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Laparoscopy versus ultrasonography for the evaluation of Müllerian duct remnants in male patients with disorder of sex differentiation

Mohamed Sayed Abd El-Monsif[1], Noha Arafa[2*], Mahmoud Marei Marei[3], Gamal Eltagy[3] and Ahmed M. K. Wishahy[3]

Abstract

Background The diagnosis of male differences of sex development is a challenging multidisciplinary team task, that requires external genital evaluation, karyotyping, hormonal profiling, radiological work up and frequently diagnostic laparoscopy and biopsy, for evaluation of internal duct system and nature of gonads. The debate still persists regarding the best diagnostic modality for accurate visualization of Müllerian duct remnants (MDRs) in those patients.

The aim of the study was to compare between laparoscopy (L) and ultrasonography (US) regarding the diagnostic accuracy in detection of Müllerian duct remnants, in addition to describing their anatomical nature and relations with the male duct system, in patients with male DSD, with various karyotypes.

Methods We prospectively included 20 patients with male DSD, mostly due to 46 XY DSD or chromosomal DSD, over 2 years. The medical and radiological data were collected and analyzed.

Results The age at the first diagnostic intervention ranged from 8 to 24 months (mean: 17 months). There were 14 patients with 46XY DSD with variable diagnoses (3 ovotesticular DSD, 3 partial gonadal dysgenesis, 6 persistent Müllerian duct remnants syndrome and 2 mixed gonadal dysgenesis). Two patients with 46XX DSD were included (one XX male, and one patient with ovotesticular DSD). One patient with chimerism (46XY/46XX) and three patients with 46XY/45XO mixed gonadal dysgenesis were also recruited. MDRs were evident in all cases (100%) by laparoscopy, only 25% ($n=5$) were visualized by US. There was a statistically significant difference between laparoscopy and US regarding gonadal and MDR visualization, being higher with laparoscopy (p values, 0.0180 and 0.001).

Conclusions Ultrasonography failed to visualize Müllerian remnants in 75% of patients with complex DSD. On the other hand, laparoscopy provided optimum visualization of MDRs and gonads in those children.

Keywords Ultrasonography, Laparoscopy, Differences of Sex Development, Müllerian Duct Remnants

*Correspondence:
Noha Arafa
Noha.hussein@kasralainy.edu.eg
Full list of author information is available at the end of the article

Background

Differences of sex development (DSD) are a diverse group of conditions, which result in discrepancy between the gonadal, chromosomal, and anatomical sex/gender of the affected persons [1]. According to Lawson Wilkins Pediatric Endocrine Society (LWPES) and European Society for Pediatric Endocrinology (ESPE) consensus of 2006, updated in 2016, the causes of DSD are classified into three main categories according to karyotype analysis (sex chromosome DSD, 46 XY DSD and 46 XX DSD) [2, 3]. Patients with 46 XY DSD have variable clinical presentations, in the form of different degrees of external genital masculinization, with variable stages of development of the Wolffian and Müllerian ducts structures [4]. Remnants of Müllerian duct structures can be caused by various disorders, which can be categorized and divided into: a) dysgenetic causes, resulting into defects in androgens and anti- Müllerian hormone (AMH) secretion (e.g. ovotesticular (OT) DSD, partial and complete gonadal dysgenesis); b) non-dysgenetic causes, due to defects in secretion or action of AMH (e.g. persistent Müllerian duct syndrome) [5]. Cases may present with variable clinical presentations, in the form of different degrees of hypospadias associated with testicular maldescent. Additionally, it could be encountered as a surprise during orchidopexy or hernia repair [6]. To reach the proper diagnosis of patients with 46XY DSD with Müllerian duct remnants (MDRs), meticulous physical examination is needed, in addition to complementary investigations in the form of hormonal profile, imaging, and genetic testing. Establishment of accurate diagnosis is a crucial point in the decision-making regarding sex assignment [7]. Over the last few years, the laparoscopic approach, either for diagnosis or management of pediatric patients with MDRs, has been widely used by pediatric surgeons and urologists [8].

The proper imaging modality is a crucial step in the accurate outline of the internal genital anatomy, and consequently proper sex determination [9]. Ultrasonography (US) has been always the widely used method as it is specific and easily accessible, but less sensitive [10]. Meanwhile, laparoscopy had been advocated through the last few years, and demonstrated by by Steven et al (2012) to be a safe and reliable method for this purpose [11].

In the current work, our aim was to compare the role of ultrasonography versus laparoscopy, within our setting, in pediatric patients with male DSD, mostly due to 46 XY DSD or chromosomal DSD with Müllerian duct remnants, regarding the diagnostic accuracy in describing the anatomical nature of MDRs and its relation with the male duct system.

Methods

After an Institutional Review Board (IRB) approval, a prospectively collated non-randomized study for comparative diagnostic accuracy, included 20 consecutive patients who were diagnosed as male DSD, either 46 XY DSD, chromosomal DSD, or Testicular/Ovotesticular variants of 46 XX DSD, all of whom were attending the Endocrinology Clinic at Diabetes, Endocrine and Metabolism Pediatric Unit (DEMPU), at Cairo University Children's hospital, during a period of two years, from August 2017 to August 2019. All included patients required a laparoscopy for a suspected gonadal abnormality or abnormally persistent Müllerian duct remnant, that required diagnostic or therapeutic laparoscopy, following a multidisciplinary review. The etiological classification of recruited patients was based upon the proposed classification by the Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Pediatric Endocrinology (ESPE), of 2006 [2]. Detailed history of recruited patients was taken including: age and principal complaint at presentation, initial sex of assignment, consanguinity, family history of any similar conditions, and history of any previous surgical procedures. Meticulous genital examination was done including: palpation of gonads, number and position of orifices, size and length of phallus/clitoris, and differentiation of labioscrotal folds. Accordingly, external masculinization score (EMS) was calculated for every patient to assess the degree of virilization [12].

The results of karyotyping and hormonal profile of patients were captured from the medical records including: short human chorionic gonadotropin (hCG) stimulation test and anti-Müllerian hormone levels (AMH) [12]. Additionally, the results of radiological investigations (e.g. ultrasonography or MRI) were recorded.

Surgical technique

For diagnostic laparoscopy, the standard technique was followed. An open Hasson technique was used for the introduction of the laparoscope, through a primary 5 mm camera port. Two 2.5-3 mm laparoscopic instruments, usually comprising a set of scissors and a Maryland forceps were then inserted portless, in both paramedian regions at the same plane of the umbilicus, or slightly below. For therapeutic laparoscopy, any further procedure was planned after visualization of the internal ductal and gonadal anatomy, if necessary, (Fig. 1).

Statistical methods

The data was analyzed into the Statistical Package of Social Science Software program, version 26 (SPSS, Chicago, Illinois). Quantitative variables were described as

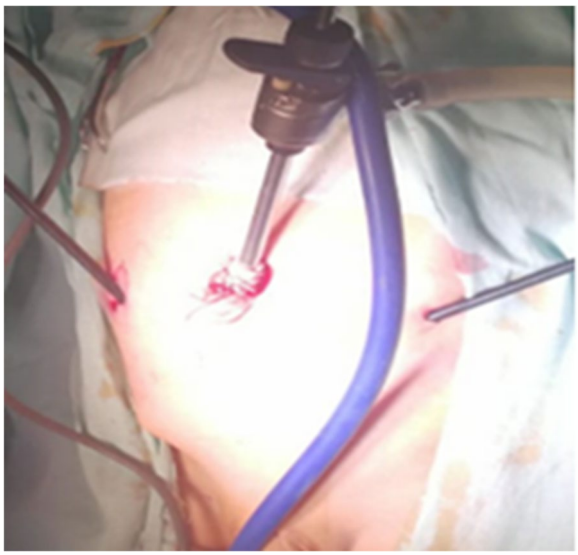


Fig. 1 Showing the arrangement of laparoscopic instruments and an example for port-site placements

mean ± SD, median, minimum and maximum, compared using independent T test and Mann Whitney U test for 2 independent groups, with significant p value at $p < 0.05$. Qualitative variables were described as frequency and percentage. Comparison for qualitative variables was done by using chi square test and fisher exact test, with significant p value at $p < 0.05$. The sensitivity and specificity of ultrasound in localizing Müllerian structures were calculated. We calculated the sensitivity as TP/(TP + FN) and the specificity as TN/(FP + TN), where TP stands for true positive cases, FN for false negative, TN for true negative and FP for false positive.

Results

Twenty patients with complex DSD were included. All of them received a preoperative US and needed laparoscopic intervention**.** The median age of recruited patients was 17 months (IQR: 8- 24). The patients were divided according to the karyotyping into: 14 patients (70%) with 46 XY, 2 patients (10%) with 46XX, with negative fluorescence in situ hybridization (FISH) for Sex Determining Region Y (SRY) gene, 3 patients (15%) had 46XY/45

Table 1 Detailed karyotyping, findings on ultrasonography and at laparoscopy, and final diagnosis of 20 patients with DSD

Age	Karyotyping	Laparoscopy		Ultrasound		Diagnosis
		Mullerian Structure	gonads	Mullerian Structure	gonads	
3m	45XO\46XY	Y	Rt:Y, Lt: N	N	Rt:Y, Lt: N	MGD
16m	45XO\46XY	Y	Rt: Y, Lt: Scrotal	Y	Rt:N, Lt:Scrotal	MGD
42m	45XO\46XY	Y	Rt: Y, Lt: N	N	Rt&Lt: N	MGD
4m	46XY	Y	Rt&Lt: Y	Y	Rt&Lt: N	PGD
8m	46XX	Y	Rt&Lt: Y	N	Rt&Lt: Y	XX-testicular DSD
9m	46XX	Y	Rt&Lt: Y	Y	Rt&Lt: Y	XX- OT- DSD
18m	46XX\46XY	Y	Rt:Y, Lt: Scrotal	N	Rt:N, Lt:Scrotal	XX/XY- OT- DSD (Chimeric)
18m	46XY	Y	Rt: Scrotal, Lt:N	N	Rt: Scrotal, Lt:N	PMDS
8m	46XY	Y	Rt:Y, Lt:Scrotal	N	Rt:N, Lt:Scrotal	XY- OT- DSD
19m	46XY	Y	Rt: Scrotal, Lt:Y	N	Rt: Scrotal, Lt:N	XY- OT- DSD
7m	46XY	Y	Rt&Lt: Y	Y	Rt&Lt: N	XY- OT- DSD
28m	46XY	Y	Rt&Lt: Y	N	Rt&Lt: Y	PMDS
108m	46XY	Y	Rt&Lt: Y	N	Rt&Lt: N	PMDS
24m	46XY	Y	Rt&Lt: Y	N	Rt&Lt: N	MGD
24m	46XY	Y	Rt:N, Lt:Scrotal	N	Rt:N, Lt:Scrotal	MGD
8m	46XY	Y	Rt: Scrotal, Lt:Y	Y	Rt: Scrotal, Lt:N	PGD
16m	46XY	Y	Rt&Lt: Y	N	Rt:Y, Lt: N	PMDS
20	46XY	Y	Rt: Scrotal, Lt:N	N	Rt: Scrotal, Lt:N	PMDS
10	46XY	Y	Rt&Lt: Y	N	Rt&Lt: N	PGD
96	46XY	Y	Rt&Lt: Y	N	Rt&Lt: N	PMDS

Y Present, *N* Absent, *Rt* Right, *Lt* left, *OT* Ovotesticular, *PMDS* Persistent mullerian duct syndrome, *PGD* Partial gonadal dysgenesis, *MGD* Mixed gonadal dysgenesis

Table 2 Comparison between ultrasonography and laparoscopy regarding gonadal visualization and Müllerian duct remnants

Parameters		Ultrasound		Laparoscopy		*P* value
		N	%	*N*	%	
Gonadal visualization	Absent both gonads	6	30%	0	0.0%	**0.018**
	Absent one gonad	4	20%	3	15%	
	Visualization of both gonads (or vas and vessels entering the canal)	10	50%	17	85%	
MDRs	Visualized	5	25%	20	100%	**0.001**
	Non- visualized	15	75%	0	0.0%	

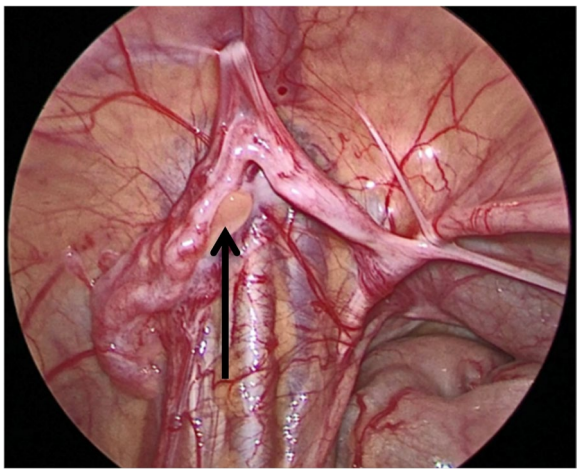


Fig. 2 MDR in a case of 46XY ovotesticular DSD, in the form of a Fallopian tube with the possibility of an atrophied uterus, with presence of an ovary (black arrow), excision was done

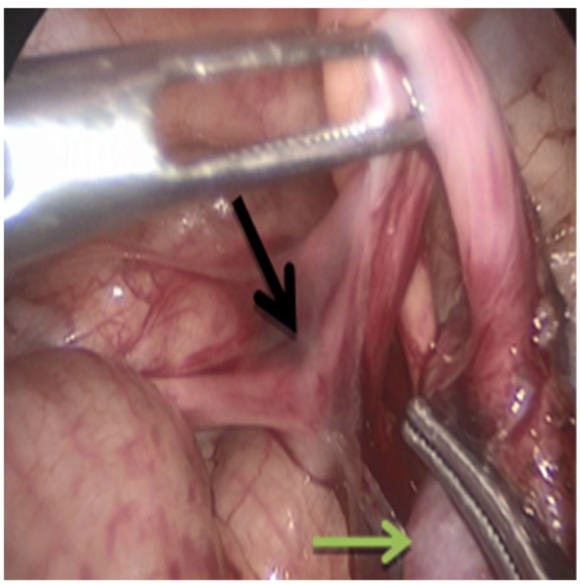


Fig. 3 A case of 46XY/45XO MGD with unilateral right undescended testis (green arrow), and unilateral relation between the MDR and the vas of the left scrotal testis, with a clear point of entry (black arrow). Excision above this point was done

XO and only 1 patient (5%) had 46XY/46XX chimerism. Consanguinity was reported in 8 patients (40%), also 2 patients (10%) had siblings with a similar condition. Before intervention, all patients were initially sexually assigned as 14 males (70%) and 6 females (30%), eventually, all bar one were assigned as males. Preoperative clinical assessment of patients revealed that **all** patients presented with undescended testis/testes, mostly were bilateral (60%) and were impalpable in 14 patients (70%). Additionally, hypospadias was found in 17 patients (85%), with most of them having scrotal (41.2%) and penoscrotal meatal positions (41.2%). Moreover, micropenis was reported in 5 patients (25%), with the phallus length ranging from 2.5 to 6 cm, and a mean length 3.63 ± 0.94 cm. EMS of patients ranged from 1 to 10.5, with a mean score of 5.88 ± 2.84. Six patients had history of recurrent attacks of urinary tract infection. The hormonal profile of patients showed normal testosterone response after short hCG stimulation in 12 patients (60%) and poor response in one patient (5%). Basal androgen

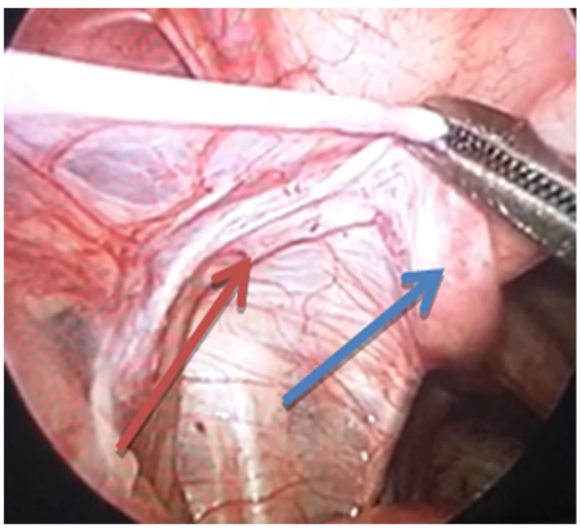


Fig. 4 A case of 46XY undervirilized male (not CAH), with an MDR in the form of a uterus (blue arrow) and a left fallopian tube (red arrow), with bilaterally absent relation between the MDR and the vas. Excision was done

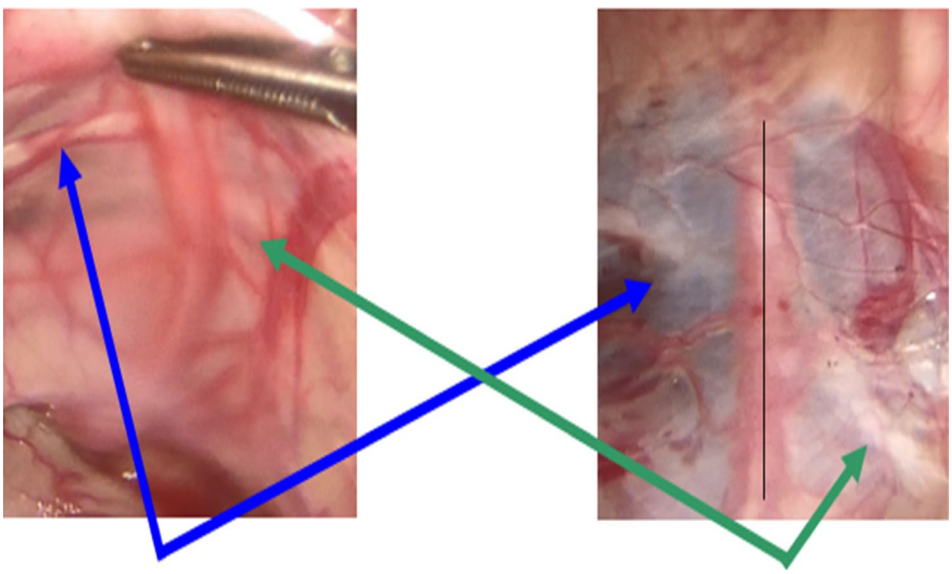
levels without stimulation were available for 7 patients (35%), 6 of them had normal values and one patient had low levels. Regarding AMH levels, 13 patients (65%) had normal values and 7 patients (35%) had low levels. Detailed diagnosis, karyotyping and comparison between laparoscopic and ultrasonographic finding of all included patients are illustrated in Table 1.

Even though MDRs were evident in all cases by laparoscopy, only 25% ($n=5$) were visualized by US, (Table 1). Additionally, 24/40 gonads (60%) were visualized by US. Two patients were found to have urinary tract anomalies; one patient had a left solitary kidney and the other one had a left hydronephrosis. However, laparoscopy visualized MDRs and gonads successfully in **all** patients. There was a statistically significant difference between laparoscopy and US regarding gonadal and MDR visualization, being understandably visualized more with laparoscopy, with significant p values, 0.0180 and 0.001 respectively, see Table 2. Figures 2, 3, 4, and 5 display various examples for laparoscopic MDR. ductal/vasal and gonadal findings, and Fig. 6 shows an example of an ultrasound finding. No false positive detections of MDRs were encountered by either modality. US sensitivity in detection of MDRs was 25%, and as both TN and FP = 0, specificity was incalculable/undefined. Additionally, there were discordances about the findings of US versus laparoscopy in detection of impalpable undescended testes. Gonadal absence/agenesis was reported unilaterally in 20% ($n=4$) and bilaterally in 30% ($n=6$) by US. Nevertheless, unilateral gonadal agenesis was reported in only 15% ($n=3$) and no cases were reported bilaterally by laparoscopy. US sensitivity and specificity in detection of impalpable undescended was 36% & 75%, respectively. In this series, 40 laparoscopic maneuvers were done; 14 diagnostic laparoscopy and biopsy and 26 therapeutic maneuvers were performed. MDRs excision was done for 12 cases (60%) and division for 6 cases (30%).

Discussion

Accurate diagnosis and management of patients with 46 XY DSD and chromosomal DSD is very challenging, as it impacts the sex assessment in addition to gonadal management [13]. MDRs in those categories of DSD can present with two different entities: enlarged prostatic utricles (PUs) or vagina masculina (VM) that can arise from the posterior and bulbar urethra, and Müllerian duct cysts (MDCs) which don't communicate with the urethra [14]. AMH secreted substantially by fetal and prepubertal Sertoli cells plays a pivotal role in activating the regression of the fetal Müllerian duct in males. Moreover, androgens secreted by Leydig cells control the stabilization and differentiation of the Wolffian duct structures and the virilization of the external genitalia. Therefore, MDRs persistence is attributed to either: AMH deficiency or AMH receptor insensitivity [15].

MDRs association with DSD is common, and they have different presentations, among them is accidental discovery during inguinal surgery for palpable gonads. In our



a- Laparoscopic view through the Douglas pouch. b- Laparoscopic view of the same case through the vesico-uterine pouch.

Fig. 5 A case of XX male, with an underdeveloped elongated MDR, with a vas running along its wall bilaterally. Division was done. Blue arrow: left vas – Green arrow: right vas

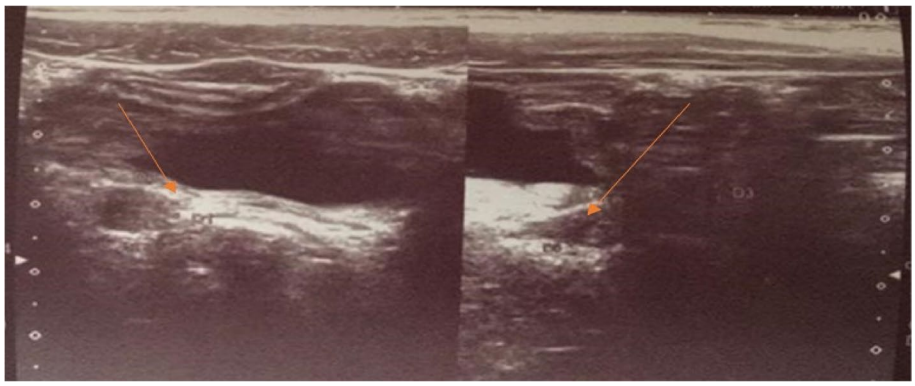


Fig. 6 Transabdominal ultrasound demonstrating atrophied uterine shadow in a patient with ovotesticular disorder of sex development

study, this was encountered in 3 cases (15%), however, Farikullah et al. (2012) reported 3 cases out of 8 with the same presentation [16]. In our study, 5 cases (25%) had a micropenis and 17 cases (85%) had a hypospadias, with variable severity degrees from mid-shaft to perineal hypospadias. This was in contrast to Sancar et al. (2018), where all cases presented without hypospadias (six cases) [17]. In the current series, 40% of cases presented with a bifid scrotum, 60% with bilateral undescended testis and 40% with unilateral undescended testis. This is comparable to Lima et al. (2004), where 50% of cases presented with a unilateral undescended testis and 50% with bilateral undescended testes [18]. On the other hand, Okur et al. (2003), reported that 100% of cases presented with unilateral undescended testes [19].

Among patients with 46 XY DSD and mixed gonadal dysgenesis, there is substantial variation regarding the extent of external masculinization and internal anatomy. The role of imaging modality is pivotal to delineate the pelvic anatomy, also to visualize the MDRs [20]. Although US is quick, affordable, available and specific imaging method; it is less sensitive to detect MDRs [20]. The value of US in visualization of MDRs and intra-abdominal gonads is a point of debate. In our work, its value for intra-abdominal gonadal visualization was limited (sensitivity: 36% and specificity: 75%). This was comparable to Shepard et al. (2017) (sensitivity: 38% and specificity: 78%) [21]. Additionally, limited value of US was found in MDRs visualization among our cohort (sensitivity: 25%, 5 out of 20 cases). Previous reports mentioned comparable sensitivity and specificity of US in visualization of MDRs. Steven et al. (2012), mentioned that US succeeded to visualize MDRs in 7 out of 15 cases (47%) and Lima et al. (2004), where US was diagnostic in 2 of the 6 cases (33.3%), equating to a 66.6% false-negative findings [11, 18].

In the current series, laparoscopy successfully visualized MDRs and gonads in all patients. There was a statistically significant difference between laparoscopy and US regarding gonadal and MDRs visualization, being understandably visualized more with laparoscopy, with p values of 0.0180 and 0.001, respectively.

Our finding was supported by previous reports [16, 22] which suggested that pelvic US can be useful preoperative modality but laparoscopy is the gold standard method for proper visualization of MDRs in patients with complex DSD.

However, a larger study is required to compare different modalities such as laparoscopy, MRI and ultrasonography for the evaluation of Müllerian structures in children with complex DSD.

Conclusion

Laparoscopy has an evident diagnostic accuracy for MDRs and abnormal gonads that could not be detected by US in patients with complex DSD. It provided significantly valuable information regarding the anatomical nature of MDRs, and their relation with the male duct system and gonads.

Abbreviations

DSD	Differences of Sex Development (previously known as Disorders of Sexual Differentiation)
LWPES	Lawson Wilkins Pediatric Endocrine Society
ESPE	European Society for Pediatric Endocrinology
AMH	Anti- Müllerian hormone
MDRs	Müllerian duct remnants
OT	Ovotesticular DSD
EMS	External masculinization score
hCG	Human chorionic gonadotropin
PMDS	Persistent mullerian duct syndrome
PGD	Partial gonadal dysgenesis
MGD	Mixed gonadal dysgenesis
US	Ultrasound Scan(s)

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Authors' contributions
Mohamed S. Abdelmonsif, Noha Arafa and Mahmoud M. Marei, the first three authors, had equal contribution to this publication. MSA: participated in the study design, recruitment of cases, data collection, performing the laparoscopy, interpretation of data, drafting of the article and final revision for publication. NA: participated in the study design, interpretation of data, drafting and writing the manuscript and final revision of the published version. MMM: participated in the study design. generating the protocol, decision-making for the enrolled cases, interpretation of data, drafting of the article, response to the reviewers and final revision for publication. GE: advised the projected and has directly overseen the clinical care and progress of all enrolled cases. AKW: participated in decision-making for the enrolled cases, performing the laparoscopy, data processing for statistical analysis, drafting of the article, and final revision for publication. All authors have read and approved the final manuscript.

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Availability of data and materials
Data is available with the authors on request.

Declarations

Ethics approval and consent to participate
The study was approved by the Research Ethics Committee of Kasr Alainy, Faculty of Medicine, Cairo University. Preliminary approval was obtained upon protocol submission, and final approval date was 16/01/2018, document reference no. CMDRF-132701.
Written informed consent was obtained from the parents of all individual participants included in the study.

Consent for publication
Written consent was obtained.

Competing interests
All authors declare no conflict of interest.

Author details
[1]Pediatric Surgery Department, Ghamra Military Hospital, Armed Forces, Cairo, Egypt. [2]Department of Pediatrics, Cairo University, Kasr Alainy School of Medicine, Cairo University Children's Hospitals, Rasheedy Street, Sayeda Zeinab, Cairo 11562, Egypt. [3]Pediatric Surgery Section/Unit, Departments of General Surgery, Cairo University, Faculty of Medicine, Cairo University Specialized Pediatric Hospital (CUSPH) and Cairo University Children's Hospital (Abu El-Reesh El-Moneira), Cairo, Egypt.

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