Original Article

Long-term outcome of genital reconstruction of Middle Eastern women with congenital adrenal hyperplasia

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Abstract

Objectives: There is a paucity of data on the long-term outcome of genital reconstruction of female children with congenital adrenal hyperplasia (CAH) as they become adult women. We report on the surgical outcome general condition and marriage status.

Materials and Methods: We reviewed the medical records of women 20 years or older with CAH who had genital reconstruction. We interviewed married patients utilizing the female sexual function index (FSFI-6) questionnaire and compared them to age-matched controls.

Results: We identified 43 women with CAH with a median age of 24.2 ± 3.9 years and a median follow-up of 23.4 ± 4.6 years. Salt wasting and the severity of virilization affected most patients, parents were commonly cousins, children were reared as boys for a protracted period and surgical reconstruction was usually complex. Only five women had married. Compared with single women, married women had significantly more frequent normal menses, emergency hospital admissions and number of repeated reconstructive surgery. There was no significant difference in FSFI score between patients and controls. Four women conceived and three gave birth to one healthy child. There was no significant difference in the number of children between patients and controls.

Conclusions: CAH has a significant impact on adult women in our region. Most of the patients remain single. Few women get married and these are able to lead a nearly normal sexual life and give birth to healthy children.

Key Words: Adrenal hyperplasia, congenital, female urogenital diseases, fertility, follow-up studies, reconstructive surgical procedures

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INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a rare condition that results in the disorder of sexual differentiation characterized by virilization of 46XX females.[1,2] The affected female children are often treated by reconstruction of their genitalia by single or staged surgical procedures.[3]

Few studies followed women with CAH into adulthood. The number of patients reported from the western world is limited.[4-9] In addition, there is a paucity of data on the surgical management of patients with CAH in our region and none on the long-term outcome in adult women.[10] It is not known whether the outcome in women native to the Middle East is affected by the different ethnic make-up, racial background, psychosocial structure or the local clinical setup.

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MATERIALS AND METHODS

The project was approved by the Institutional Research and Ethics Committees. We reviewed the medical records of patients with disorders of sex development who had a confirmed diagnosis of CAH based on blood tests for steroid hormones and electrolytes. We included all patients who were presented to the Urology Department for genital reconstruction, with a chromosomal sex 46XX and age ≥20 years at the last follow-up (FU) visit. The study included patients who had genitoplasty and/or vaginoplasty between February 1978 and March 2000. We excluded patients with any chromosomal abnormality or patients assigned to a male gender at the last FU. We reviewed the clinical history, surgical reconstruction history, marital status, fertility and medical condition at last FU. Cosmetic result was determined according to patient's perception and physician examination. We conducted a phone FU to update our records on marriage status and to interview women who had married utilizing the six-item version of the female sexual function index (FSFI-6).[11,12] We randomly recruited control women from healthy hospital visitors, who were married and 20-37 years old. A single female case manager nurse conducted the interview of patients and controls.

We compared the FSFI-6 scores, pregnancy and parity among married patients and age-matched controls. We compared married and single patients for clinical picture, management and outcome. We used descriptive statistics and the Wilcoxon rank test for analysis.[13] Missing data were excluded from the calculations. We used the statistics package of SPSS version 20 (SPSS Inc. Chicago, IL.)

RESULTS

Patient selection

We reviewed the charts of 60 patients ≥20 years old with CAH. All patients had a chromosomal sex of 46XX. We excluded two patients who were considered men at last FU. We identified 43 eligible women with age at last FU of at least 20 years. All women were Muslim natives of our country.

Patient characteristics

Patients' characteristics at presentation, details of surgical management, outcome of surgery and condition at last FU are shown in Tables 1 and 2. Salient features of our patient population included salt wasting (SW) in 95.3%, 60% were the offspring of consanguineous marriages and 81.4% had a genital Prader grade of more than III. A significant number of patients (12/43) were reared as boys for up to 200 months before sexual reassignment was done. Phone FU revealed that only 5 (11.7%) had married and three remained in wedlock at the time of FU.

Married women comparison with single women

Tables 1 and 2 summarize the characteristics of married and single women. The age at last FU and FU duration was significantly longer in married compared with single women ($P < 0.01$). There was a significant difference in the menstrual history among subjects, where married women had relatively more normal menses, less pain, less amenorrhea and less irregularity ($P = 0.02$). Repeated hospital admissions from the emergency room (ER) were more frequent ($P = 0.04$) and the ratio of patients who had repeated adrenal crisis was significantly higher in married versus single patients ($P = 0.046$). The ratio of patients who had repeated reconstructive surgery was significantly higher in married versus single women ($P < 0.001$). There were no other significant differences between married and single women in presentation, surgery, surgical outcome or condition at FU.

Married women characteristics and surgical outcome

Five women were married at a median age of 22.9 years standard deviation (SD) 4 (15.9-26.5), for a median duration of 5.2 years SD 3.2 (0.8-8.7). All five patients had SW and were on regular treatment with fluorocortisol and prednisone. Table 3 shows the details of these patients at presentation, surgical management and outcome. One-stage genitoplasty and vaginoplasty were performed in 3 (60%, 3/5) at the median age of 1.1 years (0.8-1.6); two-stage reconstruction with a deferred vaginoplasty in one at the age of 23.5 years; and no surgery in one. This last patient had circumcision of

Table 1: Patient's characteristics, surgery and outcome (continuous variables)

Variable	All patients		Single patients		Married patients		*P**
	Median (SD)	*n*	Median (SD)	*n*	Median (SD)	*n*	
Age at FU (years)	24.2 (3.9)	43	23.6 (3.4)	38	31.2 (4.2)	5	0.001
FU duration (years)	23.4 (4.6)	43	23.1 (4.1)	38	31.2 (3.9)	5	0.002
Age of presentation (days)	30 (1083.2)	42	30 (1152)	37	150 (199.1)	5	0.7
Boyhood duration (m) mm (months)	4 (62.7)	12	4 (65.1)	11	5.5†	1	0.7
Age at menarche (years)	13.9 (2.5)	30	14 (2.55)	27	11.7 (2.5)	3	0.4
Age at genitoplasty (years)	1.4 (3.1)	42	1.5 (3.3)	37	1.1 (0.3)	5	0.3
Age of vaginoplasty (years)	2.3 (6.4)	31	3 (5.7)	27	1.2 (11.2)	4	0.8
FU weight (kg)	59 (17.9)	43	60 (18.2)	38	57 (16)	5	0.5
FU height (cm)	148 (11.2)	43	147.5 (11.7)	38	152 (6.6)	5	0.6
FU BMI	28.5 (20.2)	43	28.4 (21.3)	38	29.2 (6.7)	5	0.6

*Married compared to single patients. Pearson Chi-square, †A single patient, SD: Standard deviation, BMI: Body mass index, FU: Follow-up

the labia at the local hospital before being referred to us. For one-stage repair we used the technique described by Bissada *et al*. for nerve-sparing clitoroplasty, labioplasty and flap vaginoplasty.[10] Post-operative cystoscopy and calibration with Hegar dilators under general anesthesia (GA) were carried out 1 year post-operatively, at puberty and before marriage.

Table 2: Patient's characteristics, surgery and outcome (categorical variables)

Variable	All		Single		Married		*P**
	n	%	*n*	%	*n*	%	
Characteristics							
Considered boys at birth	12	27.9	11	28.9	1	20	0.1
Salt wasting	41	95.3	36	94.7	5	100	0.6
21-hydroxylase deficiency	40	93	35	92.1	5	100	0.8
Parent consanguineous marriage	25†	58.1	23	60.5	2	40	0.7
Sibling CAH or mortality‡	23	53.5	20	52.6	3	60	0.98
Presentation							
Ambiguous genitalia	23	53.5	20	52.6	3	60	0.7
Metabolic disturbance	16	37.2	14	36.8	2	40	0.7
Genital Prader grade							
I-II	8	18.6	7	18.4	1	20	0.9
III-IV	34	79.1	30	78.9	4	80	0.9
V	1	2.3	1	2.6	0	0	0.9
Surgery							
Genitoplasty only	11	25.6	10	26.3	1	20	0.8
One stage reconstruction	19	44.2	16	42.1	3	60	0.8
Two stage reconstruction	12	27.9	11	28.9	1	20	0.8
Repeated reconstructive surgery	13	30.2	11	28.9	2	40	0.001
Vaginal dilatation under GA	14	32.5	11	28.9	3	60	0.8
Condition at FU							
Asymptomatic	11	25.6	8	21.1	3	60	0.06
Crisis recurrence	14	32.6	10	26.3	4	80	0.037
Repeated ER admissions	12	27.9	8	21.1	4	80	0.046
Symptoms of virilisation	11	25.6	11	28.9	1	20	0.2
Normal menstruation	15	34.9	13	34.2	2	40	0/028
Cosmetic result good-excellent	33	76.8	28	73.7	5	100	0.4
Marriage status							
Single	38	88.4	38	100	0	0	
Married	5	11.6	0	0	5	100	

*Married compared to single patients. ANOVA, †Number of patients with parents who are cousins (20 cases are first degree cousins), ‡Number of patients who had sisters or brothers diagnosed with CAH or died in infancy or early childhood due to crisis or unexplained reason, CAH: Congenital adrenal hyperplasia, GA: General anesthesia, ER: Emergency room, ANOVA: Analysis of variance, FU: Follow-up

Cosmetic appearance of the genitalia was good-to-excellent in all patients. Three patients requiring dilatation under GA were sent home with Hegar dilators sizes 9-11 for self-dilatation of the vaginal orifice. Revision surgery was carried out in two patients and repeat vaginal dilation under GA was required in one. Vaginal stenosis persisted in two patients.

Four patients had at least one admission because of adrenal crisis during FU, one had a crisis every year and two had crises at the end of their pregnancies. All patients with adrenal crisis had electrolyte disturbance, which was corrected by intravenous fluids and corticosteroids. In addition, one patient required emergency cesarean section during the 36w of gestation.

Married women comparison with control

Healthy controls had a median age of 33 years SD 4.04 (27-38) at last FU, median age of marriage of 30 years SD 4.6 (22-31) and duration of marriage of 3 years SD 6 (1-16). There was no significant difference between patients and controls in age at last FU, age of marriage or duration of marriage. Two patients were divorced, one within 1 year due to sexual problems related to dyspareunia resulting from vaginal stenosis and another after 5 years for nonsexual social reasons. Two control women were divorced because of social reasons in the last 2 years.

There was no significant difference in the FSFI-6 mean score between patients and controls [Table 4]. The patients' score however is below the proposed cut-off of 19 of normal sexual function.[11] There was no significant difference in each domain between groups.

The number of patients and controls, who had abnormal menstruation, pregnancy, abortion, *in vitro* fertilization (IVF) or given birth was not significantly different between groups [Table 5]. All five patients attempted pregnancy. Four patients conceived, three spontaneously and one through gonadotropin stimulation and IVF. Other than adrenal crisis

Table 3: Married patient's characteristics and outcome

Patient code	2	4	16	36	39
Sex assignment at birth	Female	Female	Male	Ambiguous genitalia	Ambiguous genitalia
Presenting symptom	Ambiguous genitalia	Crisis	Ambiguous genitalia	Crisis	Ambiguous genitalia
Prader grade	III-IV	I-II	III-IV	III-IV	III-IV
Stages of repair	2 stages	Circumcision	One stage	One stage	One stage
Age at genitoplasty (years)	1.6	1	0.8	1.3	1.1
Age at vaginoplasty (years)	23.5		0.8	1.3	1.1
No. of repeat surgery	0	0	0	2	2
No. of dilation under GA	1	0	1	0	2
Vaginal stenosis	Yes	No	Yes	No	No
Cosmetic appearance	Good	Excellent	Excellent	Excellent	Good
Menses	Painful, regular	Regular	Amenorrhea	Painful, regular	Regular
FSFI-6 score	19	12	15	25	22
No. of pregnancies	1	1	0	1	1
No. of parity	0	1	0	1	1
Marital status	Divorced	Divorced	Married	Married	Married

GA: General anesthesia, FSFI: Female sexual function index

in two patients, there was no gestation complication such as diabetes, hypertension, eclampsia, premature labor or low birth weight in any patient. Three patients gave birth to one healthy child (two boys and one girl) each by cesarean section, two elective at full-term and one emergency at 36 weeks of gestation. One patient had an abortion at 16 weeks of gestation. Four of the control women conceived unassisted while one woman had IVF, which resulted in a successful delivery of a healthy boy. All control women gave birth by vaginal delivery. One control woman had eight pregnancies and two abortions, giving birth to six children. The mean number of pregnancies, abortions and children was not significantly different between patients and age-matched controls [Table 5].

Table 4: FSFI-6 score for married patients and controls

Question	CAH	Control	*P*
Q1-desire			
Mean	3.2	3.2	1
SD	1.1	1.1	
Range	2-5	2-5	
Q2-arousal			
Mean	3.4	3.4	1
SD	1.5	0.5	
Range	1-5	3-4	
Q3-lubrication			
Mean	3	4.2	0.07
SD	0.7	1.1	
Range	2-4	3-5	
Q4-orgasm			
Mean	3.8	3.6	0.8
SD	1.1	0.9	
Range	2-5	3-5	
Q5-satisfaction			
Mean	2.2	4.4	0.022
SD	1.6	0.5	
Range	1-4	4-5	
Q6-pain			
Mean	3.2	3.8	0.5
SD	1.6	1.1	
Range	1-5	3-5	
FIFS-6 score			
Mean	18.6	22.6	0.2
SD	5.2	4.2	
Range	12-25	18-29	

Independent samples t-test, SD: Standard deviation, CAH: Congenital adrenal hyperplasia, FSFI: Female sexual function index

DISCUSSION

All patients

We selected an age cut-off of at least 20 years at FU assuming that the cohort is comparable to the general population mean age of marriage in Saudi Arabia.[14]

Compared with the international literature, our patient group is unique in certain aspects [Tables 1-4]. The majority of our patients had SW compared with 50% reported elsewhere.[8,15] This severe form of the disease is associated with poor outcome.[9] Other features include high rate of parent consanguineous marriages. The majority of patients had severe virilization with a genital Prader grade of more than III, slightly more than 71.4% reported by others.[6] A significant number of patients were reared as boys before sex reassignment, sometimes at a late age [Tables 1 and 2]. This might reflect a cultural inclination toward favoring a male gender for the newly born. Two patients, who were excluded from the study, preferred to continue as men and had surgical removal of the ovaries. The span of surgical treatment extended from infancy to adulthood in our series and in other reports.[6] Nearly, half the patients underwent one-stage nerve sparing repair in early childhood. Gastaud reported that 71% of his patients underwent one-stage reconstruction, but only two patients had nerve sparing.[6] The outcome of surgery is cosmetically good-to-excellent in most of the patients. Repeated reconstruction was similar to others reporting 28% additional surgery and vaginal stenosis.[6,16]

Married women

The number of married patients is small compared to 23% in a European series.[6] Only married women in our study were considered sexually active, whereas other studies included unmarried women.[17] The possibility that our unmarried patients had heterosexual intercourse or homosexual encounters is slim or extremely secretive because of the religious, cultural, social and legally prohibitive circumstances. For these reasons, single women were not interviewed about sexual activity.

The rate of marriage in our patients is significantly less than the reported rate of 39.3% of Saudi women 20-24 years

Table 5: Menstrual and pregnancy outcome in patients compared to controls

Variable	CAH				Control				*P* value*
	n	%			*n*	%			
Divorced	2	40			2	40			
Patients with painful menses	2	40			3	60			0.8
Patients with amenorrhea	1	20			1	20			0.3
Patients with irregular menses	0	0			2	40			0.3
Patients with pregnancy	4	80			5	100			0.4
Patients with IVF	1	20			1	20			0.3
	n	Mean	SD	Range	*n*	Mean	SD	Range	*P* value**
No. of pregnancies	4	0.8	0.4	0-1	12	2.4	3.1	1-8	0.3
No. of abortions	1	0.2	0.4	0-1	2	0.4	0.9	0-2	0.7
No. of children	3	0.6	0.5	0-1	10	2	2.2	1-6	0.2

*Pearson Chi-square,**Independent samples *t* test, CAH: Congenital adrenal hyperplasia, SD: Standard deviation, IVF: *In* vitro fertilization

old.[14] Heterosexual relationships and marriages in other parts of the world are much higher, reporting 50-68%.[15,18-20] The severity of genital virilization inversely affects the frequency of intercourse and marriage.[19] Still, the authors reported that 68% of patients with Prader III-IV were married, a much higher rate compared to our patients [Tables 1-5].[19]

One-stage feminizing genitoplasty is associated with a low incidence of vaginal stenosis of 35% and less need for vaginal dilatation.[16] This is comparable to our patients with one-stage reconstruction developing vaginal stenosis.

Married women follow-up and comparison with single women

Patients who got married had significantly more repeated surgical interventions and adrenal crisis requiring ER admission. This might reflect the cost paid by these women to pursue a successful marital relationship and seek to give birth to a child.

Married women sexual function versus controls

Sexual function total score is comparable among patients and controls in our study, which is similar to results reported elsewhere.[18] However, the total score for the patients falls just below the proposed normal cut-off value of 19.[11] This indicates that the patients had a slight sexual dysfunction that was not reflected in the statistical analysis because of the small number of patients. Dyspareunia was the cause of divorce in one of our patients and was the only domain of FSFI-6 showing significantly more patient complaints in reported series elsewhere.[6,18] In Sweden, 29% of patients had pain during intercourse and 16% had post-coital bleeding.[20] Vaginal patency was maintained by frequent secondary procedures in our patients and half the patients elsewhere.[18]

Overall, fertility in adult women with CAH was reported between 24% and 27%.[18] Among married women, live-birth rate in our study was 60% (3/5). This rate is higher than 17% reported by others.[6] The impact of SW is detrimental to fertility. In patients with SW , there is a poor live-birth rate ranging from 0% to 10% compared to 33-50% in simple virilizing patients and 65-91% in the general population or in age-matched controls.[20,21] One series reported three children born to two women out of 29 with SW.[8] In our study, however four of the married patients had SW , of whom two gave birth to healthy children compared to none in other studies.[15,22] Furthermore, there was no significant difference in the number of children born to our patients and controls. The higher fertility in our SW patients might be related to a better compliance to hormonal treatment and diligent FU. In addition, this might be attributed to a strong desire in our patients to seek fertility and lack of reporting on contraception in other series. The number of children was three in the patients and 10 in the control group; the difference was not significant probably because of the small sample and a single control woman having six children.

The psychological consequences of CAH and genital reconstruction have not been evaluated in this study. We did not evaluate sexual orientation and homosexuality as described by others in married and single women.[6] We reported sexual activity only in women who got married. The cultural difference between our region and the developed world population mandated this restriction.

CONCLUSION

The number of adult women with CAH who underwent genital reconstruction in childhood is sparse world-wide. The condition has a significant impact on these women in our region. Regional factors may affect the outcome in different parts of the world. General characteristics can be identified in our patients: SW and the severity of virilization affected most patients, parents were commonly cousins, children were reared as boys for a protracted period and surgical reconstruction was usually complex. Most patients remained single. Few women got married and these were able to lead a nearly normal sexual life and give birth to healthy children. The ratio of married patients who needed repeated surgery, vaginal dilatation under GA and ER admissions for adrenal crisis was high. To improve the outcome of genital reconstruction in women with CAH in our region, there is a further need to evaluate the unique factors that influence the management of the condition and integration within the "normal" native women population. In particular, genetic, cultural, social and psychological factors may cause significant diversity in the presentation, management, FU and integration in the society in different parts of the world.

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