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ORIGINAL ARTICLE

Boris Chertin · Dmitry Koulikov · Josef Alberton
Irit Hadas-Halpern · Pethachia Reissman
Amicur Farkas

The use of laparoscopy in intersex patients

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Abstract The management of intersex patients is a challenge. Although in the majority of patients the diagnosis may be made on the basis of cytogenetic and biochemical tests, there is a selective group of patients with difficulties in the establishment of final diagnosis and gender assignment. Since laparoscopy has been used in the management of impalpable gonads in the normal male population, it may be an alternative method for the diagnosis and surgical management of intersex patients. Thus we have evaluated our experience with laparoscopy in intersex population. Over the last 10 years (1995–2005) more than 80 intersex patients underwent surgical correction at our department. Out of those, 14 patients with a median age of 3 years (range 2–18 years) underwent laparoscopic surgery. Laparoscopic gonadectomy with subsequent estrogen replacement was performed following gonadal biopsy in five patients with androgen insensitivity syndrome (AIS). In three patients with mixed gonadal dysgenesis (MGD) gonadal biopsy was performed. In two of those the initial diagnosis was changed to true hermaphroditism, and they underwent removal of ovotestis from one side and orchidopexy of the normal testis on the other. In one patient with MGD, timed gonadectomy following laparoscopic biopsy was performed due to malignant potential of the streak gonads. In two patients with persistent müllerian duct syndrome (PMDS), laparoscopic orchidopexy was performed following gonadal biopsy. Three patients with total gonadal dysgenesis (TGD) underwent laparoscopic gonadectomy and one with true hermaphroditism underwent laparoscopic biopsy followed by bilateral inguinal orchiectomy with preservation of the ovarian tissue. Our data show that the laparoscopic gonadal biopsy remains the only way to obtain morphologic gonadal structure and to establish a final diagnosis in doubtful cases. Magnification and easy access to the pelvic cavity allow removal of gonads or ductal structures with the advantages of minimally invasive procedure.

Keywords Laparoscopy · Intersex · Sex assignment

B. Chertin (✉) · D. Koulikov · A. Farkas
Department of Urology, Shaare Zedek Medical Centre,
P.O. Box 3235, 91031, Jerusalem, Israel
E-mail: bchertin@yahoo.com
Tel.: +972-2-6555560
Fax: +972-2-6555160

J. Alberton · P. Reissman
Department of Surgery, Shaare Zedek Medical Centre,
Jerusalem, Israel

I. Hadas-Halpern
Department of Diagnostic Radiology,
Shaare Zedek Medical Centre, Jerusalem, Israel

B. Chertin (✉) · D. Koulikov · J. Alberton · I. Hadas-Halpern
P. Reissman · A. Farkas
Faculty for the Health Sciences, Ben-Gurion University
of the Negev, Jerusalem, Israel

Introduction

Management of intersex patients remains a challenging problem for the clinician [1]. In order to establish a correct diagnosis some of these patients require gonadal biopsy in spite of the currently available genetic and biochemical evaluation. Furthermore in patients with impalpable gonads a precise localization of the gonads should be determined in order to proceed with orchidopexy or their removal when indicated [2]. The laparoscopic biopsy has an important impact not only on the establishment of the final diagnosis but also on the decision of the appropriate rearing of a baby with ambiguous genitalia. Female infants with congenital adrenal hyperplasia (CAH) and even severe virilization almost always have XX karyotype and should be raised as girls. Also, male infants with male pseudohermaphroditism (MPH) due to 5-a reductase deficiency, 17-β hydroxysteroid dehydrogenase type 3 deficiency and 17-ketoreductase deficiency have XY karyotype and should be raised as males regardless of the severity of hypospadias and penile size. However, in patients with complete androgen insensitivity, gonadal dysgenesis and

XY CAH, the decision of appropriate rearing of a newborn baby should be based on the morphological structure of the gonads on biopsy.

Historically this type of surgery was done through laparotomy. Laparoscopy is a minimally invasive procedure, associated with low morbidity, shorter postoperative recovery period and better cosmetic appearance of the cutaneous scar and enables a better and magnified visualization of the pelvic organs. In the recent decades laparoscopy has been employed for intersex patients [3]. However, the information in the literature is sporadic. We aimed to evaluate our experience with laparoscopy in the management of these patients.

Patients and methods

Over the last 10 years (1995–2005) more that 80 patients with different intersex states underwent surgical correction at out department. Of those, 14 patients with a median age of 3 years (range 2–18 years) underwent laparoscopic surgery. The clinical data on these patients are presented in Table 1. Four patients with androgen insensitivity syndrome (AIS) presented with primary amenorrhea at 16–17 years of age. One patient with female phenotypic appearance underwent herniotomy at 2 months of age that revealed gonad in hernia sac, which turned to be a testis. Subsequent gonadal biopsy demonstrated testicular tissue. Chromosomal analyses and hormonal tests confirmed diagnosis of AIS in all patients.

In two patients the diagnosis of persistent müllerian duct syndrome (PMDS) was made following inguinal herniorrhaphy when müllerian tissue was found in the hernia sac. They had 46 XY karyotype and were raised as a male. Chromosomal analyses revealed mutation on the short arm of chromosome 19 in both children.

Three patients with mixed gonadal dysgenesis (MGD) presented to our clinics for repair of penoscrotal hypospadias at the age of 7 months two patients and the remaining patient at the age of 8 months. One had karyotype 20% XO, 80% XYq (deletion of long arm), the second had 45 xo/48 xxyy mosaicism, and the third patient had 45 XO/46 XY (80%/20%) mosaicism. The patients were assigned as males following parental request and consultation between endocrinologist, psychologist and approval.

In two patients with total gonadal dysgenesis (TGD) the diagnosis was based on the presence of two dysgenetic testes. One of them was born with ambiguous genitalia. Chromosomal analyses revealed 46 XY karyotype. The child had a good size vagina, bilateral fallopian tubes and uterus, and therefore she was raised as a girl. The other one had phenotypically female external genitalia and was raised as a female. Due to electrolyte abnormality diagnosis of lipoid CAH was suspected and routine chromosomal analyses revealed 46 XY karyotype. One patient, who was raised as a female, presented at the age of 14 with primary amenorrhea. She had 46 XY karyotype and suspected gonads were identified in the abdominal cavity on ultrasound.

A child with the working diagnosis of true hermaphroditism presented at birth with ambiguous genitalia and clitoromegalia. She had a 46 XX karyotype and no gonads were identified on both abdominal ultrasound and MRI.

Surgical technique

Under general anesthesia, the child's external genitalia were carefully inspected with palpation of the inguinal area. If no palpable gonads were recognized laparoscopy was started.

In case of a child older than 3 years, Veress needle is introduced into the peritoneal cavity and pneumoperitoneum is obtained with a pressure of 12 mmHg. Through an umbilical incision, 5 mm trocar is then introduced. In those patients who had previous abdominal surgery or who were less than 3 years, open Hasson technique is utilized. In patients younger than the age of 3 the upper limit of gas pressure was 10 mmHg. Five or ten millimeter 30° telescope is used. The location of gonads and their vessels, location of müllerian and wolffian derivates and the presence of a patent processus vaginalis were recognized. Subsequent surgery was planned according to the laparoscopic findings. One or two additional 5 mm trocars are inserted in the iliac regions when needed.

Results

Laparoscopic gonadectomy with subsequent estrogen replacement was performed following gonadal biopsy in five patients with AIS. Patients with PMDS required laparoscopic orchidopexy; one of them underwent two-staged Fowler–Stephens procedure bilaterally. Postoperative follow-up revealed that both testicles were normal size and good looking on duplex ultrasound examination. In one patient hysterectomy and bilateral salpingoophorectomy was performed. In the second patient rudimentary uterus was left in place.

Children with TGD underwent laparoscopic gonadectomy because of malignant potential of the dysgenetic gonads.

In one patient with MGD, diagnostic laparoscopy showed rudimentary uterus, right gonad with the fallopian tube in the abdomen and left gonadal vessels and vas joining together at the internal inguinal ring with a normal testis in the inguinal channel. Right gonadal biopsies revealed streak gonad and therefore gonadectomy was performed with subsequent left orchidopexy. The rudimentary uterus was left in place.

In two patients the initial diagnosis of MGD diagnostic laparoscopy with gonadal biopsies has changed our diagnosis to true hermaphroditism. One child had right abdominal and left scrotal gonads; laparoscopic

Table 1 Patients characteristics

Pt no	Age of Dx	Gender	Initial diagnosis/ karyotype	Gonads/place		Müllerian derivates	Laparoscopic management	Final diagnosis
				Rt	Lt			
1	16 years	Female	AIS 46 XY	Test/abd	Test/abd	–	Gonadectomy	AIS 46 XY
2	17 years	Female	AIS 46 XY	Test/abd	Test/abd	–	Gonadectomy	AIS 46 XY
3	17 years	Female	AIS 46 XY	Test/abd	Test/abd	–	Gonadectomy	AIS 46 XY
4	16 years	Female	AIS 46 XY	Test/abd	Test/abd	–	Gonadectomy	AIS 46 XY
5	2 months	Female	AIS 46 XY	Test/abd	Test/abd	–	Gonadectomy	AIS 46 XY
6	2 months	Male	PMDS 46 XY	Test/abd	Test/abd	Uterus, bil. fallopian tubes	Gonadal bx, orchidopexy	PMDS 46 XY
7	18 years	Male	PMDS 46 XY	Test/abd	Test/abd	Uterus, bil. fallopian tubes	Gonadal bx, orchidopexy	PMDS 46 XY
8	At birth	Female	TGD 46 XY	Dysgenetic testis/ abd	Dysgenetic testis/ abd	Uterus, bil. fallopian tubes	Gonadectomy at 3 years	TGD 46 XY
9	At birth	Female	TGD, lipoid CAH 46 XY	Dysgenetic testis/abd	Dysgenetic testis/abd	Bil. fallopian tubes	Gonadectomy at 26 months	TGD, Lipoid CAH 46 XY
10	14 years	Female	TGD/46 XY	Dysgenetic testis/abd	Dysgenetic testis/abd	–	Gonadectomy at 15 years	TGD/46 XY
11	At birth	Male	Mixed gonadal dysgenesis 45 XO/46 XY (80% /20%)	Streak gonad/abd	Test/inguinal channel	Uterus, rt. fallopian tube	Gonadectomy/orchidopexy, hysterectomy	Mixed gonadal dysgenesis
12	7 months	Male	Mixed gonadal dysgenesis 45 XO/XYq (20%/80%)	Ovotestis /abd	Test/inguinal channel	Uterus, rt. fallopian tube	Gonadectomy/orchidopexy,	True hermaphroditism
13	8 months	Male	Mixed gonadal dysgenesis 45 XO/48 XXYY	Test/abd	Ovotestis/abd	Uterus, bil. fallopian tubes	Awaiting gonadectomy/ orchidopexy,	True hermaphroditism
14	At birth	Female	True hermaphroditism 46 XX	Labia majora	Inguinal channel	–	Bil. orchiectomy	True hermaphroditism

biopsy of right gonad revealed tissue of ovotestis and left gonadal biopsy showed testicular tissue. Laparoscopic removal of ovotestis was performed. The second patient had bilateral intra-abdominal gonads. Laparoscopic biopsies showed ovotestis on the left side and testis on the right side (Fig. 1). He is awaiting a second laparoscopic procedure for removal of the ovarian tissue and right orchidopexy. In the patient with true hermaphroditism, laparoscopy demonstrated gonadal vessels on both sides entering internal rings. No vas or müllerian duct structures were found. Bilateral inguinal exploration with biopsy revealed both separate testis and ovary and fallopian tubes from each side. Due to her karyotype and gender assignment by her parents, bilateral orchiectomy was performed and müllerian duct structures were placed inside the abdominal cavity.

Discussion

Recently laparoscopy has gained wide acceptance as a method for surgical treatment of various pathological entities in pediatric urology. Although some urologists have employed laparoscopy in patients with intersex conditions, the related reports are relatively few.

Careful evaluation and correct diagnosis of the primary disease are crucial in intersex patients. They prevent therapeutic misconduct, particularly regarding sex assignment. Although in the majority of patients the diagnosis is made on the basis of cytogenetic and biochemical tests, there is a group of patients for whom gonadal biopsy is required in order to establish a correct diagnosis.

According to a classification system of abnormal sexual differentiation, utilized by Grumbach and Conte [4], several groups of patients require laparoscopic intervention for their management.

The first group includes patients with syndromes of gonadal dysgenesis. This group contains patients with Turner's syndrome, patients with MGD with the presence of Y chromosomal material and 46 XY patients with complete gonadal dysgenesis. All of them require removal of the streak gonads because of their malignant potential [5]. Patients with uncertain diagnosis and gender assignment require gonadal biopsies. Patients with male gender assignment and well-differentiated testes need orchidopexy.

The second group includes female pseudohermaphroditism. In most of these patients diagnosis is best established using laboratory test and imaging studies and there is no need for laparoscopic management.

The third group of patients is with MPH. Previously we reported and described the subgroup of these patients which required masculinizing genitoplasty [6, 7]; therefore they are not included in this article. Most patients in this group need laparoscopic orchidopexy for their intra-abdominal testes. Patients with disorders of androgen-dependent target tissue, Leydig cell agenesis and some patients who were raised as females need timed gonad-

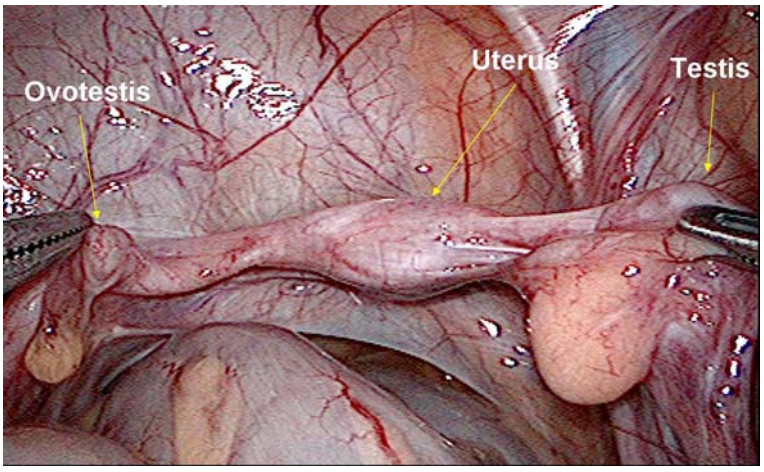

Fig. 1 The child with primary diagnosis of mixed gonadal dysgenesis. Ovotestis on one side and normal testis on the other were found and the diagnosis was changed to true hermaphroditism

ectomy. Children with PMDS usually require orchidopexy. Some authors recommend removal of the rudimentary müllerian structures [8], but this approach raises the risk of injury to the vasa deferentia and gonadal vessels with testicular atrophy or subsequent infertility. Furthermore, malignancy of the retained müllerian structures has not been reported and so we do not perform routine resection of these müllerian structures.

Magnification and easy access to the pelvic cavity during laparoscopy allow identification of the gonads and müllerian structures. Our data support this.

In all patients we have easily visualized all internal genitalia utilizing umbilical 5 mm port only. In cases where surgical manipulation is required additional access with 5 mm trocar is needed. Furthermore, 3 mm instruments may be easily applied in those patients for whom only diagnostic procedure is scheduled. In the majority of the cases, gonadectomy was performed utilizing Harmonic knife (Ethicon Endo Surgery, Jonson & Jonson) without surgical clips. We have had no complications during our procedures. All children were discharged on the day of surgery or the following day. The most valuable use of laparoscopy is in patients with true hermaphroditism [9]. Although the vast majority of these patients have 46 XX karyotype, there were some cases with 46 XY/XO chromosomal mosaicism. Laparoscopic gonadal biopsy remains the only way to obtain morphologic gonadal structure and to proceed with the removal of streak gonads or ovotestis (when impossible to divide testicular tissue from ovary tissue) with simultaneous laparoscopic orchidopexy in those patients who were assigned as males. In our series in two patients who have been assigned as males prior to the referral to our clinic with the diagnosis of MGD, laparoscopic biopsy revealed testis on the one side and ovotestis on the other. Therefore the diagnosis has been changed to true hermaphroditism.

As we mentioned before there is no agreement regarding the removal of the rudimentary müllerian structures. Two patients with rudimentary müllerian duct structures are followed conservatively. So far, we do not have enough data regarding spontaneous involution of müllerian structures or their malignant transformation. Recently an intriguing case of malignant transformation of the remnant female genitalia in a boy with PMDS was reported [10]. The authors recommend considering surgical removal of the female internal genitalia in children with PMDS who were raised as males. However, further studies with longer follow-up and large patients' population will decide the feasibility of this approach.

Our data show that the laparoscopic gonadal biopsy remains the only way to obtain morphologic gonadal structure and to establish a final diagnosis in doubtful cases. Magnification and easy access to the pelvic cavity allow removal of gonads or ductal structures with the advantages of minimally invasive procedure.

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