Journal of Pediatric Surgery 55 (2020) 1965–1968

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Changing trends in the referral and timing of treatment for congenital cryptorchidism: A single-center experience from Bosnia and Herzegovina

Zlatan Zvizdic [a], Belma Islamovic [b], Emir Milisic [a], Asmir Jonuzi [a], Semir Vranic [c,*]

[a] Clinic of Pediatric Surgery, University Clinical Center Sarajevo, Sarajevo, Bosnia and Herzegovina
[b] Public Medical Center Visoko, Visoko, Bosnia and Herzegovina
[c] College of Medicine, QU Health, Qatar University, Doha, Qatar

ARTICLE INFO

Article history:
Received 21 July 2019
Received in revised form 12 August 2019
Accepted 17 August 2019

Key words:
Cryptorchidism
Congenital
Orchidopexy
Timing of surgery
Guideline adherence

ABSTRACT

Background: Cryptorchidism is the most common male urogenital tract disorder identified at birth. Treatment delays of cryptorchidism may be associated with significant complications such as subfertility and testicular cancer. The currently recommended age for performing orchidopexy is between 6 and 12 months of age and no later than 18 months. The aim of this study was to investigate the trends in the pattern of referral and age of boys at the time of operative treatment of congenital cryptorchidism at the largest tertiary care center in Bosnia and Herzegovina.

Methods: The study included all boys who underwent orchidopexy for congenital cryptorchidism during two equivalents periods: 2008–2010 and 2015–2017. We assessed the referral age of patients, the age of patients at the time of orchidopexy, laterality of cryptorchidism, position of cryptorchidic testes palpated before surgery, the intraoperative position of cryptorchidic testis, a clinical position of the testis at follow up, and risk factors for late orchidopexy.

Results: In total, 324 patients with 386 testes underwent orchidopexy for congenital cryptorchidism during the study periods. Of these patients, 62 received a bilateral orchidopexy (19.1%). Total referral age of patients with congenital cryptorchidism was 23 months (range, 4–74.5 months). Total median age at surgery was 24 months (range, 6–74 months). One hundred and eleven patients (28.8%) underwent surgery at less than the age of 12 months, 136 (35.2%) at less than the age of 18 months, and 250 (64.8%) patients underwent surgery after the age of 18 months. The analysis of the observed two periods (2008–2010 and 2015–2017) showed a statistically significant decrease in the mean referral age and the mean age at surgery over the last 5 years (2015–2017) ($p = 0.007$ and $p = 0.003$, respectively).

Conclusions: Current guidelines for timely operative treatment for congenital cryptorchidism have not been fully implemented in Bosnia and Herzegovina but a gradual improvement is evident. The main factor contributing to delays in orchidopexy was delayed or neglected referral by referring physicians. Optimizing the time of orchidopexy will require an improved coordination at all levels of pediatric health care to diminish the long-term consequences of cryptorchidism.

Type of study: Retrospective.

Level of evidence: III.

Cryptorchidism or undescended testis (UDT) is the most common congenital anomaly of the male genitalia, affecting ~3% of full-term and up to 30% preterm neonates [1]. Congenital UDT has the potential of spontaneous descent during the first months of life but after the sixth month of life, approximately 1–2% of boys have cryptorchidism, which is an indication for surgical treatment [1].

It is well established that cryptorchidism causes impairment of germ cell maturation and subsequently leads to infertility that is also associated with a greater risk of development of germ cell tumors [2,3]. On the other hand, surgical repositioning of the testis during an optimal timeframe may optimize a fertile potential and protect against testicular cancer [2–5].

According to current evidence and knowledge of germ cell development, the recommended age for orchidopexy is between 6 and 12 months, and by 18 months at the latest [6–8]. However, most studies that investigated adherence to these guidelines have revealed that only

* Corresponding author at: College of Medicine, QU Health, Qatar University, 2713 Doha, Qatar. Tel.: +974 4403 7873.
E-mail addresses: semir.vranic@gmail.com svranic@qu.edu.qa (S. Vranic).

https://doi.org/10.1016/j.jpedsurg.2019.08.013
0022-3468/

a minority of boys undergo a repair of cryptorchidism before 18 months [9–17].

No study has explored the time of orchidopexy for congenital cryptorchidism in Bosnia and Herzegovina. Therefore, we decided to explore the time of orchidopexy for boys with congenital cryptorchidism at the largest tertiary care facility in Bosnia and Herzegovina. We also assessed the surgical outcome as well as factors that affect the delayed treatment of cryptorchidism.

1. Materials and methods

1.1. Study population and selection

This study was conducted at the Clinic Center of the University of Sarajevo, which represents the largest pediatric tertiary care center in Bosnia and Herzegovina and the only pediatric surgery institution in the Sarajevo Canton. The total population of Sarajevo Canton is estimated at 413,593 inhabitants (323 inhabitants/km^2). 15.3% of the Canton's population are youth up to 14 years of age, 70.7% are between 15 and 64 years of age, and some 14% are more than 65 years of age. We analyzed the demographic data of the patients subjected to orchidopexy in the period between 2008 and 2010 and 2015–2017 exploring the information system of our institution by searching the terms “congenital cryptorchidism” and/or “orchidopexy”.

1.2. Inclusion and exclusion criteria

The study included all patients who underwent orchidopexy for congenital uni/bilateral cryptorchidism. The patients who underwent orchidopexy for acquired cryptorchidism, retractile testis, ectopic testis or testicular torsion were excluded from the study.

1.3. Definition and study variables

The diagnosis of cryptorchidism was according to the International Classification of Diseases, Ninth Revision (ICD-9) code 752.51 and the International Classification of Diseases, Tenth Revision (ICD-10). Congenital cryptorchidism was defined as an undescended testis in which a scrotal location had never been documented since birth. Intraoperative testis position was classified as abdominal (testis proximal to the internal inguinal ring), high canalicular (testis near to the external inguinal ring) and low canalicular (testis near to the external inguinal ring).

Using the current guidelines consensus on the recommended treatment time for cryptorchidism surgery by 18 months at the latest [6–8], all patients were divided into four groups depending on their age in which they were operated: group A (˂12 months old), group B (13–-18 months), group C (19–24 months), and group D (˃24 months).

The success rate of operative treatment was defined as a scrotal position of the testis without atrophy. Associated genitourinary malformations were divided into minor and major anomalies. Minor anomalies included those that did not require surgical treatment (phimosis, hydrocele, and mild renal pelviectasis) while major anomalies were defined as those that require surgical treatment (hypospadias and ureterocele).

The registered variables included referral age of patients, age of patients at the time of orchidopexy, laterality of cryptorchidism (unilateral or bilateral), position of cryptorchidic testis palpated before surgery, intraoperative position of cryptorchidic testis, clinical position of the testis at follow up, and the occurrence of any intraoperative or postoperative complications.

The Institutional Review Board (IRB) of the Clinical Center University of Sarajevo approved the study (Number: 09-01-2-3929/18).

1.4. Statistics

Descriptive statistics were used to characterize the patient cohort. The association between timing of orchidopexy and referral age of patients, laterality of cryptorchidism (unilateral or bilateral), side of cryptorchidism (right or left), a position of cryptorchidic testis palpated before surgery and intraoperative position of cryptorchidic testis was evaluated using Chi-square analysis. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) IBM Version 25 (SPSS) (UNICOM Systems, Inc.). A p-value <0.05 was considered statistically significant.

2. Results

The clinical preoperative, intraoperative findings, operative details, and complications in boys who underwent orchidopexy in the 2008–2010 and 2015–2017 periods are summarized in Table 1.

During the studied 6-year period, 324 boys underwent orchidopexy (386 orchidopexies) for congenital cryptorchidism at our institution. The surgical procedures were performed by nine pediatric surgeons of which three (Z.Z., A.J. and E.M.) were involved in the present study.

Of these patients, 62 received a bilateral orchidopexy (19.1%). In the first observed period (2008–2010), 225 orchidopexies were performed and 161 orchidopexies were performed in the second observed period (2015–2017). During the studied period, all orchidopexies were performed in one stage. In the first period, 219 orchidopexies (97.3%) were performed using the dartos pouch technique and six orchidopexies were performed using a single-stage Fowler–Stephens procedure (2.7%). In the period between 2015 and 2017, the dartos pouch technique was performed in 152 cases (94.4%) and a single-stage Fowler–Stephens procedure was performed in nine cases (5.6%).

Of the 324 patients, 280 (86.4%) patients were evaluated by ultrasound prior to orchidopexy, most of which were performed at our institution (235/83.9%). These examinations aimed to explore the testicular volume prior and after its reposition. The remaining ultrasound examinations (45/16.1%) were performed at other institutions.

Follow-up of for all patients started 7 days after surgery and was carried out after a month, three months and at least one year after the performed orchidopexy.

Of 386 orchidopexies, nine (2.3%) failed and resulted in recurrent cryptorchidism. Of 225 orchidopexies in the first period, five (2.2%) and of 161 orchidopexies in the second period, four (2.5%) failed causing the recurrent cryptorchidism and required reoperation. Testicular atrophy occurred in 18 (4.7%) of testicular units, slightly higher in the first

Table 1
Clinical preoperative and intraoperative findings, operative details and complications in boys underwent orchidopexy between 2008 and 2010 and 2015–2017.

	2008–2010 (n = 225)	2015–2017 (n = 161)
Preoperative testicular position		
Low canalicular	54.2%	49.7%
High canalicular	30.2%	34.9%
Nonpalpable	15.6%	15.4%
Intraoperative testicular position		
Low canalicular	55.1%	50.9%
High canalicular	31.1%	38.5%
Abdominal	13.8%	10.6%
Laterality		
Right	47%	51%
Left	30.1%	34.8%
Bilateral	22.9%	14.2%
Inguinal hernia	31.2%	27.5%
Complications		
Recurrence	2.2%	2.5%
Atrophy	4.9%	4.3%
Other (wound infection or keloid scar formation)	1.8%	1.9%

observed period (11 or 4.9%) than in the second period (7 or 4.3%). Other complications included wound infection and keloid scar formation and affected only four patients (1.8%) in the first period and three patients (1.9%) in the second period (Table 1). In both periods, right-sided cryptorchidism was more frequent in comparison to left-sided or bilateral cryptorchidism [86 (47%) vs. 55 (30.1%) vs. 42 (22.9%) cases in the first period and 72 (51%) vs. 49 (34.8%) vs. 20 (14.2%) cases in the second observed period, respectively].

Associated congenital anomalies were seen in 58 boys (17.9%) and affected most frequently the genitourinary tract. The most common major genitourinary malformation was hypospadias and were present in 20 boys (6.2%). The clinical congenital inguinal hernia was present in 31.2% in the first observed period and 27.5% in the second observed period.

Further analysis revealed that the median referral (range) age throughout the two observed periods was 23 months (range, 3–-83 months) and the median (range) age at orchidopexy was 24 months (range, 6–84 months). By analyzing the age distribution of operated patients, a bimodal distribution was observed with peaks at 1 and 5 years.

There was a significant change in the mean age at referral and orchidopexy during the two periods (2008–2010 and 2015–2017). We observed a significant decrease in the mean age at referral and orchidopexy from 30 (range, 4–83 months) and 31 months (range, 6–-84 months), respectively, in the first period, to 19 months (range, 3–-68 months) and 20 months (range, 6–65.6 months) in the second period ($p = 0.007$ and 0.003, respectively).

Out of 386 orchidopexies, 111 (28.8%) patients underwent orchidopexy beyond the age of 12 months and 136 patients (35.2%) beyond the age of 18 months. Two hundred fifty operations (64.8%) underwent surgery after the age of 18 months. In contrast to the period of 2008–2010 when it was noted that 55 boys (24.45%) underwent surgery at less than the age of 12 months, 10 (4.45%) at less than the age of 18 months, and 20 boys (8.9%) at less than the age of 24 months, a statistically significant decrease in age at orchidopexy was observed in the period from 2015 to 2017 ($p < 0.001$). During that period, 56 patients (34.8%) underwent surgery at less than the age of 12 months, 15 (9.3%), at less than the age of 18 months, and 13 patients (8.1%) at less than the age of 24 months (Fig. 1). One hundred and forty patients (62.2%) underwent surgery after the age of 24 months in the first period and 77 patients (47.8%) in the second observed period.

3. Discussion

The results from our study indicate that the median age of orchidopexy in boys with cryptorchidism is gradually decreasing in the recent period but still, nearly two-thirds of boys in the largest area in Bosnia and Herzegovina underwent surgical treatment at age >1 year and more than half at age >2 years. It also revealed that the mean referral age and the mean age at surgery gradually decreased over the last few years.

There is clear evidence that early orchidopexy has a substantially beneficial effect on germ cell development [2,18,19]. During the last five decades, there has been a gradual decrease regarding the recommended age for orchidopexy, from preadolescence in the 1970s to about two years in the 1980s [20,21], and since 1990s to the first year of life [22,23]. Comparable modifications in European recommendations emerged somewhat later. The European Association of Urology has recommended orchidopexy before the second birthday in 2001 [24]. In 2007, the Nordic Consensus recommended orchidopexy to be performed in a period from 6 to 12 months [6]. This trend of decreasing the recommended age for performing the orchidopexy was caused by the knowledge of the influence of untimely-corrected cryptorchidism on fertility and consequently the increased risk of testicular malignancy [20–22,25]. However, it is well known that medical recommendations are difficult to implement in clinical practice [26,27]. There are still a gap between what the general public perceives as the ideal age for orchidopexy and what primary care providers believe is the optimal age (3 to 4 years), compared to the recommended age for orchidopexy among pediatric surgery subspecialists [28]. In a survey of pediatricians and general practitioners, Steckler et al. have noted that only 24% of pediatricians and general practitioners recommended surgery during the first year of life while 10–30% recommended orchidopexy between 3 and 10 years of age [29]. Furthermore, some general surgeons may be reluctant to perform surgery in very young patients in whom orchidopexy is technically demanding and potentially associated with higher failure rates than when orchidopexy is performed later [30]. An additional aggravating circumstance related to the general acceptance of the earlier operative treatment of cryptorchidism is the ambiguity about the possible anesthetic harm on the developing brain in children younger than one year [31].

Several recent studies have analyzed the implementation of these recommendations and most of them have found that the recommended

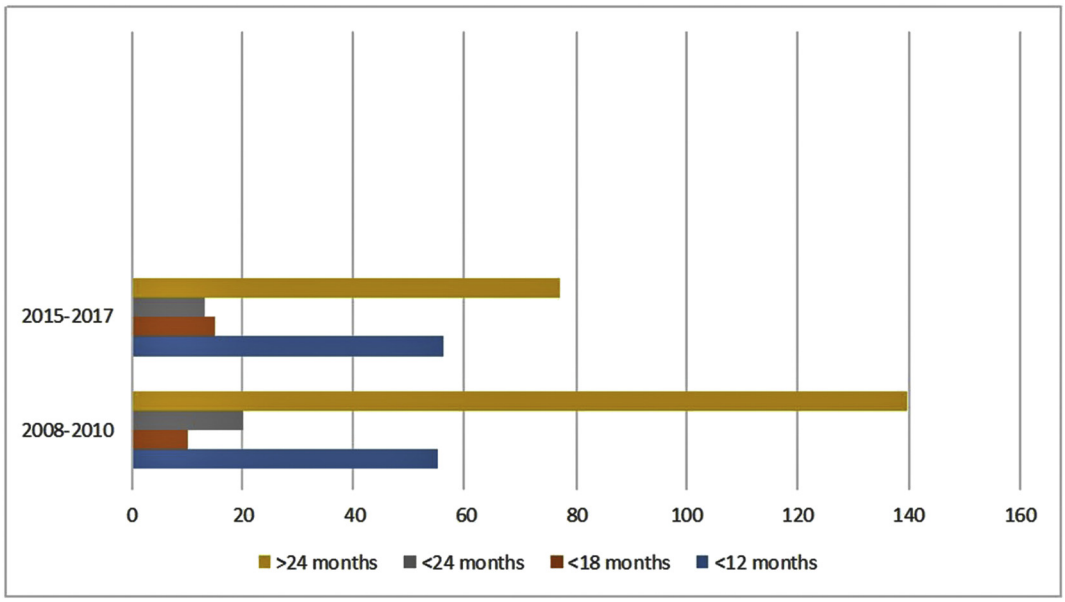

Fig. 1. Differences between ages at orchidopexy during two separate periods.

orchidopexy age has not been achieved [9–17,32,33]. A large database study that included more than 28,000 patients from 41 pediatric hospitals in the United States revealed that only 16% of children with cryptorchidism underwent orchidopexy before 1 year of age and 43% before 2 years [34]. Hrivatakis et al. in the recent study found that only 18.7% patients underwent orchidopexy in Germany before 1 year of age [16] while the UK study revealed that after the initial drop in the age for orchidopexy in 2000, no subsequent improvement was seen over the following decade [15]. Poor adherence to the guidelines on the timing of orchidopexy has also been reported in several national studies [9–15,17,27]. The main factors that contribute to a delayed orchidopexy included the unavailability of pediatric surgery services, rural environment, lower socioeconomic status, and insurance status [9,14]. In addition, a delay to late referral and long waiting time [10–17], significant variations among primary care providers regarding the age of orchidopexy for congenital cryptorchidism and unnecessary imaging workup [11] affect the time of orchidopexy.

Our study found the late referral as a major factor of late orchidopexy, which is understandable given that the median referral time of 23 months was far from the ideal age recommended for the referral. For orchidopexies to be performed within the recommended period of 6–12 months of age, the referral time of boys with cryptorchidism should be 3–6 months of age since the waiting lists at our center are ≤1 month. Causes of late referral were mainly owing to the poor education of referring physicians as well as owing to the inadequate distribution and implementation of the recommendations from higher levels of the health system in Bosnia and Herzegovina. As the decision for a referral is based only on the primary care physician's physical examination [35], it is not rare to result in insufficient differentiation of congenital undescended testes from retractile testes, with a consequently delayed referral for subspecialist evaluation. The main reasons for the substantial improvement in the mean referral age and time of surgery in the latter period were related to improved communication between different levels of the health care providers and dissemination of new attitudes through publications, policies, and local guidelines focused to referring physicians.

Contrary to some previous studies [9,34], pediatric surgery services, racial differences, and insurance status had no significant influence on the time of surgery.

Recurrence and testis atrophy were the most serious postoperative complications in both periods, which is consistent with the results from the previous studies that reported the recurrent rate of 1–2% and the testicular atrophy rate of 5–12% [36,37].

The limitations of our study were related to its retrospective nature, relatively small patients' population, restriction to a single pediatric surgical center in Bosnia and Herzegovina and the inability to calculate population-based rates. We did not have enough information about primary health-care physicians who conducted examinations of patients with various forms of undescended testis.

We confirm that only 1/3 of patients with congenital cryptorchidism underwent orchidopexy at less than the age of 12 months and ~50% at less than the age of 24 months. Despite the marked improvement, we aim to put additional efforts to educate primary care pediatricians and family doctors as well as boys' parents to achieve the optimal time for orchidopexy in Bosnia and Herzegovina.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

We thank Dr. Orhan Lepara, School of Medicine, University of Sarajevo for providing the statistical analysis for the study.

References

[1] Barthold JS, Gonzalez R. The epidemiology of congenital cryptorchidism, testicular ascent and orchiopexy. J Urol. 2003;170:2396–401.
[2] Virtanen HE, Toppari J. Cryptorchidism and fertility. Endocrinol Metab Clin North Am. 2015;44:751–60.
[3] Walsh TJ, Dall'Era MA, Croughan MS, et al. Prepubertal orchiopexy for cryptorchidism may be associated with lower risk of testicular cancer. J Urol. 2007;178:1440–6 [discussion 1446].
[4] Virtanen HE, Bjerknes R, Cortes D, et al. Cryptorchidism: classification, prevalence and long-term consequences. Acta Paediatr. 2007;96:611–6.
[5] Rey RA. Early orchiopexy to prevent germ cell loss during infancy in congenital cryptorchidism. J Clin Endocrinol Metab. 2012;97:4358–61.
[6] Ritzen EM, Bergh A, Bjerknes R, et al. Nordic consensus on treatment of undescended testes. Acta Paediatr. 2007;96:638–43.
[7] The BAPU Consensus statement on the management of undescended testes. British Association of Paediatric Urologists. British Association of Paediatric Urologists; 2011.
[8] Kolon TF, Herndon CD, Baker LA, et al. Evaluation and treatment of cryptorchidism: AUA guideline. J Urol. 2014;192:337–45.
[9] Boehme P, Geis B, Doerner J, et al. Shortcomings in the management of undescended testis: guideline intention vs reality and the underlying causes — insights from the biggest German cohort. BJU Int. 2018;122:644–53.
[10] Alhazmi H, Junejo NN, Albeaiti M, et al. Timing of orchidopexy at a tertiary center in Saudi Arabia: reasons for late surgery. Ann Saudi Med. 2018;38:284–7.
[11] Williams K, Baumann L, Shah A, et al. Age at orchiopexy for undescended testis in the United States. J Pediatr Surg. 2017. https://doi.org/10.1016/j.jpedsurg.2017.10.020 (pii: S0022-3468(17)30642-5).
[12] Hidas G, Ben Chaim J, Udassin R, et al. Timing of orchidopexy for undescended testis in Israel: a quality of care study. Isr Med Assoc J. 2016;18:697–700.
[13] McLatchie LM, Fry CH. ATP release from freshly isolated guinea-pig bladder urothelial cells: a quantification and study of the mechanisms involved. BJU Int. 2015;115:987–93.
[14] Dobanovackic D, Vuckovic N, Slavkovic A, et al. Variations in timing of elective orchidopexy. Med Pregl. 2016;69:106–9.
[15] Bradshaw CJ, Corbet-Burcher G, Hitchcock R. Age at orchidopexy in the UK: has new evidence changed practice? J Pediatr Urol. 2014;10:758–62.
[16] Hrivatakis G, Astfalk W, Schmidt A, et al. The timing of surgery for undescended testis - a retrospective multicenter analysis. Dtsch Arztebl Int. 2014;111:649–57.
[17] Springer A, Subramaniam R, Krall C, et al. Orchidopexy patterns in Austria from 1993 to 2009. J Pediatr Urol. 2013;9:535–41.
[18] Zini A, Abitbol J, Schulsinger D, et al. Restoration of spermatogenesis after scrotal replacement of experimentally cryptorchid rat testis: assessment of germ cell apoptosis and eNOS expression. Urology. 1999;53:223–7.
[19] Kollin C, Stukenborg JB, Nurmio M, et al. Boys with undescended testes: endocrine, volumetric and morphometric studies on testicular function before and after orchidopexy at nine months or three years of age. J Clin Endocrinol Metab. 2012;97:4588–95.
[20] Hinman Jr F. Unilateral abdominal cryptorchidism. J Urol. 1979;122:71–5.
[21] Mengel W, Wronecki K, Schroeder J, et al. Histopathology of the cryptorchid testis. Urol Clin North Am. 1982;9:331–8.
[22] Kogan SJ, Tennenbaum S, Gill B, et al. Efficacy of orchiopexy by patient age 1 year for cryptorchidism. J Urol. 1990;144:508–9 [discussion 512-503].
[23] Canavese F, Cortese MG, Magro P, et al. Cryptorchidism: medical and surgical treatment in the 1st year of life. Pediatr Surg Int. 1998;14:2–5.
[24] Riedmiller H, Androulakakis P, Beurton D, et al. EAU guidelines on paediatric urology. Eur Urol. 2001;40:589–99.
[25] Park KH, Lee JH, Han JJ, et al. Histological evidences suggest recommending orchiopexy within the first year of life for children with unilateral inguinal cryptorchid testis. Int J Urol. 2007;14:616–21.
[26] Karbach U, Schubert I, Hagemeister J, et al. Physicians' knowledge of and compliance with guidelines: an exploratory study in cardiovascular diseases. Dtsch Arztebl Int. 2011;108:61–9.
[27] Smith SC, Nguyen HT. Barriers to implementation of guidelines for the diagnosis and management of undescended testis. F1000Res. 2019;8.
[28] Canning DA. Re: a 22-year retrospective study: educational update and new referral pattern of age at orchidopexy. J Urol. 2018;199:882.
[29] Steckler RE, Zaontz MR, Skoog SJ, et al. Cryptorchidism, pediatricians, and family practitioners: patterns of practice and referral. J Pediatr. 1995;127:948–51.
[30] Thorup J, Jensen CL, Langballe O, et al. The challenge of early surgery for cryptorchidism. Scand J Urol Nephrol. 2011;45:184–9.
[31] Sinner B, Becke K, Engelhard K. General anaesthetics and the developing brain: an overview. Anaesthesia. 2014;69:1009–22.
[32] Jiang DD, Acevedo AM, Bayne A, et al. Factors associated with delay in undescended testis referral. J Pediatr Urol. 2019. https://doi.org/10.1016/j.jpurol.2019.03.029 (pii: S1477-5131(19)30078-6) [Epub ahead of print].
[33] Yi W, Sheng-de W, Lian-Ju S, et al. Management of undescended testis may be improved with educational updates and new transferring model. Ital J Pediatr. 2018;44:58.
[34] Kokorowski PJ, Routh JC, Graham DA, et al. Variations in timing of surgery among boys who underwent orchidopexy for cryptorchidism. Pediatrics. 2010;126:e576–82.
[35] Mau EE, Leonard MP. Practical approach to evaluating testicular status in infants and children. Can Fam Physician. 2017;63:432–5.
[36] Ein SH, Nasr A, Wales PW, et al. Testicular atrophy after attempted pediatric orchidopexy for true undescended testis. J Pediatr Surg. 2014;49:317–22.
[37] Noseworthy J. Recurrent undescended testes. Semin Pediatr Surg. 2003;12:90–3.