Study of the Quality of Life in Children and Adolescents with Disorders of Sex Development (DSD)

Original Article

Mohamed Samir Zamzam[1], Inas Mohammad Mazen[1], Hend Mehawed Abdel Latif[2], Manal M. Thomas[1] and Ghada Mohammad Anwar[2]

Department of [1]Clinical Genetics, National Research Centre, [2]Paediatrics Department, Faculty of Medicine, Cairo University, Egypt.

ABSTRACT

Background: Disorders of sex development (DSD), are medical conditions in which development of chromosomal, gonadal, or anatomical sex is atypical. Quality of life (QOL) includes important aspects of physical and mental health as well as social interactions, economic conditions, personal views, and their connections the environment. limited researches are available regarding QOL in DSD patients especially children. However, recent studies showed reduction in QOL in DSD patients.

Aim of the work: The aim of the study is to assess the quality of life in DSD patients to improve clinical practice in the management of disorders of sex development.

Patients and Methods: This cross-sectional study to assess the health-related QOL in 50 DSD children and adolescents who attended the endocrinology clinic at Cairo University Children's Hospital and National Research Centre (NRC) from March 2018 to December 2019, in addition to 50 healthy controls.

Results: While comparison between DSD patients who were reared as males and those who were reared as females as regards WHOQOL domains score showed a significant difference in all WHOQOL domains and total score except in physical domain only there was no significant difference. There was a significant difference between 46, XX DSD, 46, XY DSD and Sex chromosome DSD in psychological (D2), environmental domain (D4) and to lesser extent in social domain (D3). Sex chromosome DSD patients were the most affected patients in the 4 WHOQOL domains, which was significantly lower than 46, XX DSD (217.50±66.76) and 46, XY DSD (255.06±48.95) with *P* value= 0.001. Comparison between 46, XX DSD, 46, XY DSD and sex chromosome DSD patients in age, family history, consanguinity, educational level, surgical and hormonal treatment showed significant difference between the 3 groups in family history and consanguinity with higher percentage of positive family history and consanguinity in 46, XX DSD then 46, XY DSD. DSD patients who received hormonal treatment and underwent surgical correction had significant higher scores in WHOQOL.

Conclusion: Pediatric patients with DSD have significantly lower HRQOL in psychological and social aspects rather than in physical and environmental aspects. HRQOL is relatively more affected in Sex chromosome DSD patients. DSD patients reared as males had a significant better HRQOL than DSD patients reared as females. DSD patients who underwent surgical correction showed a statistically significant positive effect on HRQOL.

Key Words: Disorders of sex development, Quality of life, Sex chromosome DSD.

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Corresponding Author: Mohamed Samir Zamzam, Clinical Genetics Department, National Research Centre, Egypt,
Tel.: 01007779604, **E-mail**: Dr,msz89@gmail.com

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INTRODUCTION

Quality of life (QOL) is a multifaceted notion that includes important aspects of physical and mental health as well as social interactions, economic conditions, personal views, and their connections to important environmental characteristics. The patient's scene of well-being in physical, psychological, and social life is called health-related quality of life, or HRQOL (**Daher *et al*., 2011**).

Disorders of sex development (DSD) are medical diseases affecting the reproductive system. These phrases explicitly refer to "congenital diseases in which chromosomal, gonadal, or anatomical sex development is abnormal." (**Daher *et al*., 2011**). Recent research revealed that differences of sex development (DSD) could have a direct impact on HRQOL on the following conditions: loss of psychosexual milestones, genital ambiguity, decreased growth, increased prevalence of obesity, metabolic syndrome, and hypertension. However, there is limited evidence on how the disorder impacts these individuals' HRQOL (**Gilban *et al*., 2014**).

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In DSD, hormone replacement treatment tries to treat the underlying hormonal imbalance and restore hormonal balance for normal life expectancy and HRQOL. However, in some patients, the clinical course includes a wide range of issues, such as abnormal pubertal development, decreased ultimate height, obesity, and changed reproductive function in adulthood, which may have a substantial impact on HRQOL (**Bachelot *et al*., 2008**). Numerous other factors, including genital surgery, the severity of the mutation, short stature, obesity, and hirsutism, affect DSD patients quality of life (QOL) (**Kamoun *et al*., 2013**).

Recent research has shown that patients with DSD have lower QOL, especially in the social aspects. Patients with DSD were more likely to be single, to have lower levels of sexual activity, to have more negative body images, and to have lower levels of self-acceptance, sociability, and confidence (**Arlt *et al*., 2010**).

AIM OF THE WORK:

The aim of the study was to assess the quality of life in DSD patients to improve clinical practice in the management of disorders of sex development by investigating the potential benefits versus hazards of corrective genital surgery or hormonal treatment and their effect on QOL of DSD patients.

PATIENTS AND METHODS:

The study was carried out after approval of the Ethical Committee of NRC and an informed consent from the parents or guardians of the patients, this cross-sectional study was conducted to assess the health-related QOL in 50 children and adolescents of both sexes with DSD who have attended the endocrinology clinic at the Diabetes Endocrine and Metabolism pediatric Unit (DEMPU) at Cairo University Children's Hospital and National Research Centre (NRC) from March 2018 to December 2019, in addition to 50 healthy control with matched age and sex.

Inclusion criteria: Patients with DSD conditions as defined by *Hughes et al.* age between 6 and 16 years old (**Hughes *et al*., 2006**).

Exclusion criteria: Patients with neurocognitive dysfunction.

Study Procedures: Patients were subjected to:

Clinical Evaluation

1- Medical history: This included age, sex, history of the present illness including onset, presenting symptoms and clinical findings. Developmental milestones were documented for each patient. Anthropometric measurements at the time of clinical assessment as regards to weight, height, arm span and head circumference were assessed.

Pedigree Analysis: Three generations pedigree was done for all patients taking into consideration the consanguinity, similarly affected siblings and other abnormalities in family members.

3- Physical examination: General physical examination was done for all patients with special emphasis on genital examination. Genital ambiguity was classified according to *Quigley* (**Quigley *et al*., 1995**), for under-virilized males and using Prader scale for virilized females. Assessment of secondary sexual characters was performed according to *Tanner* staging (**Tanner, 1962**).

Investigations:

All patients were routinely investigated for: chromosomal analysis which was done using GTG banding technique, a total of 15 well banded metaphase plates were analysed and karyotyped, Abdomino-pelvic ultrasound to evaluate gonads and uterus and hormonal investigations including FSH, LH total testosterone, dihydrotestosterone and delta 4 androstenedione before and after stimulation to classify the DSD patients.

Questionnaire:

The WHOQOL-BREF questionnaire, was chosen for the present investigation for several reasons. First, it is one of the most commonly used generic QOL questionnaires and has an official Arabic version approved by the WHOQOL Group. Second, it is convenient for clinical trials because of its short length (**WHOQOL *et al*., 1998**).

There were 26 items in the questionnaire. If they could read well enough, patients would fill out the form themselves. We conducted interviews with younger patients while the parent was present. Each inquiry was explained by the investigator.

The items assess four main domains that cover the aspects proposed to judge QOL. The assessed domains included:

Physical health:

Physical pain that patients feel that hinders her/him from performing their daily tasks, the need for medical care to function in daily life, having enough energy for daily activities, getting a good night's sleep, being able to perform their daily activities, and their ability to learn.

Psychological health:

The patient's capacity to tolerate his or her physical appearance, level of happiness, focus, sense of self-worth, and perception of the importance of life, as well as how frequently the patient experiences negative emotions including depression, anxiety, and despair.

Social relationships:

Satisfaction with interpersonal interactions and assistance received from the patient's friends. Environmental domain:

How safe the patient feels in his or her daily life, including: satisfaction with the patient's physical environment; satisfaction with the circumstances of the patient's living space; satisfaction with transportation; satisfaction with access to health services; having the opportunity for leisure activities; and the availability of the information that the patient needs in daily life.

Scores are scaled in a positive direction, with higher scores denoting higher QOL. Each item is scored on a 5-point Likert scale (1-5) and a mean score calculated for each domain. Mean score is subsequently transformed into a 0 to 100 scale score, directly comparable to the WHOQOL-100. Scoring, checking data and computing domain scores were done according to instructions in the WHOQOL Brief manual (**WHOQOL *et al*., 1998**).

Statistical analysis:

All collected questionnaires were revised for completeness, Quantitative data were statistically represented in terms minimum, maximum, mean and standard deviation (SD). Comparison between different groups in the presents study was done using independent samples *T-Test* for comparing two parametric groups, and using Mann-Whitney Test for comparing two nonparametric groups, and using Oneway ANOVA Test for comparing between more than two parametric groups, and using Kruskall-Wallis Test was used when comparing between more than two nonparametric groups.

Qualitative data were statistically represented in terms number and percent. Comparison between different groups in the presents study was done using Crosstab Chi-Square Test. Correlation between various variables was done using Spearman rank correlation coefficient (R).

A probability value (*p value*) less than or equal to (0.05) was considered significant. All statistical analysis was performed using statistical software SPSS (Statistical Package for Social Science) statistical program version (21.0). Graphs were done using SPSS statistical program version (21.0) and Microsoft Excel program version 2016.

RESULTS:

The study included 50 DSD patients aged from 6 to 16 years with a mean age 12.10±3.62 in addition to 50 healthy children and adolescents from 6 to 16 years with a mean age 11.52±3.2 served as a control with no significant age difference (*p value*= 0.401).

11(22%) of our patients were reared as males and 39 (87%) were reared as females, while in the control group 17(34%) were males and 33(66%) were females with no significant difference (*P* value= 0.181).

Our patients were divided into three groups: (Figure 1).

The 1st Group (46, XX DSD): included 8 patients (16%), 3(6%) of them were diagnosed as CAH (21 hydroxylase deficiency), 4(8%) were diagnosed as mullerian agenesis, one (2%) was XX SRY –ve male.

The 2nd group (46,XY DSD): included 16 patients (32%), 6(12%) were diagnosed as 5 Alpha reductase deficiency, 3(6%) of them were diagnosed as CAH (21 hydroxylase deficiency), 3(6%) were diagnosed as 17-β-Hydroxysteroid dehydrogenase III deficiency, one case (2%) was AIS, one (2%) was Leydig cell hypoplasia, one (2%) was XY gonadal dysgenesis and one (2%) was diagnosed as 17α hydroxylase deficiency.

The 3rd group (Sex Chromosome DSD): included 26 patients (52%), 19(38%) of them were diagnosed as Turner syndrome, 4(8%) were diagnosed as Mixed gonadal dysgenesis, 2(4%) were Klinefelter syndrome and one was diagnosed as Triple X female (2%).

Table (2) shows that no significant difference in all domains except in psychological domain only, males score was better than females with a significant difference (70.65±12.08 vs 58.58±17.34 respectively with *p value* 0.014).

Table (3) shows that while comparison between DSD patients who were reared as males and those who were reared as females as regards WHOQOL domains score showed a significant difference in all WHOQOL domains and total score except in Physical domain only there was no significant difference.

Table (4) shows comparison between control and patients which revealed significant difference between patients and control in psychological (D2), Social (D3) and environmental domain (D4) while there was no significant difference between patients and control in physical domain (D1) and Total score.

Table (5) shows no significant difference in all WHOQOL domains score.

Table (6) shows decreased WHOQOL domains score in female patients with significant difference in social (D3), environmental (D4) in addition to the total score.

Table (7) shows a significant difference between 46, XX DSD, 46,XY DSD and Sex chromosome DSD in psychological (D2), environmental domain (D4) and to lesser extent in social domain (D3).

Sex chromosome DSD patients were the most affected patients in the 4 WHOQOL domains score with mean total score 182.12±57.46 which is significantly lower than 46, XX DSD (217.50±66.76) and 46,XY DSD (255.06±48.95) with *P* value= 0.001.

Comparison between 46, XX DSD, 46,XY DSD and sex chromosome DSD patients in Age, family history, consanguinity, educational level shows significant difference between the 3 groups in family history and consanguinity with higher percentage of positive family history and consanguinity in 46, XX DSD then 46,XY DSD and lastly sex chromosome DSD which had the lowest percentage of positive family history and consanguinity. There is no significant difference between the 3 groups in educational level.

Table (8) shows that there was a significant difference between the three groups of DSD in number of patients that did surgical correction with the higher percentage in 46,XY DSD (56.20%) then 46, XX DSD (25.00%) and lastly Sex chromosome DSD (3.80%). However, there was no significant difference between the three groups of DSD in number of patients under hormonal treatment.

Table (9) shows a significant difference between 46, XX DSD patients and control only in social domain and there was no significant difference in the other 3 domains and the total score.

Table (10) shows a significant difference between sex chromosome DSD patients and control in all WHOQOL domains and total score. Thus, sex chromosome DSD patients was the most affected group among studied DSD patients in comparison to the control in all domains and total score.

Table (11) shows no significant difference between 46,XY DSD patients and control in all domains and total score.

Table (12) shows a significant differences in physical and psychological domains between patients who received hormonal treatment and DSD patients who didn't receive it.

Table (13) shows that comparison between DSD patients who underwent correctional surgery and those who didn't, revealed a statistically significant positive effect on physical, psychological and environmental domain as well as the total score.

Table (14) shows that DSD patients who received hormonal treatment and underwent surgical correction had significant higher scores in all WHOQOL domains score in addition to the total score than patients who received hormonal treatment or underwent surgical correction alone except in psychological domain there was no significant difference.

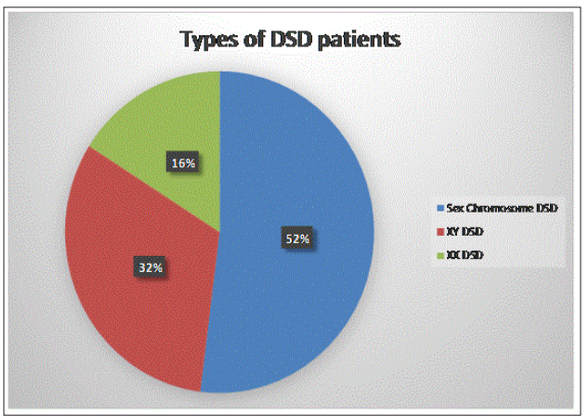

Figure 1: Frequency of different diagnosis of DSD among studied patients

Table 1: Family history, consanguinity, educational level, hormonal and surgical treatment among studied patients:

Parameters	Groups	*N*	Percent
Family history of similar conditions	+ve	6	12%
	-ve	44	88%
Consanguinity	+ve	22	44%
	-ve	28	56%
Educational Level	Illiterate	8	16%
	Preparatory Stage	8	16%
	1ry Stage	24	48%
	High school	10	20%
Hormonal treatment	+ve	37	74%
	-ve	13	26%
Surgical treatment	+ve	12	24%
	-ve	38	76%
Both hormonal and surgical treatment	+ve	6	12%

Table 2: Comparison between control males and females as regards WHOQOL domains score:

Parameters	Groups	Min.	Max.	Mean±S.D.	*P* value[a]
D1 (Physical)	Male	38	94	67.47±18.46	0.776
	Female	31	100	65.88±18.67	
D2 (Psychological)	Male	50	88	70.65±12.08	0.014*
	Female	31	94	58.58±17.34	
D3 (Social)	Male	31	100	64.29±21.79	0.359
	Female	19	94	58.33±21.47	
D4 (Environmental)	Male	31	100	63.71±16.27	0.858
	Female	38	94	64.58±16.23	
Total	Male	194	338	266.12±40.72	0.212
	Female	156	357	247.36±53.61	

[a]: *P* value between Male and Female using (Independent Samples T-Test); *: Number of males vs females is 17:33.

Table 3: Comparison between DSD patients who were reared as males and those who were reared as females as regards WHOQOL domains score:

Parameters	Groups	Min.	Max.	Mean±S.D.	*P* value [a]
D1 (Physical)	Male	13	88	66.18±24.29	0.201
	Female	31	88	57.36±18.64	
D2 (Psychological)	Male	13	88	65.45±19.78	0.037*
	Female	19	94	52.74±16.62	
D3 (Social)	Male	19	94	64.27±22.10	0.006*
	Female	0	94	38.46±27.00	
D4 (Environmental)	Male	25	88	63.73±18.86	0.030*
	Female	6	81	48.87±19.57	
Total	Male	126	332	259.64±67.47	0.004*
	Female	101	312	197.44±57.13	

*: Number of males vs females is 11:39.

Table 4: Comparison between control and DSD patients in WHOQOL domains score:

Parameters	Groups	Min.	Max.	Mean±S.D.	P value
D1 (Physical)	Control	31	100	66.42±18.43	0.068[a*]
	Patients	13	88	59.30±20.08	
D2 (Psychological)	Control	31	94	62.68±16.66	0.042[a*]
	Patients	13	94	55.54±17.96	
D3 (Social)	Control	19	100	60.36±21.55	0.004[b*]
	Patients	0	94	44.14±27.96	
D4 (Environmental)	Control	31	100	64.28±16.08	0.004[b*]
	Patients	6	88	52.14±20.21	
Total	Control	156	357	253.74±49.99	0.001[a*]
	Patients	101	332	211.12±64.33	

*: Number of controls vs patients is 50:50.

Table 5: Comparison between control males and male patients as regards WHOQOL domains score:

Parameters	Groups	Min.	Max.	Mean±S.D.	*P* value [a]
D1 (Physical)	Control	38.00	94.00	67.47±18.46	0.875
	Patients	13.00	88.00	66.18±24.29	
D2 (Psychological)	Control	50.00	88.00	70.65±12.08	0.395
	Patients	13.00	88.00	65.45±19.78	
D3 (Social)	Control	31.00	100.00	64.29±21.79	0.998
	Patients	19.00	94.00	64.27±22.10	
D4 (Environmental)	Control	31.00	100.00	63.71±16.27	0.997
	Patients	25.00	88.00	63.73±18.86	
Total	Control	194.00	338.00	266.12±40.72	0.753
	Patients	126.00	332.00	259.64±67.47	

[a]: *P* value between Control and Patients using Parametric test (Independent Samples *T-Test*); *: Number of male controls vs male patients is 17:11.

Table 6: Comparison between Control females and female patients as regards WHOQOL domains score:

Parameters	Groups	Min.	Max.	Mean±S.D.	*P* value[a]
D1 (Physical)	Control	31.00	100.00	65.88±18.67	0.058
	Patients	31.00	88.00	57.36±18.64	
D2 (Psychological)	Control	31.00	94.00	58.58±17.34	0.150
	Patients	19.00	94.00	52.74±16.62	
D3 (Social)	Control	19.00	94.00	58.33±21.47	0.001*
	Patients	0.00	94.00	38.46±27.00	
D4 (Environmental)	Control	38.00	94.00	64.58±16.23	0.001*
	Patients	6.00	81.00	48.87±19.57	
Total	Control	156.00	357.00	247.36±53.61	0.001*
	Patients	101.00	312.00	197.44±57.13	

[a]: *P* value between Control and Patients using Parametric test (Independent Samples *T-Test*); *: Significant *P* <0.05; *: Number of female controls vs female patients is 33:39.

Table 7: Comparison between 46,XX DSD, 46,XY DSD and Sex chromosome DSD in WHOQOL domains score:

Parameters	Groups	*N*	Min.	Max.	Mean±S.D.	*P* value
D1 (Physical)	46,XX DSD	8	44.00	88.00	63.50±15.83	0.081[a*]
	46,XY DSD	16	31.00	88.00	66.94±18.62	
	Sex chromosome DSD	26	13.00	88.00	53.31±20.79	
D2 (Psychological)	46,XX DSD	8	31.00	81.00	59.38±17.65	0.005[a*]
	46,XY DSD	16	38.00	94.00	65.69±15.18	
	Sex chromosome DSD	26	13.00	81.00	48.12±16.69	
D3 (Social)	46,XX DSD	8	0.00	81.00	43.00±25.32	0.050[b*]
	46,XY DSD	16	0.00	94.00	57.88±25.91	
	Sex chromosome DSD	26	0.00	94.00	36.04±27.58	
D4 (Environmental)	46,XX DSD	8	25.00	75.00	51.63±20.15	0.011[b*]
	46,XY DSD	16	38.00	88.00	64.56±15.45	
	Sex chromosome DSD	26	6.00	75.00	44.65±19.65	
Total	46,XX DSD	8	144.00	319.00	217.50±66.76	0.001[a*]
	46,XY DSD	16	188.00	332.00	255.06±48.95	
	Sex chromosome DSD	26	101.00	313.00	182.12±57.46	

[a]: *P* value using Parametric test (Oneway ANOVA *Test*); [b]: *P* value using None-Parametric test (Kruskal-Wallis *Test*); *: 46,XX DSD/ 46,XY DSD/sex chromosome DSD is 8:16:26.

Table 8: Comparison between 46,XX DSD, 46,XY DSD and Sex chromosome DSD groups as regards hormonal and surgical treatment:

Groups			46,XX DSD	46,XY DSD	Sex chromosome DSD	*P* value[a]
Hormonal treatment	+ve	N	4	11	22	0.126
		%	50.00%	68.80%	84.60%	
	-ve	N	4	5	4	
		%	50.00%	31.20%	15.40%	
Surgical treatment	+ve	N	2	9	1	0.001*
		%	25.00%	56.20%	3.80%	
	-ve	N	6	7	25	
		%	75.00%	43.80%	96.20%	

[a]: *P* value between groups and Type of Chromosome for each parameter using Chi-Square Test.

Table 9: Comparison between 46,XX DSD patients and control in WHOQOL domains score:

Parameters	Groups	Min.	Max.	Mean±S.D.	*P* value
D1 (Physical)	Control	31	100	66.42±18.43	0.674[a]
	46,XX DSD	44	88	63.50±15.83	
D2 (Psychological)	Control	31	94	62.68±16.66	0.607[a]
	46,XX DSD	31	81	59.38±17.65	
D3 (Social)	Control	19	100	60.36±21.55	0.043[b*]
	46,XX DSD	0	81	43.00±25.32	
D4 (Environmental)	Control	31	100	64.28±16.08	0.051[b]
	46,XX DSD	25	75	51.63±20.15	
Total	Control	156	357	253.74±49.99	0.075[a]
	46,XX DSD	144	319	217.50±66.76	

[a]: *P* value between Control and Patients using Parametric test (Independent Samples *T-Test*); [b]: *P* value between Control and Patients using None-Parametric test (Mann-Whitney Test); *: Number of control Vs 46,XX DSD patients is 50:8.

Table 10: Comparison between sex chromosome DSD patients and control in WHOQOL domains and total score:

Parameters	Groups	Min.	Max.	Mean±S.D.	*P* value
D1 (Physical)	Control	31	100	66.42±18.43	0.006[a*]
	Sex chromosome DSD	13	88	53.31±20.79	
D2 (Psychological)	Control	31	94	62.68±16.66	0.001[a*]
	Sex chromosome DSD	13	81	48.12±16.69	
D3 (Social)	Control	19	100	60.36±21.55	0.001[b*]
	Sex chromosome DSD	0	94	36.04±27.58	
D4 (Environmental)	Control	31	100	64.28±16.08	0.001[b*]
	Sex chromosome DSD	6	75	44.65±19.65	
Total	Control	156	357	253.74±49.99	0.001[a*]
	Sex chromosome DSD	101	313	182.12±57.46	

[a]: *P* value between Control and Patients using Parametric test (Independent Samples *T-Test*); [b]: *P* value between Control and Patients using None-Parametric test (Mann-Whitney Test); *: Number of control Vs sex chromosome DSD patients is 50:26.

Table 11: Comparison between 46,46,XY DSD patients and control in WHOQOL domains and total score:

Parameters	Groups	Min.	Max.	Mean±S.D.	*P* value
D1 (Physical)	Control	31	100	66.42±18.43	0.923[a]
	46,XY DSD	31	88	66.94±18.62	
D2 (Psychological)	Control	31	94	62.68±16.66	0.524[a]
	46,XY DSD	38	94	65.69±15.18	
D3 (Social)	Control	19	100	60.36±21.55	0.868[b]
	46,XY DSD	0	94	57.88±25.91	
D4 (Environmental)	Control	31	100	64.28±16.08	0.951[a]
	46,XY DSD	38	88	64.56±15.45	
Total	Control	156	357	253.74±49.99	0.927[a]
	46,XY DSD	188	332	255.06±48.95	

[a]: *P* value between Control and Patients using Parametric test (Independent Samples *T-Test*); [b]: *P* value between Control and Patients using None-Parametric test (Mann-Whitney *Test*); *: Number of control Vs 46,XY DSD patients is 50: 16.

Table 12: Comparison between DSD patients who received hormonal treatment and those who didn't receive hormonal treatment:

Parameters	Hormonal treatment	Min.	Max.	Mean±S.D.	*P* value
D1 (Physical)	+ve	13.00	88.00	55.92±20.79	0.020[a*]
	-ve	44.00	88.00	68.92±14.64	
D2 (Psychological)	+ve	13.00	94.00	52.57±18.73	0.047[a*]
	-ve	44.00	88.00	64.00±12.63	
D3 (Social)	+ve	0.00	94.00	45.78±26.98	0.477[b]
	-ve	0.00	94.00	39.46±31.25	
D4 (Environmental)	+ve	6.00	88.00	49.27±20.87	0.085[b]
	-ve	25.00	81.00	60.31±16.21	
Total	+ve	101.00	332.00	203.54±66.55	0.162[a]
	-ve	144.00	326.00	232.69±54.11	

[a]: *P* value between Control and Patients using Parametric test (Independent Samples *T-Test*); [b]: *P* value between Control and Patients using None-Parametric test (Mann-Whitney *Test*); *: Number of patients received hormonal treatment Vs those who didn't receive treatment is 37:13.

Table 13: Comparison between DSD patients who did correctional surgery and those who didn't undergo correctional surgery in WHOQOL domains and total score:

Parameters	Surgical treatment	Min.	Max.	Mean±S.D.	*P* value
D1 (Physical)	+ve	44.00	88.00	73.08±14.20	0.005[a*]
	-ve	13.00	88.00	54.95±19.83	
D2 (Psychological)	+ve	38.00	94.00	67.17±15.32	0.009[a*]
	-ve	13.00	88.00	51.87±17.31	
D3 (Social)	+ve	0.00	81.00	52.58±24.77	0.205[b]
	-ve	0.00	94.00	41.47±28.68	
D4 (Environmental)	+ve	25.00	88.00	64.17±18.84	0.015[b*]
	-ve	6.00	88.00	48.34±19.32	
Total	+ve	188.00	332.00	257.00±51.86	0.004[a*]
	-ve	101.00	326.00	196.63±61.50	

[a]: *P* value between Control and Patients using Parametric test (Independent Samples *T-Test*); [b]: *P* value between Control and Patients using None-Parametric test (Mann-Whitney *Test*); *: Number of patients who underwent correctional surgery Vs those who didn't undergo surgery is 12: 38.

Table 14: Comparison between DSD patients who received hormonal treatment or underwent surgical correction and those who did both:

Parameters	Groups	Min.	Max.	Mean±S.D.	*P* value
D1 (Physical)	Hormonal treatment	13.00	88.00	52.61±19.81	0.010 [a]*
	Surgical treatment	63.00	88.00	73.17±10.09	
	Both Hormonal & Surgical treatment	44.00	88.00	73.00±18.48	
D2 (Psychological)	Hormonal treatment	13.00	81.00	49.84±17.45	0.018 [a]*
	Surgical treatment	56.00	81.00	67.67±10.07	
	Both Hormonal & Surgical treatment	38.00	94.00	66.67±20.35	
D3 (Social)	Hormonal treatment	0.00	94.00	42.35±27.15	0.195 [b]
	Surgical treatment	0.00	81.00	41.67±26.37	
	Both Hormonal & Surgical treatment	31.00	81.00	63.50±19.18	
D4 (Environmental)	Hormonal treatment	6.00	88.00	44.87±19.40	0.008 [b]*
	Surgical treatment	25.00	81.00	56.33±22.25	
	Both Hormonal & Surgical treatment	56.00	88.00	72.00±11.76	
Total	Hormonal treatment	101.00	313.00	189.68±60.32	0.004 [a]*
	Surgical treatment	188.00	319.00	238.83±49.14	
	Both Hormonal & Surgical treatment	188.00	332.00	275.17±52.05	

[a]: *P* value using Parametric test (Independent Samples *T-Test*); [b]: *P* value using None-Parametric test (Mann-Whitney *Test*); *: Number of patients receiving only hormonal treatment: patients receiving only surgical treatments: those who received both treatments is 31:6:6.

DISCUSSION

Disorders/Differences of sex development (DSD) are medical diseases affecting the reproductive system in which chromosomal, gonadal, or anatomical sex development is abnormal (**Daher *et al*., 2011**).

QOL means interaction between one's environment, personal views, social relationships, psychological state, independent abilities, and physical health. Since 1996, WHOQOL-BREF has been utilised extensively in the field of medicine and can make it simple to successful management (**Wang and Tian, 2015**).

In chronic diseases like DSD, health-related quality of life (HRQOL) is frequently used to estimate how the disease and its management can affect the lives of the patients (**Hasanah, 2003**).

Proper and early psychosocial management is very important for those with genital ambiguity (**Cohen, 2010**).

In patients with DSD, these scores can indicate whether or not a given medical intervention has improved their quality of life (**Savanelli *et al*., 2008**).

Abnormal sex hormone exposure was the main subject of some studies working on the quality of life (QOL) in people with DSD, however minority of researchers have looked at QOL in children. Since there is no special questionnaire for DSD, multiple alternative questionnaires were used in all trials. So, it was challenging to compare the results (**Musa *et al*., 2017**).

Congenital adrenal hyperplasia (CAH) patients have been the subject of most researches in this field, with minority working on other DSD patients (**Savanelli *et al*., 2008**).

Although there are many QOL studies on a single group of DSD like CAH, TS, or AIS (**Mnif *et al*., 2012**), there is very little information about the combined QOL of multiple DSD individuals (**Jürgensen *et al*., 2014**).

Our study is a cross-sectional to assess health related quality of life (HRQOL) using WHOQOL-BREF in 50 DSD patients aged from 6 to 16 years old in addition to 50 healthy children with matched age and sex served as control.

Our study showed overall decrease in HRQOL of DSD children and adolescents in comparison to control and that psychological and social domains have lower scores than physical and environmental domains. This may be explained by facing many challenges, such as living with a rare chronic disease, the risk of inappropriate management, school absences due to several medical procedures, possible adverse hormonal effects on behavior, risks for infertility, and/or potential psychosocial and emotional problems.

We also compared each group with the control, when we compared sex chromosome DSD patients to the control, we found that sex chromosome patients showed lower significant scores in all WHOQOL domains and also the total score may be due to the possible high risk of growth disturbance and infertility.

These results are consistent with a study employing the Version 4.0 (PedsQL) questionnaire, which discovered that the DSD patients had an impaired quality of life in comparison to control (**Savanelli *et al*., 2008**).

Additionally, our findings were consistent with Martina *Jürgensen's* study utilising the KINDL-R Questionnaire (2001), which found that DSD children aged 8 to 12 had generally lower HRQOL than control (**Jürgensen *et al*., 2014**).

Furthermore, our findings were consistent with *Wang and Tian's* research on children with DSD using WHOQOL-BREF, which demonstrated that psychological and environmental domains had lower ratings than physical and social domains but with no statistical difference (**Wang and Tian, 2015**).

Also, our findings were consistent with *Yau's* study on children with CAH using the PedsQL 4.0 questionnaire, which revealed lower HRQOL as well as a higher percentage of CAH children with impaired physical, emotional, social, and academic life (**Yau *et al*., 2015**).

Another study employing the CHQ and PedsQol 4.0 questionnaires found that children and adolescents with CAH have significant lower overall score with physical and psychological scores when compared to healthy children and adolescents (**Gilban *et al*., 2014**).

Numerous studies found that being a child or adolescent with DSD increases the risk of psychological problems (**Liang *et al*., 2008**).

Additionally, there are reports of increased anxiety and suicidal thoughts in DSD patients (**Mnif *et al*., 2012**).

So, to provide proper management for DSD patients and their families, the European Society of Paediatric Endocrinology (ESPE) guidelines give special importance to the role of a clinical psychologist in multidisciplinary team management (**Hughes *et al*., 2006**).

On the other hand, a recent study of children with CAH in a Dutch population revealed few negative effects of CAH on physical, social, and psychological life using a self-designed questionnaire, and the children QOL was fair. Despite having a number of daily health-related issues, those children were still able to participate in daily life and activities. The QOL instrument's questions, were developed from a study that evaluating quality of life through parents, so they might not reflect the child personal wellbeing (**Sanches *et al*., 2012**). Also good results of psychosocial assessment were documented in another study that included both adults and children with DSD (**Berenbaum *et al*., 2004**).

Interestingly a study found that early management and good follow up of DSD patients showed very good outcome even exceeding controls (**Finkielstain *et al*., 2012**).

On the other hand, a study conducted by (**Warne *et al*. 2005**) reported that, HRQOL in DSD patients is near to that of general population.

Aother Swedish study about HRQOL in adult women with CAH found no significant differences (**Frisen *et al*., 2009**).

Similar results were found in patients with a variety of chronic conditions with proper and early management plans for the illness (**Frisen *et al*., 2009**).

In our study we found no significant correlation between age and WHOQOL domains score. This was similar to *Yau* who found no statistically significant differences in overall HRQOL or specific domains as regarding age (**Yau *et al*., 2015**). *Idris's* study also reported no relationship between psychological adjustment and mean age at diagnosis (**Idris *et al*., 2014**).

In contrast, another study by *Musa et al.* reported lower overall QOL score besides psychological and social domains in older DSD children and adolescents (**Musa *et al*., 2017**).

Also, our study showed no significant correlation between educational level and WHOQOL domains score.

The comparison between 46,XY DSD and the control, revealed no significant difference in all WHOQOL domains and the total score. While the comparison between 46,XX DSD and the control revealed lower WHOQOL domains score with a significant difference in only social one.

In addition, when we compared between DSD patients who were reared as males and those who were reared as females and when we compared both sex with the corresponding control, we found that DSD patients reared as males had better HRQOL than DSD patients reared as females with a significant difference in all WHOQOL domains and total score except in physical domain there was no significant difference, this may be explained by androgen effects in children with DSD reared as girls which increases the risk of gender identity insecurity or dysphoria.

While the comparison between males and females in control group showed no significant difference in all domains except in psychological domain, males score was better than females with a significant difference.

This came in line with **Selveindran *et al.*, 2017** study on DSD patients using the PedsQL, in which DSD female

patients scores were lower than males but with no statistical difference (**Savanelli *et al*., 2008**).

Additionally, *Crawford's et al.* study, which included 54 DSD children aged 5 to 10 and their parents using the PedsQL quality-of-life measure, revealed that female patients and their parents showed lower psychological scores (**Crawford *et al*., 2009**).

Also, according to *Engberg* and his colleagues, when compared to controls, DSD patients reared as females had a higher risk for psychiatric problems (**Engberg *et al*., 2015**).

Another study in Egypt on CAH patients using WHOQOL questionnaire found that females had statistically significant lower psychological scores in comparison to male patients (**Musa *et al*., 2017**).

The QOL and psychological assessment of 34 Italian girls with 46, 46,XY DSD revealed bad scores with much more possibilities of psychological problems (**D'Alberton *et al*., 2015**).

According to a study by *Zainuddin et al.,* females with DSD is facing multiple challenges, including a chronic medical condition, mandatory continuous treatment and frequent follow-ups, surgery and its sequel, psychosexual problems, body image, and risk of infertility, undoubtedly, each of these had a bad effect on their quality of life (**Zainuddin *et al*., 2013**).

Contrary to our study, (**Gilban *et al*., 2014**) and (**Yau *et al*., 2015**) found no differences in HRQOL between DSD patients who were reared as males or females.

Also, compared to controls, *Idris* and his colleagues reported similar psychological assessment with CAH girls, while psychological problems were found to be prevalent among boys with CAH (**Idris *et al*., 2014**). Similarly, male and female DSD patients QOL was the same, according to *Halper* and his colleagues (**Halper *et al*., 2017**).

When we compared the 3 three groups of DSD patients (46,XX DSD, 46,XY DSD and sex chromosome DSD) in relation to different WHOQOL domains and total score we found that sex chromosome DSD patients were the most affected group with statistically lower scores in psychological, social, environmental domain and also the total score.

This was consistent with another study which reported that 46,XY DSD patients have good quality of life scores but with also psychological problems (**D'Alberton *et al*., 2015**). While (**Wang and Tian, 2015**) study on kids with DSD using WHOQOL-BREF, found no significant differences between DSD subgroups.

We also compared between our three DSD groups in age, weight and height and we found that there was a significant difference only in height with the least mean height in sex chromosome group, this is almost due to presence of many patients diagnosed as Turner syndrome in this group.

When we compared between the DSD groups in family history and consanguinity, we found significant difference between the 3 groups in family history and consanguinity with higher percentage of positive family history and consanguinity in 46,XX DSD then 46,XY DSD and lastly sex chromosome DSD.

Studying surgical correction in our DSD patients, 24% underwent surgical correction. When we compared QOL in DSD patients who underwent surgical correction and those who didn't undergo surgical correction, DSD patients with surgical correction showed a statistically significant positive effect on physical, psychological and environmental domain and also the total score. DSD patients who received both hormonal treatment and surgical correction had significant higher scores in all WHOQOL domains in addition to the total score than patients who received each of hormonal treatment or surgical correction alone, except in psychological domain there was no significant difference.

This agrees with *Savanelli et al.,* who recommended early proper surgical correction of external genitalia to reduce the anxiety of the parents and children, increases self-esteem and QOL.

Additionally, a research on CAH in Egypt found that women who underwent surgical correction showed statistically significant higher scores in psychological domain than women who did not have surgery (**Musa *et al*., 2017**).

Several other studies documented that DSD patients had better quality of life and mental health with significant decrease in psychological problems after corrective surgery (**Slijper and Drop, 1998; Warne *et al.*, 2005)**.

Contrarily, other studies revealed impaired quality of life in children and adolescents with DSD after surgical correction with negative impact on body image and physical wellbeing (**Crawford *et al*., 2009; Cull, 2005; Zhu *et al*., 2012; Kreukels *et al*., 2019**).

Additionally, a study on the well-being of 46,XY DSD patients reported dissatisfaction in high percentage of female 46,XY DSD patients following genital surgery (**Köhler *et al*., 2012**).

While a study evaluated the quality of life (QOL) of patients with androgen insensitivity syndrome who had

late surgery of gonadectomy in youth and those who had early surgery. They found no distinctions between the two groups (**Tang *et al*., 2017**).

That was comparable to another study that found no link between the number of procedures and PedsQL scores (**Savanelli *et al*., 2008**).

According to (**Kreukels *et al*., 2019**) study performing genital surgery on DSD patients should be done with extreme caution due to higher incidence of psychosexual problems after surgery. The worse outcomes have been related to either premature surgical decision before proper diagnosis or before gender identity is studied, late genital surgery, poor surgical results, or painful memories may lead to lower quality of life after surgery (**Johannsen *et al*., 2006**).

In our study 74% of our DSD patients were on hormonal treatment. Compared to those who didn't receive any treatment, they only showed significant differences in physical and psychological domains.

This may be explained by the high number of patients on hormonal treatment compared to the other group and the relatively small sample size. Also, it has been shown that severity of illness or even relevant functional limitations could show limited influence on HRQOL. Furthermore, receiving daily continuous drugs has a bad impact on physical, psychological and social wellbeing.

This was consistent with an Egyptian study that found patients receiving high doses of mineralocorticoids had statistically significant lower QOL scores at psychological domain and total scores of WHOQOL, explained by the fact that patients who take high amounts of mineralocorticoids have more severe salt losing CAH and take high doses of medications, which results in poorer QOL scores (**Musa *et al*., 2017**). As increasing the daily drug doses the bad impact on physical, psychological and social wellbeing increases. This was emphasized by a longitudinal study on CAH patients that revealed increased quality of life by reducing the daily drug doses (**Bleicken *et al*., 2012**).

That was in contrast to a study by **Falhammar and Thorén, 2012**, which revealed that patients receiving high doses of GC had lower HRQOL outcomes than those receiving low doses, indicating the significance of having proper androgen levels.

CONCLUSION

Paediatric patients with DSD have significantly lower HRQOL in psychological and social aspects rather than in physical and environmental aspects. HRQOL is most affected in sex chromosome DSD and least affected in 46,XY DSD patients. DSD patients reared as males had a significant better HRQOL than DSD patients who reared as females. DSD patients who underwent surgical correction showed a statistically significant positive effect on physical, psychological and environmental domain and also the total score. The QOL of DSD patients can be hopefully improved after early and proper management by multidisciplinary team with continuous follow up.

CONFLICT OF INTEREST

There are no conflicts of interest.

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