect a different level of success in the psychiatric treatment of individual patients. Also, we cannot say from this study how strongly any depression, anxiety or panic disorders are related, if at all, to FG or classic CAH, as they are also prevalent in the nonoperated population.

The technique of clitorrectomy is nowadays correctly regarded as a form of female genital mutilation and it was unfortunately performed in 11 of the analyzed patients with CAH between the 1980s and the beginning of 1990s by a pediatric gynecologist. These patients were offered further vaginoplasty surgery at puberty. The

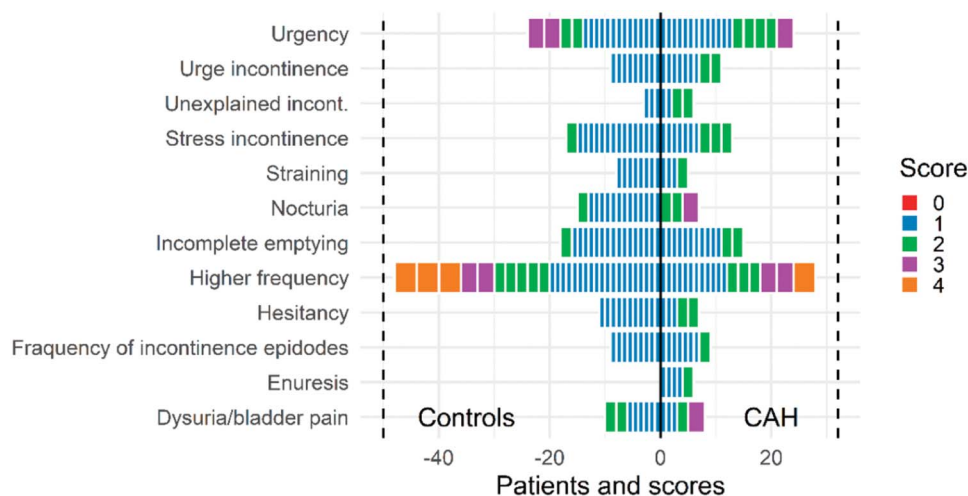


Figure 3. Comparison of lower urinary tract symptoms in patients with CAH and controls

WHO-5 Well-Being Index is a tool that, in our opinion, cannot show objectively and with scientific rigor how the patients after clitorrectomy have subjectively been affected by this surgery. Accepting this, our data would suggest a higher prevalence of depressive disorder in those patients who underwent clitorrectomy.

Davies et al suggested in 2005 that there was a higher prevalence of LUTS amongst patients with CAH.⁹ They assessed a cohort of 19 young females (16 after FG) 17 to 40 years old compared with 19 age-matched controls using the Bristol Female Lower Urinary Tract Symptoms questionnaire. They found a significantly higher percentage of patients with CAH suffering from urge incontinence, unexplained incontinence and hesitancy and concluded that about two-thirds of patients with CAH do not avoid dysfunctional bladder symptoms after FG in childhood. Other studies, except 1 very recent one,¹⁴ have failed to identify similar abnormal prevalence of urinary symptoms in patients with CAH.^{10–15}

Bogdanska et al recently published a cohort of 17 adult patients with CAH who were assessed for persistent LUTS.¹⁴ We compared all 3 studies using similar questionnaires (table 2). Bogdanska et al concluded that patients with CAH after FG have a higher prevalence than controls of urgency, frequency and urge, unexplained and nocturnal incontinence. The reliability of this conclusion is weakened by the study limitations: small sample size and low participant response rate (29% [21/72]), as well as no age-matched national control group.

In our study, 3 of the most frequent complaints in the CAH group were urgency (56%), higher frequency (56%) and intermittent stream (41%). However, out of 18 patients with CAH reporting urgency, 13 answered the question “Do you have a sudden need to rush to the toilet to urinate?” by

clicking on “Occasionally”, only 4 clicked on “Sometimes” and 1 clicked on “Most of the time.” Similarly, out of 18 females with CAH reporting higher frequency, 12 answered they passed urine 7 to 8 times per day. If we would apply less strict criteria for the definition of higher frequency, as Bogdanska et al did (abnormal frequency 9+),¹⁴ our higher frequency prevalence in patients with CAH would be 19% (6/32) instead of the reported 56% (18/32). Seeing the fact that many people experience occasional urgency and mild frequency during their everyday life, this high rate needs to be interpreted cautiously and in comparison with a representative control group.

There are limitations of retrospective data collection, limitations of the questionnaires included being dependent on recalled history and only a 50% response rate in our study. In particular the low response rate may bias the results in favor of patients who are satisfied with their outcomes. Despite the high qualities of the WHO-5 Well-Being Index questionnaire, the given responses express the subjective level of well-being during a very short period of the past 2 weeks and do not reflect the complexity of a long-term quality of life.

CONCLUSIONS

Our data do not support the hypotheses that adult women with CAH and 46XX karyotype after FG performed in childhood or puberty suffer either poorer subjective psychological well-being or higher prevalence of LUTS compared to healthy controls.

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