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Original Article

Elastosonographic evaluation of the post-operative morpho-volumetric recovery of the gonad in the cryptorchid patient

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Abstract: Background: Cryptorchidism is associated with alteration of fertility potential. The aim of this study is to evaluate mid/long-term morphology and volume of the operated testis for undescended testes by using elastosonography. Materials and methods: The medical records of consecutive patients who had received orchiopexy at the Authors' Institution between January 2014 and January 2017 were retrospectively considered. The patients enrolled in the study were divided into different groups depending on their age at the time of the procedure and on the time elapsed from it. The radiological and surgical examinations examined position, volume and trophism of both testes. Results: During the study period 270 patients received surgery; only 34 patients complied with the inclusion criteria: 19 with right orchiopexy and 15 with left orchiopexy ($P > 0.05$) ($P = 0.57$). The mean testicular volume of the operated testis was 0.59 ± 0.32 ml, while the mean testicular volume of non-operated testis was 0.88 ± 0.34 ml ($P < 0.05$). The elastosonographic comparison between operated and non-operated testis showed that the operated testis had a higher elastosonographic result (grade 2-3) ($P < 0.05$). Higher grades at elastosonography corresponded to smaller testicular volume. Conclusion: This study demonstrates that the patient's age at surgery is correlated with significative differences in terms of volume and elasticity (testicular quality). The study also shows that there is not a progressive improvement of elasticity at follow-up.

Keywords: Criptorchidism, recovery, elastosonography, treatment

Introduction

Cryptorchidism at birth has a prevalence of about 9% and it requires a timely suitable treatment for its particularly negative sequelae which may involve: increased risk of infertility and higher incidence of testicular neoplasia. Cryptorchidism is reported, in fact, in 2-9% of infertile adult patients and 2-10% of those with testicular cancer [1-3].

Prospective studies report a prevalence of this disease in newborn babies between 1.6 and 9% and show that in the last 20 years there has been an increasing trend in the disease, from 2.1 to 8.4%. It is well-known, however, that the incidence of the disease is lower in the months following birth (1% at 1 year of age) thanks to the spontaneous descent of the testis.

The most significant variables predictive of cryptorchidism are the following: low birth weight (< 2500 g), gestational age (SGA) and prematurity (< 37 weeks). According to *Berkowitz et al* a low birth weight is a risk factor independent of the gestational age of the newborn. *Berkowitz* also found that at 1 year of age prematurity is a two-fold risk factor for the testicular retention regardless of the patient's weight [4]. The literature shows that 20% of undescended testes are defined as 'not palpable'. Of this figure, 50% is represented by the gonads located at intra-abdominal, inguinal and ectopic level as well as at the internal inguinal orifice, 20% is represented by all the cases of failed testicular development (agenesis), and the remaining 30% includes all cases of testicular atrophy (anorchia). If from a strictly surgical

point of view a successful outcome is the presence of the operated gonad within the scrotum time after surgery, little is reported in the literature on the real long-term quality of the gonad. For this reason, the aim of this study is to assess the morphovolumetric quality of the operated gonads at medium and long term using bilateral testicular elastosonography to identify possible alterations that may affect the fertility potential of the patients.

Materials and methods

The medical charts of patients aged between 8 months and 13 years at surgery treated for cryptorchidism at the Author's Unit between January 2014 and September 2017 were evaluated. After approval from the IRB (Institutional Review Board) of the Pediatric Adolescent Fertility Lab research group of the Department of Surgical, Odontostomatological and Mother-and-Child Sciences, devoted to the preservation of fertility in pediatric adolescents, the patients were invited by a phone call to a clinical, ultrasound and elastosonographic post-op checkup. The study patients were divided into different groups depending on their age at the time of surgery and on the timespan elapsed from it. To enroll the patients in the study, the following inclusion and exclusion criteria were created. All patients receiving unilateral orchidopexy were considered to avoid bias during the volumetric comparison of the gonads at follow-up; only patients with true cryptorchidism were considered, excluding patients with surgery for an oscillating testis (indication to surgery only in the presence of a volumetric reduction of the gonad); patients without metabolic, genetic, or chronic inflammatory conditions were considered; only patients receiving a single surgical intervention on the genital organs and on other systems (e.g. urinary or gastrointestinal systems) and without other associated malformations were considered. Exclusion criteria included the following: patients with intra-abdominal cryptorchid testis; patients treated with trans-scrotal orchidopexy, a nonstandardized surgical technique which has not obtained a consensus among surgeons; patients treated with the laparoscopic technique to mobilize the sperm vessels; patients to whom the surgical surgeon also fixed the non-cryptorchid (contralateral) testis in the scrotum at surgery; the last exclusion criterion was considered essential for the unbiased evaluation of the testicular volume at follow-up.

Trophism of the gonad, presence of patency of the peritoneal-vaginal duct, anatomical position (thus excluding ectopias) and position within the inguinal canal (upper, middle and inferior third) were intrasurgically evaluated.

Clinical and instrumental evaluation

At follow-up neither the radiologist nor the pediatric surgeon was aware of the patient's clinical condition. The surgical-radiological examination assessed position, volume and consistency of both testes.

The radiologist calculated the testicular diameters of both gonads at ultrasounds, recording their length, width and height. The testicular volumes were calculated using the Lambert formula V = L * H * W * 0.71, and the elasticity of the testes was elastosonographically determined. In this study real-time elastography was used to determine the elasticity index of both healthy and treated testes [5]. The elastosonographic measures were expressed using a three-digit semi-quantitative scale: GRADE 1: the most elastic tissue (green and red); GRADE 2: medium elastic tissue (displaying mixed green and blue color); GRADE 3: the least elastic tissue (mostly blue). The elastosonographic examination was performed with a 12.5 MHz Philips U 22 linear probe supplied with an elastographic software (ElaXto, Esoate). The study group radiologist (an expert clinician with at least 5 years of experience with this technique) performed all the study elastosonographic scans to reduce the bias involved in this operator-dependent imaging technique.

The statistical analysis was performed using different statistical tests: Student's T test for paired and non-paired data, chi-square test with SPSS Chicago IL USA, 16.0 program for Windows. A p value < 0.05 was considered as statistically significant.

Results

During the study period, 270 patients aged between 8 months and 13 years received surgery at the Authors' Institution for undescended testis. The study excluded the following

Table 1. Ultrasound and elastosonographic evaluation

Nr	Age at surgery	Untreated		Treated		Nr	Age at surgery	Untreated		Treated	
		V (ml)	E	V (ml)	E			V (ml)	E	V (ml)	E
1	23 m	0.84	1	0.54	1	18	2 yrs	0.78	2	0.54	1
2	22 m	1.33	1	0.71	1	19	13 m	0.89	2	0.45	3
3	11 m	0.91	1	0.65	2	20	3 yrs	0.72	3	0.89	2
4	4 yrs	0.68	2	0.42	3	21	5 yrs	1.00	1	0.80	1
5	10 m	0.71	1	0.27	2	22	18 m	0.80	1	0.15	2
6	4 yrs	1.33	2	0.81	1	23	4 yrs	1.11	1	1.16	1
7	19 m	0.65	1	0.58	1	24	18 m	0.43	1	0.29	1
8	4 yrs	0.56	1	0.64	3	25	10 m	1.06	2	0.52	1
9	4 yrs	1.48	1	1.75	1	26	4 yrs	0.95	2	0.83	3
10	4 yrs	0.66	1	0.64	1	27	2 yrs	0.35	1	0.19	2
11	18 m	0.82	1	0.66	2	28	14 m	1.15	1	0.48	1
12	10 m	2.24	1	1.26	1	29	2 yrs	0.82	1	0.28	2
13	2 yrs	0.70	1	0.51	1	30	15 mesi	0.77	1	0.61	2
14	3 yrs	0.85	2	0.46	2	31	2 yrs	0.85	1	0.30	1
15	18 m	1.14	1	0.66	2	32	14 m	0.72	1	0.26	2
16	11 m	0.82	2	0.87	1	33	8 m	0.70	1	0.33	1
17	10 m	0.50	2	0.39	2	34	16 m	0.60	1	0.31	2

Legend: m: months; yrs: years; V: volume*; E: elastosonographic evaluation grade 1 to 3.*

patients: 16 with bilateral cryptorchidism; 13 with intrabdominal testis at surgery; 12 patients because during the same surgery they received a laparoscopic procedure to find the position of the gonad (non-palpable testis at anesthesia); 26 patients receiving surgery with the trans-scrotal technique; 3 patients for previous inguinal surgery; 9 for the concomitant trans-scrotal orchiopexy of the contralateral gonad; 9 patients for orchiectomy following marked hypotrophy and hypoplasia; 4 patients for patency of the peritoneal-vaginal duct (presence of intra-surgical ipsilateral hydrocele).

Other 90 patients were excluded for concomitant congenital malformations such as renal ectopia, calico-pyelic ectasia, trisomies, infantile cerebral palsy, neural tube defects, hip dysplasia, hypospadias, testicular traumatism at anamnesis and contralateral oscillating testis. Ninety-four patients from the medical records met the study inclusion criteria. Of these patients, 58 received right orchidopexy and 36 left orchidopexy ($P > 0.05$, $P = 0.06$).

Fifty-seven patients were contacted on the phone by the study clinicians and 34 subjects (19 orchidopexes and 15 left orchidopexy) participated ($P > 0.05$) ($P = 0.57$).

The study patients were divided according to age at surgery and post-operative follow-up: 8 patients operated in 2014, 9 patients operated in 2015, 8 patients operated in 2016, 9 patients operated in 2017.

Sixteen patients underwent surgery within 18 months of age, while the remaining 18 patients were older than 18 months at surgery ($P > 0.05$). The gonads of all the subjects that received a follow-up visit before the radiological scan were normally located within the scrotum.

Ultrasound and elastosonographic evaluation

The two main study groups, surgically treated and untreated testis regardless of the patient's age, showed comparable data and it was therefore possible to point out that the mean volume of the treated testis was statistically smaller than the volume of the untreated testis: mean treated testicular volume 0.59 ± 0.32 ml, mean untreated testicular volume 0.88 ± 0.34 ml ($P < 0.05$) (**Table 1**).

No structural changes (US) on the parenchyma of either gonad (i.e. microcalcifications or parenchymal gaps) were reported by any of the patients. There was not statistical difference between the testicular volume and the affected side ($P > 0.05$), this indicating that cryptorchidism itself does not inherently influence the development of the gonad.

A comparison of the values obtained at elastosonography for the treated and untreated testis showed that the treated testis has a higher elastosographic value (grade 2 and 3) than the untreated gonad ($P < 0.05$) (**Table 1**). Also, it was possible to point out that there is not a statistically significant difference in terms of testicular volume between grade 1 treated testes and their healthy contralateral counterpart ($P > 0.05$). The same was not observed in grades 2/3 treated testes with their healthy counterpart. These findings indicate that the post-op growth of the gonad is independent from its

correct position in the scrotum; they also show that the less the gonad is damaged at surgery the more it shows a correct development at medium-long term. In the group of healthy untreated gonads, 24 gonads had an elastosonographic degree of 1, 8 gonads had grade 2 and 0 grade 3. The statistical analysis excluded two elastosonographic results from untreated gonads: one for non-compliance during the procedure and the other for hydrocele; both cases were considered as bias related to the elastosonographic scan (grade 3). The exclusion from the evaluation in case of hydrocele shows how sensitive and specific the elastosonographic procedure is. A comparison of the testicular volumes of untreated testes that were classified as degree 1 and 2 at elastosonography showed no statistically significant differences ($P > 0.05$).

The elastosonographic degree 1 was statistically more frequent in the untreated testis group, and this could demonstrate how the development of the gonads is not influenced by the contralateral gonad ($P < 0.05$). Regardless of the untreated side (right or left) there is no significant elastosonographic difference ($P > 0.05$).

In the group of surgically treated gonads, 17 had grade 1, 12 had grade 2 and 4 gonads had grade 3. In the group of treated testes, those with elastosonographic grade 2 showed a testicular volume smaller than testes with degree 1 ($P < 0.05$). This demonstrates how the elastosonographic evaluation can identify the actual parenchymal alteration, independently from the volume of the healthy contralateral. Two further aspects emerged from the analysis of the data: from a volumetric and elastosonographic point of view, there are no statistically significant differences at 2 and 4 years from surgery. The patient's age at surgery showed a statistically significant difference between the volumetric and the elastosonographic values in the patients treated before and after 3 years of age ($P < 0.05$).

This elastosonographic, although not volumetric, difference appears for those children surgically treated before and after 2 years of age. Therefore, age at surgery proved that there is no statistically significant difference in the elastosonographic values or in the testicular volume of patients treated before and after 2 years of age for either gonad. The differences in the group of treated gonads are significant when the data from children treated before and after 3 years of age are compared ($P < 0.05$).

Despite the guidelines suggesting a surgical procedure within 18 months from birth in order to safeguard the patient's fertility potential, this finding indicates that there is not a qualitative difference in the gonads up to a cut-off of 3 years of age at surgery.

Discussion

The main goal of orchidopexy is the preservation of the fertility potential. This procedure aims at avoiding any negative effect that the abnormal testicular position has on the development of the germ cells. The success rate of this surgery, defined as a scrotal position of the gonad and the lack of atrophy (long-term evaluation), depends on three main variables: palpable testis, surgical procedure and patient's age at surgery. From a strictly clinical point of view, the patient's fertility potential cannot be identified early in the pediatric age, with a trophic gonad in the scrotum suggesting a positive prognostic development. Therefore, it is essential to find radiological methods that can support the clinical follow-up for these patients. Thanks to its flexible use in the treatment of a variety of conditions and diseases, elastosonography has gained an increasingly crucial role in the clinical practice. The results of this study highlight an interesting finding, which is the base of this research: the mean testicular volume of treated testes is significantly smaller than the measures recorded for their healthy contralateral testes. This is in line with most of the relevant literature; however, despite a difference in volume between a treated and an untreated gonad, several studies confirm that the volumetric parameter and the germ cell count of the operated gonad (testicular biopsy performed during surgery) are not reliable enough in predicting a patient's fertility potential.

The literature reports a comparison between Ultrasound (US) and Elastosonography (EUS) in two recent works, neither of which accounted for a significant difference in the volumes of healthy and treated gonads, probably because the study populations were small and the patients' age range wide (1-18 years). In the study by *Çildag*, US and EUS assessments were performed only before surgery on gonads locat-

ed in the inguinal canal. This does not indicate the real parenchymal quality, which is also affected by subcutaneous fat and, anatomically, by the testicular mobility within the inguinal canal [6-8].

If it is true that in adult patients the testicular volume reflects the parenchymal quality, this cannot be confirmed for patients with cryptorchidism based on testicular volume at ultrasounds alone. The first elastosonographic evaluation on the criptorchid testis was performed by *Ağladioğlu et al* in 2015, who were the first to perform an elastosonographic assessment on the criptorchid testis with the same real-time method used in the present study [7]. This study showed that real-time elastosonography has a suitable accuracy to successfully assess the parenchymal quality. Both studies demonstrated a statistically significant difference in the elasticity of healthy and treated gonads using a different EUS method called the shear-wave technique. According to the study by *Hattapoğlu et al* published in 2016, there is a strong negative linear correlation between the volume and the EUS shear-wave alteration in the cryptorchid testis postoperatively. This correlation could not be detected in healthy untreated testes [8]. A comparison of the results from previous studies with the results obtained from our study showed some differences and highlighted some new significant findings. Grade 2 treated testes had a significantly smaller volume than grade 1 testes; no evidence of a significant qualitative difference between the gonads up to the age of 3 years at surgery; no volumetric and elastosonographic difference at 2 and 4 years from surgery; the healthy testis is not affected by the cryptorchid testis in terms of volume and elastosonographic results; no significant statistical difference in the prevalence of affected side, with hydrocele being a possible bias correlated with the EUS examination.

The study results also show another important point: the elastosonographic difference between the gonads stays in the long term, regardless of the patient's age at surgery. This means that there seems to be no long-term post-op recovery. If a testicle shows an elastosonographic degree at 2 years after surgery, it will probably remain so in the long term.

This study also showed that the gonads with an EUS grade 2 and those with an EUS grade 1 had a statistically significant difference. This is an important finding showing that the elastosonographic degree reflects more accurately the quality of the testis and the real parenchymal alteration independently of its volume. In fact, there is no significant correlation between volumetric difference and elastosonographic degree in healthy testes.

This study showed that the real advantage emerges when patients are treated before 3 years of age. This finding agrees with the histopathological evaluation of a 2012 study by *Hadziselimovic*. In this paper the author described an intrasurgical testicular biopsy with subsequent postoperative collection of the seminal fluid. The results suggested that when orchidopexy is performed before 3 years of age, it has a positive effect on the quality of the seminal fluid [8-11]. Another study carried out on the semen time after surgery showed that the sperm count is higher and the motility is enhanced when orchidopexy was performed within 2 years from birth (75%), showing even better outcomes when the patients were treated within their first year of life (95% of the patients). However, the long-term qualitative and quantitative evaluation of the seminal fluid may involve a variety of biases, also correlated with the patients' lifestyles or other concomitant conditions.

Other studies, suggesting surgery before 2 years, rerported similar results focusing on germ cells and Leyding Cells alterations [9-17].

As for testicular growth over the years, a randomized study by *Kollin et al* evaluated children surgically treated at 9 months and 3 years. The results showed that children who were 9 months old had a partial recovery of testicular growth up to the age of 4 years; the same did not occur in children who were treated later. Unlike this latter study, the results reported in our study showed that there is no significant morpho-volumetric difference between the cryptorchid testes at 2 and 4 years from surgery. This is true also for the development of the untreated gonads [10-15].

The literature does not include studies regarding the correlation with the contralateral gonad. This could result in non-comparable data with this study, although its results showed that there was not a statistically significant difference in the volume of the testes, regardless of

their elastosonographic degree. This could mean that the healthy gonad is not affected by the contralateral cryptorchidism. Our series included a patient with a healthy testis in the scrotum with hydrocele. A recent study by *Kocaoglu et al* carried out in 2018 found a statistically significant difference in the elastosonographic values of the gonads with and without hydrocele [16]. As for our excluded patient, It is our opinion that hydrocele, as well as inguinal fat, can modify its elastosonographic degree, with consequent purely technical errors. This legitimates the opinion that these technical errors do not threaten the validity and sensitivity of elastosonography, whose clinical value lies in the hands of the skilled operator.

Conclusions

Preservation of the fertility potential of patients with cryptorchidism is the main outcome. At present there are not clinical elements that can predict fertility, although the post-op presence of a trophic testicle in the scrotum is a critical factor. If from a morphological point of view Ultrasounds can reveal the presence of a homogeneous testicular parenchyma without discontinuities or alterations such as microcalcifications, elastosography has proved to be more sensitive and specific in the morpho-volumetric assessment of the testis.

Disclosure of conflict of interest

None.

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