

# Severity of Virilization Is Associated with Cosmetic Appearance and Sexual Function in Women with Congenital Adrenal Hyperplasia: A Cross-Sectional Study

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## ABSTRACT

**Introduction.** Women with the classical form of congenital adrenal hyperplasia (CAH) are born with different degrees of virilization of the external genitalia. Feminizing surgery is often performed in childhood to change the appearance of the genitalia and to enable penile–vaginal intercourse later in life. There are suggestions that this affects sexual functioning.

**Aims.** The aim is to study the anatomical, surgical, cosmetic, and psychosexual outcomes in women with CAH.

**Methods.** Forty women with CAH, aged over 15 years, from two referral centers for management of Disorders of Sex Development in the Netherlands were included. Physical and functional status were assessed by a gynecological interview and examination. Sexual functioning was assessed with the Female Sexual Function Index and Female Sexual Distress Scale—Revised scales and compared with a reference group.

**Mean Outcome Measures.** Surgery performed, anatomy, cosmetic score, sexual function and distress.

**Results.** Thirty-six of the 40 women had undergone feminizing surgery; 25 women (69%) underwent more than one operation. Resurgery was performed in seven of the 13 (54%) women who had had a single-stage procedure. Anatomical assessment showed reasonable outcomes. Multiple linear regression showed that only level of confluence had a significant effect on cosmetic outcome, the impact depending on the number of surgeries performed. Cosmetic evaluations did not differ between the women and the gynecologists. Only 20 women had experience of intercourse. Eight women reported dyspareunia; seven women reported urinary incontinence. The women's perceived sexual functioning was less satisfactory than in the reference group, and they reported more sexual distress.

**Conclusion.** The level of confluence was the major determinant for cosmetic outcome; the impact depended on the number of surgeries performed. Fifty-four percent of the women required resurgery after a single-stage procedure in childhood. Anatomical assessment showed reasonable outcomes. The women evaluated their sexual functioning and functional outcome less favorable than the reference group, and they experienced less often sexual intercourse.

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**Key Words.** CAH; Outcome; Sexual Function; Female Genital Self-Image; Anatomy; Surgery

## Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders resulting from the deficiency of one of the five enzymes required for the synthesis of cortisol in the adrenal cortex. About 90–95% of individuals with CAH have a mutation in the *CYP21A2* gene, encoding the 21-hydroxylase enzyme [1]. There are two types of CAH: the classical and a nonclassical form or late onset CAH. Genital ambiguity at birth is present only in the classical form, which can be subdivided in simple virilizing CAH (SV-CAH) when only a defect in cortisol biosynthesis is present and salt wasting CAH (SW-CAH) when the patient also show a concurrent defect in aldosterone biosynthesis. Patients with the nonclassical form and untreated or insufficiently treated patients with the classical form have manifestations of androgen excess such as hirsutism, menstrual dysfunction, and acne [2]. The excessive amount of androgens circulating in the fetus probably also affects brain development in a masculine direction, leading to virilization of personality and cognitive, psychosocial, and psychosexual functioning [3,4]. Female patients with moderate or severe genital virilization may undergo feminizing surgery, e.g., clitoroplasty, vaginoplasty, and labioplasty, with the aim to create female appearing external genitalia and to enable sexual intercourse. Genital surgery is controversial as loss of sensitivity resulting in diminished sexual functioning has been reported [5–12]. However, available data are conflicting possibly because of confounding factors.

## Aims

The aim is to study the long-term anatomical, surgical, cosmetic, and psychosexual outcomes of a large cohort of women with CAH.

## Methods

### Study Design

Cross-sectional study.

## Patients

Eighty-nine patients with CAH (>15 years of age) were invited to participate in the study between 2007 and 2009. Participating centers were Erasmus MC Rotterdam (N = 53) and Radboud University Nijmegen MC, Nijmegen (N = 36), The Netherlands. The study was approved by the Medical Ethics Committees of both centers. Participants signed a written consent. Participants were free to refuse parts of the gynecological examination or the psychological assessment.

## Procedure

The study consisted of two parts. Data on genital virilization at birth and genital surgery were collected retrospectively from medical files. Patients were invited to take part in a follow-up study consisting of a standardized gynecological examination, psychosocial assessment on sexual functioning, and an interview.

## Outcome Measures

### Surgery and Level of Confluence

A description of the urogenital sinus (UGS) was available in the medical records [13]. Therefore, the degree of virilization was classified by the level of confluence of the vagina into the UGS at birth. Three levels were distinguished: low, i.e., the junction of the vagina and urethra is near the perineum (N = 14); high, i.e., the junction is near the neck of the bladder (N = 8); and no confluence, i.e., clitoral hypertrophy only (N = 5). From 13 patients, we had no data on level of virilization.

### Gynecological Examination

The standardized gynecological examination consisted of visual inspection (size of clitoris, labia majora, and labia minora; pigmentation; and meatus externus urethrae, hair growth, labial scarring, and perineal length), speculum examination (assessment of vagina, internal hair growth, granulation tissue, epithelial atrophy, and presence of a cervix), and pelvic examination (accessibility of the vagina by number of fingers, vagina length, and width [measured by Hegar], strictures, pelvic floor tone, and vaginal discharge).

The three gynecologists who performed the gynecological examination had not been involved previously in the care of these patients.

The gynecologist and the patient herself independently rated the general appearance and the appearance of different parts of the vulva (i.e., clitoris, labia majora, and minora) on a 1–10 scale (1 = extremely poor, 10 = excellent, <6 was considered insufficient). The cosmetic outcome score per patient was calculated as the mean of the gynecologists' scores for the different parts of the genitalia.

### Psychosexual Assessment

Psychosexual functioning was assessed by the Dutch versions of the Female Sexual Function Index (FSFI) [14,15] and the Female Sexual Distress Scale—Revised (FSDS-R) [15,16]. The FSFI assesses sexual functioning by six key dimensions of female sexual function in the preceding 4 weeks: desire, subjective arousal, lubrication, orgasm, global emotional/relational satisfaction, and pain. The FSDS-R assesses perceived stress with respect to sexuality. The combined results of the FSFI and FSDS-R suggest the diagnosis of one or more sexual dysfunction(s) according to the Diagnostic and Statistical Manual of Mental Disorders (version four, text revision) (DSM-IV-TR) [17]. An FSFI score <26.55 combined with a FSDS-R score >11 implies the existence of at least one sexual dysfunction according to the DSM-IV-TR [17]. As questions in the FSFI and FSDS-R relate mainly to the 4-week period before completing the surveys, and some items can only be filled out when having a partner (i.e., satisfaction domain of the FSFI), or when having intercourse (i.e., pain domain of the FSFI), a “valid” total FSFI score could only be calculated for a minority of the women. Therefore, we did not interpret zero responses (“no sexual activity in last 4 weeks”) as extreme degrees of dysfunction but excluded these women from further analyses [18,19]. Patients' psychosexual scores were compared with data of a Dutch reference group of 108 healthy women with mean age of 27.1 years (standard deviation 9.4) [15]. These authors had made up a reference group of women who were all engaged in heterosexual partner relationships and had reported they had no sexual dysfunctions. By making use of these inclusion criteria, the reference group is probably not representative for the Dutch female population. Analysis showed that the reference group is similar to our study group with respect to age ( $P = 0.43$ ) and educational level ( $P = 0.67$ ). On the FSFI and FSDS-R, the reference group did not report prob-

lems in psychosexual functioning. The psychological interview inquired about the age sexual developmental milestones had been passed, such as age at first engagement in a romantic relationship, including kissing and touching the partner without sexual intercourse, and age at sexarche (i.e., first peno-vaginal intercourse).

### Statistical Analysis

Univariate and backward stepwise linear regression analysis were used to identify factors associated with cosmetic outcome. Intercorrelated variables were evaluated for the presence of confounding and/or effect modification in stratified analysis. Effect modification was twice identified: between “level of confluence,” and “number of surgeries,” and between “level of confluence,” and “age at first surgery.” We looked for a significant contribution of the interaction effects to the predictive ability of the model by adding the interaction effects to the main effects (backward stepwise linear regression analysis).

Comparisons between groups were assessed with descriptive statistics: the chi-square test for nominal/ordinal variables, Student's  $t$ -test for normally distributed continuous variables, and the Wilcoxon signed-rank test for paired variables with skewed distributions. Comparisons of continuous variables with skewed distributions were evaluated with the Mann–Whitney  $U$ -test (two groups) or the Kruskal–Wallis test (three or more groups).

A  $P$  value <0.05 (two sided) was considered a significant difference. As patients were free to refuse parts of the gynecological examination and the psychological assessment, number of participants may vary across analyses.

## Results

### Patient Group

Forty of the 89 invited women participated (response rate: 45%). The remaining 49 women either declined participation (45%), or could not be reached personally (i.e., by phone, e-mail, or post mail). Characteristics from the nonresponders and participants are depicted in Table 1. By inspection, it seems that the groups did not significantly differ in the medical variables.

Of the 40 participants, 38 fulfilled the criteria of 21 hydroxylase deficiency (32 had SW-CAH and six had SV-CAH) and two had 11 beta-hydroxylase deficiency. The median age at participation was 29 years (range 15–46).

**Table 1** Age and medical characteristics of nonresponders and participants

Characteristics	Participant	Nonresponders	P values
Mean age (range)	29 (15–46)	30 (18–54)	0.75*
Type			0.88†
SW	32	37	
SV	6	9	
LO	2	3	
LOC			0.51†
High	8	10	
Low	14	15	
No	5	12	
Unknown	13	12	
Mean number of surgeries (range)	1.8 (0–4)	1.5 (0–5)	0.15‡

We did not find statistical differences between the two groups.

\*Student's *t*-test

†Chi-square test

‡Mann–Whitney *U*-test

SW = salt wasting; SV = simple virilizing; LO = late onset; LOC = level of confluence

Most patients with SV-CAH, and those with SW-CAH, had been diagnosed within the first year of life; only three SW-CAH and two SV-CAH patients were diagnosed after the age of 1 (mean age 3.3 and 4.0, respectively). Those with late onset CAH ( $N = 2$ ) were diagnosed at a mean age of 12 years and were included because they attended the clinic with virilized genitalia; they both had clitoral hypertrophy. Main features of the 40 women are presented in Table 2. Height was below  $-2$  standard deviation score (SDS) in 12 of the women, calculated on Dutch reference data for age 21 years [20]. Family history was positive for CAH in 13 patients, and parental consanguinity was present in three patients, all of whom had SW-CAH.

### Surgical Procedures

Thirty-six of the 40 patients had undergone feminizing surgery of the external genitalia. Figure 1 gives an overview of the surgical procedures performed.

In 13 of those 36 patients, surgery consisted of a single-stage clitoroplasty and vaginoplasty. The median age at surgery was 3 years (range 0–17 years). Seven patients (7/13, 54%) needed resurgery later in life. In 20 patients (median age 2 years, range 0–19), first surgery comprised only clitoroplasty. Additional vaginoplasty was performed in 16 patients (16/20, 80%) at the median age of 13 (range 4–22 years). Several patients (see Figure 1) had more than one additional surgical procedure.

In three patients (median age 11, range 2–16 years), first surgery comprised only vaginoplasty.

One of these women requested additional clitoroplasty at the age of 17 even though clitoromegaly was only mild.

A redo-operation was performed in 25 of the 36 patients (69%). Eleven of these patients had their first surgery before the age of 13 months, and 14 patients had their first surgery between 13 months of age and 6 years.

In almost all cases ( $N = 32$ ), clitoroplasty comprised reduction of the clitoris with preservation of the neurovascular bundle and glans. Two patients had a clitorrectomy: for one patient, that was the standard procedure at that time (42 years ago), the other patient underwent clitorrectomy because of persisting painful erections. The total number of surgical procedures in the patients assigned to the high confluence group ( $N = 8$ ) was significantly higher than that in the patients assigned to the low confluence group ( $N = 14$ ) or that in patients with no confluence ( $N = 5$ ) ( $P = 0.004$ ). As expected, the total number of clitoral or vaginal surgeries was higher in the SW group than the SV group but, given the small sample size, the difference did not reach statistical significance ( $P = 0.381$  and  $P = 0.092$ , respectively).

### Gynecological Examination

The results of the anatomical assessment during gynecological examination are presented in Table 3. Assessment data were available for 17 (Hegar examination) and 29 (labia majora) women. Characteristics between patients who refused gynecological examination compared with who did not were not different for CAH type (i.e., SW or SV), or number of surgeries (1.8 [1–4] vs. 1.8 [0–4]), but the groups did differ in age of attendance. The patients who participated were significantly older with a mean age of 32.6 years (18–46) compared with a mean age of 23.1 years (16–34) for those who did not participate ( $P = 0.03$ ).

The clitoris was scored absent in two cases (due to clitorrectomy), small in five patients, normal in 15 patients, and enlarged in six patients. Visible labial scarring was present in 15 patients; only in one woman the scars were very pronounced. One patient had a vagina shorter than 6 cm after a pull-through procedure. In four patients, digital examination was possible with one finger only; they were virgins, i.e., had never had sexual intercourse. The Hegar width of the vagina was in the normal range in almost all patients; in only one woman it was smaller than 20 mm. Thirteen women refused speculum examination. Speculum examination was physically impossible in five patients. One patient

**Table 2** Main features of the participants

	Age (years)	BMI	Height (SDS)	Partner	CAH type	Therapy		Menarche (years)
						Glucocorticoids	Mineralcorticoids	
1	36	23.4	-1.64	No	SW	Hc 15-0-20 mg	Fc 62.5-62.5 ug	13
2	37	28.3	-1.02	No	SV	Dexa 0.25 mg		14
3	28	23.9	-0.86	Yes	LO	Hc 10-5-5 mg		13
4	37	24.8	-0.40	Yes	SW	Hc 10-0-25 mg	Fc 62.5 ug	15
5	32	36.3	-0.71	No	SW	Hc 10-0-5 mg	Fc 62.5-94 ug	17
6	23	25.7	2.07	Yes	SW	Hc 15-0-20 mg	Fc 125-125 ug	15
7	29	26.3	-1.33	Yes	SW	Hc 7.5-5-2.5 mg	Fc 62.5-62.5 ug	16
8	22	27.8	-2.72	No	SW	Hc 10-10 mg	Fc 62.5-62.5 ug	13
9	38	32	-2.10	Yes	SW	Dexa 0.125-0.125 mg	Fc 125-125 ug	15
10	36	23.3	-1.17	No	SW	Dexa 0.25-0.25 mg	Fc 62.5 ug	11
11	18	25.4	-3.03	No	SW	Dexa 0.25-0.25 mg	Fc 62.5 ug	12
12	21	27	-1.64	No	SW	Hc 15-10 mg	Fc 30-30 ug	12
13	28	22.6	1.61	No	SW	Hc 5-5-15 mg	Fc 25-25 ug	16
14	22			No	SW	Hc 10-10 mg	Fc 50-50 ug	
15	19	24.6	0.06	Yes	LO	Hc 10-10 mg		15
16	24			Yes	SW	Hc 10-5-10 mg	Fc 62.5-62.5 ug	
17	30			Yes	SW	Hc 15-5-5 mg	Fc 62.5-62.5 ug	
18	40	29.1	-0.40	Yes	SW	Dexa 0.50 mg	Fc 62.5 ug	18
19	40	25.3	-1.02	Yes	SW	Hc 10-10 mg	Fc 125 ug	12
20	26			Yes	SW	Hc 10-15 mg	Fc 62.5-62.5 ug	
21	23			Yes	SW	Dexa 0.25-0.25 mg	Fc 45-45 ug	
22	19	28.2	-1.17	No	SW	Dexa 5 mg	Fc 62.5 ug	16
23	34			Yes	SV	Hc 20-0-10 mg		
24	44	29.3	-1.33	Yes	SV	Dexa 0.5 mg		13
25	24	35.5	-2.88	Yes	SW	Dexa 0.5-0.5 mg	Fc 100-100 ug	11
26	16	21.8	-0.94	No	SW	Hc 8-4-8 mg	Fc 62.5-62.5 ug	14
27	19			Yes	SV	Hc 10-10 mg		
28	38	19.6	-2.10	No	SW	Hc 10-10 mg	Fc 100 ug	14
29	46	26.1	-3.34	Yes	SW	Hc 5-5-5 mg	Fc 62.5 ug	12
30	22	22.6	-2.72	Yes	SW	Hc 20 mg, Dexa 1.5 mg	Fc 100-50 ug	15
31	46	29.7	-1.17	Yes	SW	Hc 25 mg	Fc 62.5 ug	13
32	44	22.8	-0.86	Yes	SW	Hc 15-15 mg	Fc 62.5-62.5 ug	15
33	35	26.7	-2.72	No	SW	Hc 7.5-5-12.5 mg	Fc 125-125 ug	12
34	18	20	-2.41	No	SV	Hc 12 mg, dexa 0.2 mg		12
35	19	22.6	-0.17	No	SV	Hc 10-10-10 mg		16
36	46	37.3	-3.88	No	SW	Hc 25 mg	Fc 62.5-62.5 ug	14
37	25	26	-1.95	No	SW	Hc 15-10 mg, Dexa 0.10 mg	Fc 40 ug	17
38	32	23.6	-1.10	Yes	SW	Hc 10-10 mg	Fc 62.5-62.5 ug	15
39	45	28.8	-2.10	Yes	SW	Hc 15-15 mg	Fc 75-75 ug	17
40	20	19.7	-4.34	No	SW	Hc 6-3-3 mg	Fc 62.5-62.5 ug	15

All visited the endocrinologist on a regular basis. Only one had hirsutism (patient number 30, Ferriman Gallway Score for hirsutism was 25). In general, the women were small, with 12 women below -2 SDS in height.

SW = salt wasting; SV = simple virilizing; LO = late onset; Hc = hydrocortisone; Dexa = dexamethasone; Fc = fludrocortisone; SDS = standard deviation score; BMI = body mass index; CAH = congenital adrenal hyperplasia

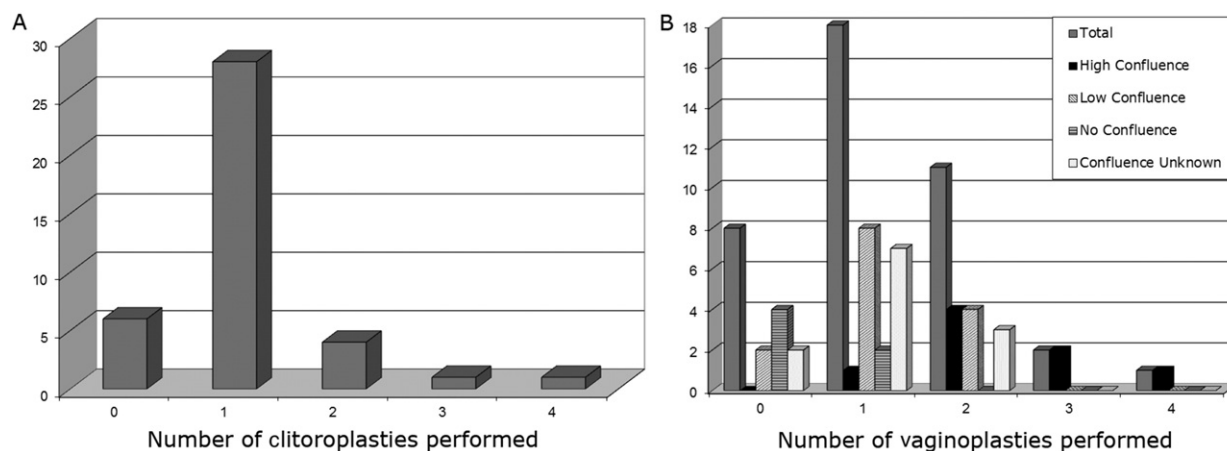
was diagnosed with vaginism, whereas another had recently undergone a vaginoplasty. Only two patients showed abnormalities (increased vaginal secretions and atrophy, respectively). Seven patients had vaginal strictures. Although variations in genital appearance were established during gynecological examination, appearance was in the normal range in the majority of women. Again, differences between the SW-CAH and SV-CAH groups did not reach statistical significance because of small sample size (see Table 3).

### Cosmetic Ratings

Cosmetic results of surgical and medical treatment was evaluated in 28 patients. Both the patient and

the gynecologist who did the examination of the patient scored cosmetic outcome for various parts of the external genitalia on a 10-point scale. The median total score of all parts was 7 for patients and 7 for gynecologists, which reflects overall satisfaction with cosmetic outcome ( $P = 0.467$  for comparison of patients and gynecologists [ $N = 27$  Wilcoxon signed-rank test]). Twenty-five percent (7/28) of the patients vs. 21% (6/28) of the gynecologists scored the cosmetic outcome as insufficient (i.e., a mean score <6).

Age at first surgery and level of confluence were significantly associated with the mean cosmetic outcome score (univariate analysis,  $P = 0.021$  and  $P < 0.01$ , respectively [ $N = 27$ , Kruskal-Wallis test



**Figure 1** Numbers of clitoroplasties and vaginoplasties performed in the total patient group (N = 40). (A) Number of clitoroplasties performed. (B) Number of vaginoplasties performed and total number of vaginoplasties with breakdown by severity of virilization.

and one-way analysis of variance]). Stratified analysis revealed that number of operations and age at first surgery were effect modifiers of the association between level of confluence and cosmetic outcome.

Multiple regression analysis (Table 4) showed that after adjustment for the effect modifiers, only level of confluence had a significant effect on cosmetic outcome. The adjusted impact of the level of confluence on cosmetic outcome is  $1.055 - 0.987 \times \text{number of surgeries}$ . The adjusted  $R^2$  of this model was 0.335.

#### Functional Assessment

Assessment of sexual function consisted of an interview with a gynecologist—as part of the gynecological checkup—and an interview and questionnaire assessment with a psychologist. The questionnaire results are shown in Table 5.

The gynecological interview was completed by 32 women. Twenty of the 32 (62.5%) women had experienced vaginal penetration (median 28.5 years, 19–46 years), and 12 (37.5%) women had not (median 33.5 years, 16–46 years). Two of the latter considered their vagina too narrow; two were embarrassed by the look of their body; two considered themselves too young (ages 16 and 19); three had sexual experiences in female homosexual relationships only, whereas three patients did not give a reason. Eighty-three percent of women reported they were able to achieve orgasm. Eight women reported dyspareunia (8/33, 24%), all of whom had experienced vaginal penetration. Neither width nor length of the vagina correlated with dyspareunia (median Hegar width: 25.5 with

dyspareunia vs. 26.0 without dyspareunia,  $P = 0.86$ ; median length 10.0 cm vs. 10.0 cm,  $P = 0.152$ ). Physical examination revealed vaginal strictures in two of the eight women who reported dyspareunia. Whereas five other patients with vaginal strictures did not report dyspareunia, two of them were virgins. Seven out of 33 women reported urinary incontinence (three stress incontinence, three urge incontinence, and one both). None of them had sought medical attention for the incontinence. They lost small amounts of urine and sometimes used panty liners for this. Two women reported incontinence that started after genital surgery.

All but three women filled in the FSFI questionnaire, and all but five women filled in the FSFS-R questionnaire. However, many questions remained unanswered. Twenty-five percent of the women (10/37) did not have sex regularly. Sexually experienced women with CAH had passed sexual milestones later than the Dutch reference sample (romantic engagement 17.7 years vs. 15.6 years,  $P = 0.04$ ; sexarche 18.9 years vs. 18.3 years,  $P = 0.36$ ). At the time of follow-up, half of the participant group (22/40) reported to be in a stable relationship.

A total FSFI score can be calculated for women who had sexual intercourse in the last 4 weeks; in our patient group, only 11 women had been sexually active during this period. The mean score of 29 (range 19.9–33.7) on the total FSFI did not differ significantly from the score of the Dutch reference group of 108 nonaffected women with a partner. All but one had had feminizing surgery and had no confluence or low confluence of the

**Table 3** Anatomical assessment

Outcome	Result		Total (N = 40)	P value*
	SW (N = 32)	SV (N = 8) <sup>†</sup>		
<b>Anatomical assessment</b>				
Clitoris				0.918
Absent	2	0	2	
Small	4	1	5	
Normal	12	3	15	
Large	5	1	6	
Labia majora				#0.126
Normal	13	5	18	
Abnormal	11	0	11	
Scrotal effect	9		9	
Labia minora				0.393
Normal	9	3	12	
Abnormal	14	2	16	
Absent	5		5	
Small	5		5	
Labial scarring				0.502
Absent	10	3	15	
Present	13	2	15	
Satisfactory	6	0	6	
Neutral	6	2	8	
Not satisfactory	1	0	1	
Vagina				
Length <sup>‡</sup>				0.531
Short	1	0	1	
Normal	15	6	21	
Digital examination				0.191
1 finger	4	0	4	
2 fingers	13	6	19	
Introitus (Hegar)				0.588
<15 mm	0	0	0	
15–20 mm	1	0	1	
20–25 mm	3	0	3	
25–30 mm	6	1	7	
>30 mm	4	2	6	
Speculum examination <sup>§</sup>				0.714
Physically impossible	4	1	5	
Normal	15	5	20	
Abnormal	2	0	2	
Stricture <sup>¶</sup>				0.147
Minimal	2	2	4	
Moderate	3	0	3	
Meatus externus urethrae				0.694
Normal	6	2	8	
Superficial	3	1	4	
Deep	14	2	16	

\*Overall P value between SW and SV (chi-square test or # Fisher's exact test)

<sup>†</sup>Includes patients with *CYP11B1* deficiency

<sup>‡</sup>Short = 0–6 cm, normal > 6 cm

<sup>§</sup>Physically impossible for the following reasons: virgin, recent operation, vaginismus

Abnormal: too much fluor, atrophy

<sup>¶</sup>2–3 cm = minimal, 1–2 cm = moderate

SW = salt wasting; SV = simple virilizing

vagina into the UGS at birth. However, when considering the separate FSFI domains, women with CAH had significantly lower functioning on the subscales of desire, arousal, lubrication but also pain compared with the reference group. No differences were found for satisfaction, or orgasm. On the FSDDS-R, women with CAH indicated to experience more sexual distress in comparison with the reference group (Table 5). Twenty-nine

percent (10/35) had a score above the clinical cutoff of 11. When combining the (valid) FSFI and FSDDS-R data, only one woman suffered from a sexual dysfunction, as defined in DSM-IV-TR. Kruskal–Wallis tests showed no significant differences between women with a high or low confluence level, or no confluence, possibly because of the small sample sizes. In addition, no significant difference existed in perception of sexual function between SW and SV women as tested with Mann–Whitney *U*-tests.

## Discussion

We report on genital anatomy and ratings of cosmetic and functional outcome in women with CAH with and without feminizing surgery. We integrated gynecological and psychosexual outcome with the aim to add new insight in the long-term outcome of genital surgery in these women.

Level of virilization, assessed as level of confluence, proved to be the most important factor in

**Table 4** Multiple regression model for cosmetic appearance with mean gynecological score as dependent variable

Multiple regression model for cosmetic appearance			
	B	Standard error	P value
Constant	4,631	1,278	0.002
Level of confluence	1,055	0,489	0.045
Number of surgeries	0,181	0,305	0.560
Age at first surgery	0,078	0,056	0.180
Level of confluence × number of surgeries	−0,987	0,539	0.084

Adjusted  $R^2$ : 0.335

Only level of vaginal confluence had a significant effect on mean gynecological score. The adjusted impact of level of confluence depends on the number of surgical procedures performed.

**Table 5** Mean scores (SD) on the different domains of the FSFI (range 0–6), total FSFI (range 0–36), FSDDS-R (range 0–52) comparing CAH women and a nonaffected reference group [18] (independent samples *t*-tests)

	Control	CAH	P value
Desire	4.0 (0.8) N = 108	3.5 (1.2) N = 37	0.017*
Arousal	5.3 (0.8) N = 108	4.4 (1.6) N = 31	0.004**
Lubrication	5.7 (1.0) N = 108	5.0 (1.1) N = 26	0.004**
Orgasm	5.1 (1.1) N = 108	4.6 (1.6) N = 26	0.131
Satisfaction	5.4 (0.8) N = 108	5.2 (1.0) N = 22	0.442
Pain	5.7 (0.8) N = 108	4.5 (1.7) N = 13	0.025*
Total FSFI	31.2 (3.9) N = 108	29.0 (4.2) N = 11	0.107
Total FSDDS	5.1 (6.4) N = 108	8.8 (8.8) N = 35	0.02*

\*\* $P < 0.01$ ; \* $P < 0.05$

SD = standard deviation; FSFI = Female Sexual Function Index; FSDDS-R = Female Sexual Distress Scale—Revised; CAH = congenital adrenal hyperplasia

cosmetic outcome; cosmetic appearance was judged as less favorable in case of a high vaginal confluence. In addition, patients with a high vaginal confluence underwent significantly more surgical procedures than the remainder of the women. Our regression model clearly showed that the adjusted impact of level of confluence on cosmetic outcome is modified by the number of surgical procedures. As shown in Table 4, the impact of the level of confluence on cosmetic outcome is larger or smaller, depending on the number of surgeries performed. More than half of the patients who had single-stage surgery initially underwent additional procedures. Our results are in line with Nordenström et al. [21], who reported that surgery is more extensive in severely virilised patients, whereas other groups have reported either disappointing, or reasonably good outcomes after resurgery in puberty [6,15,16]. A practical advice is that parents should be informed on the fair chance of reoperation in adolescence.

In this study, patients and gynecologists both rated genital appearance as sufficient. In contrast, Wisniewski et al. [10] and Nordenström et al. [21] reported that patients were more negative than doctors. This might be due to a different composition of the group, or different approaches toward surgery. Female genital self-image, assessed using a four-point scale (FGSIS), was shown to be related to sexual function [22]. Although further research is needed, especially in patients born with genital anomalies like CAH, this scale might be useful in a clinical setting to create talking points that enhance patient–doctor communication and to better understand requests for additional surgery [22,23].

Our findings probably underestimate the delay in experience of romantic and sexual encounters because there was a considerable number of virgins and a considerable number of nonresponders.

Comparisons using the FSFI scores were limited to women who were sexually active in the last 4 weeks, having a partner, and having penile–vaginal intercourse as described by Brotto [18]. Only one (1/11) of the women suffered from sexual dysfunction according to DSM-IV-TR criteria [17]. We suspect that the real number is considerably higher. Women with CAH achieved sexual milestones later than Dutch reference women, and a substantial part never had been engaged in a sexual relationship. Women with CAH experienced a significantly less satisfactory sexual functioning (desire, arousal, lubrication, and pain) and experienced more sexual distress compared with a Dutch

reference group of healthy females. These data are in line with findings from Wisniewski et al. [10] and Gastaud et al. [7]. In our study, 24% of the CAH women reported dyspareunia (deep and superficial). In a large Dutch study, 5.4% of 2,024 healthy females reported dyspareunia, whereas 29.6% sometimes experienced pain during intercourse [24]. In females who have undergone vaginal surgery, dyspareunia might be related to vaginal stenosis [25], but in our study, only two of the eight patients who reported dyspareunia had vaginal strictures. Eighty-three percent reported they were able to achieve orgasm, although with more difficulty compared with healthy reference women. Other authors [6,21] have reported that the clitoral sensitivity was affected in nearly all the women who had had surgery. These findings indicate that clitoral surgery may affect genital sensitivity. However, additional factors are likely to play a role as well, for example, degree of virilization and psychological factors. They are likely to be interrelated and little is known about their effects on outcome. For example, women with CAH reported high satisfaction levels. One possible explanation, suggested by Minto et al., is that living with CAH has contributed to low expectations of sexual functioning, that is, the women might have felt that sexual difficulties were to be expected and that they should not be dissatisfied [26]. Additionally, the paternalistic attitude of physicians and past practice of secrecy relating to the Disorders of Sex Development (DSD), especially experienced by the older women in this study, might have resulted in inadequate information and lack of opportunity for discussion. Alternatively, infrequent sexual contact, associated with sexual dissatisfaction, might indicate a withdrawal from sexual intercourse and a relief from facing problems of sexual difficulties [27].

This study has drawbacks that need to be addressed. First, the study has a cross-sectional design, and part of the data have been retrieved retrospectively from medical files. Therefore, the study was limited by information available in these files. Second, 55% of the CAH women who had been under medical treatment in childhood, adolescence, and adulthood in our hospitals did not participate in the follow-up study. Most refused to participate, and in some cases, we were unable to contact them. We did not find significant differences, demographical and medical, in characteristics between responders and nonresponders. However, we cannot exclude the possibility that the nonresponders may have worse functioning



than the participants. Women may not want to participate because participation meant a confrontation with a painful and distressing aspect of their disease, i.e., sexual functioning. Women who participated in the gynecological examination were significantly older compared with those who did not. We cannot explain this difference, but assume that women, as they become older, for medical purposes have undergone several gynecological examinations before and got familiar with this type of examination. Familiarity probably makes them feel more comfortable to participate in a gynecological examination with a research goal. Third, to measure sexual functioning, we selected FSFI and FSDS-R. These scales are considered the first choice screening tool because they have excellent psychometric qualities, are easy to administer, and are available in many languages [15,19]. Its utility has been demonstrated in diverse conditions, for example, vaginoplasty in females with Mayer-Rokitansky-Küster-Hauser Syndrome [28]. However, the FSFI will artificially inflate scores toward the sexual dysfunction pole in females who are not sexually active or who did not experience vaginal penetration in the 4 weeks prior to the test [18]. The results in our study revealed that only 55% of the women had a partner. The Dutch reference group only included women who had a sexual partner. In order to improve applicability of the scales in patient groups, the scales need adaptation. Additional data in different patient and reference populations including females suffering from different types of somatic, emotional, and sexual problems should be collected.

### *Clinical Implications*

We showed that cosmetic appearance and functional outcomes are associated with the degree of virilization at birth and that the impact of level of confluence on cosmetic outcome depends on the number of surgical procedures performed. These data might be used in the discussion whether or not to treat pregnant women at risk of carrying a child with CAH with dexamethasone. Incidence of reported dyspareunia is high in women with and without vaginal strictures, stenosis, or other visible anomalies. Parents and patients need to be informed extensively about the multiple aspects that contribute to outcome after feminizing surgery. They need to be informed that there will be a fair change that reoperations will be necessary in adolescence. Despite their sexual problems, only a few women reported sexual problems to a gynecologist or psychologist, or

had sought help from a sexologist. We would like to make a plea for assessing sexual well-being at follow-up visits and to discuss sexuality and work toward acceptance of the genital anatomy that may always remain different from the perceived norm. Ultimately, referral to a sexologist may be needed.

### **Conclusions**

The level of confluence appeared to be the major determinant for cosmetic outcome, and the impact depends on the number of surgical procedures performed. The outcome of corrective genital surgery is positive with respect to genital appearance but less favorable with respect to sexual functioning. Vaginoplasties to improve sexual function should only be performed after consulting a multidisciplinary DSD team and after ample vaginal examination and counseling. We would advocate that surgeons inform and discuss these aspects with parents and patients so they can make a balanced decision.

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