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Research Article

Management of Undescended Testis: Italian Experience of a Single Center of Pediatric Surgery

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Abstract

The undescended testis (UDT) is a common male genital anomaly. Sub fertility and testicular hypotrophy are considered the principal long-term consequences of UDT. There are two modes of treatment of UDT: hormonal and surgical treatment surgical that can be used alone or as complementary methods.

Testicular histology, testicular volume (TV) and hormonal evaluation are considered to be the most relevant measure to establish future potential fertility. During follow-up each patient undergoes physical and ultrasound examination after three, twelve months and then five years. Serum level of gonadal hormone (LH, FSH, Inhibin B, LDH, Free Testosterone and DHEA) is evaluated before surgery and six months after orchidopexy.

We assumed that testis biopsy is more predictive about future potential fertility than TV. Our patients have been found to have higher levels of LH and FSH and lower levels of inhibin B. To discern the presence of an effect of hormonal treatment we decided to consider the Testicular Atrophy Index (TAI), which is applicable only in unilateral UDT. Due to the necessity to consider also the case of bilateral UDT, we have introduced the normalized Testicular Atrophy Index (TAIn).

Through the performed management, it has been possible to provide an estimate of the future fertility of these children. We noted that the degree of reduction in testicular volume does not seem to correlate with the severity of histological findings, nor does it seem to affect future fertility. The patients with a TAIn ≥ 20 % treated with preoperative and post-operative GnRHa therapy have a significant increase in TV after 5 years of follow-up, as shown by the relative reduction of TAIn values. Immediate and delayed post-surgery complications have not occurred. In the cases treated with hormonal therapy, a slight accentuation of secondary sexual characteristics occurs but it is completely regressed after discontinuation of the treatment (one month post-surgery). There have been no recurrences UDT after orchidopexy.

INTRODUCTION

The undescended testis (UDT) is a common male genital anomaly in which one or both testicles are not properly located in the scrotum [1-3]. Its incidence is about 1-3% in term neonates, and as high as 30% in preterm neonates [4-5].

The pathogenesis of UDT includes genetic, hormonal and environmental factors. The regulation of testicular descent is not fully explained, since it is a complex interaction between hormonal and anatomical factors. Human chorionic gonadotropin (hCG) secreted by the placenta and the fetal pituitary LH and FSH are important factors because they regulate the production of androgens by testes, as well as the Insulin-like 3 peptide (INSL3) derived from the Leydig cells and Müllerian inhibitor substance (MIS) and anti-Müllerian hormone (AMH) derived from the Sertoli cells. The transabdominal phase of descent is influenced by INSL3, promoting the growth of fetal gubernaculums. In fetal development and inguino-scrotal migration, androgens have an important role: deficiencies in prenatal androgen secretion secondary to insufficient pituitary gonadotropin stimulation or low production of prenatal gonadotropin are common causes of UDT [6].

At the age of 3 months, a hormonal surge of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) takes place, followed by a transient rise in testosterone, in MIS, AMH and inhibin B. Levels of testosterone decline slowly thereafter, usually by age 4–6 months, to typical childhood levels. This hormone peak seems to be necessary for the maturation of germ cells to adult-dark spermatogonia (AD-S). In cryptorchid infants, this process can be altered leading to the rise of the risk of future infertility [7]. Individuals with bilateral UDT are 6 times more likely to be infertile compared to the general population [5]. On the other hand, individuals with unilateral UDT have twice the risk of infertility compared to the general population [8]. In these individuals, the germinal count was found to be reduced in both the undescended and the normally positioned testis [9].

Testicular histology, testicular volume (TV) and hormonal evaluation are considered to be the most relevant measure to establish the future potential fertility in children and adolescent patients [5,10].

Orchidopexy has a beneficial effect in this regards and should be performed as early as possible (by 6-12 months of age) [5,11,12]. Surgery should be avoided during early infancy to prevent degeneration of the testes and consequent infertility in adulthood, to avert malignancy, and to reduce the chance of testicular torsion [2,5].

Hormonal treatment (HT) is based on the deficiency of the hypothalamic-pituitary-testicular axis at the end of gestation or after birth. This therapy is usually carried out using hCG, gonadotropin releasing hormone (GnRH, *luteinizing hormone releasing hormone* – LHRH) or their combination. It can be administered as a neoadjuvant therapy prior to the orchiopexy or as a supplementary treatment after surgery [2,7].

Gonadotropin-releasing hormone analog (GnRHa) - also known as luteinizing hormone-releasing hormone analog (LH-RHa) - therapy seems to be able to correct the testicular histological abnormalities of germ cells (13).

To discern the presence of an effect of HT we consider the Testicular Atrophy Index (TAI), introduced by Niedzielski et al. (14) that it is applicable only in unilateral UDT. Due to the necessity to consider also the case of bilateral UDT, we have introduced a new parameter, the normalized testicular atrophy index (TAIn) [7].

MATERIALS AND METHODS

Pre-operative management

We considered 45 clinical cases: 35 patients (77,8%) with unilateral undescended testis. 62,9% (22/35) had right-sided unilateral cryptorchidism, while 37,1% (13/35) had unilateral left-sided UDT. 10 patients (22,2%) had bilateral undescended testes. The mean age of patients at the time of surgery was 4.75 years (range: 18 months-8 years).

Tanner stage was assigned for each patient (All patients were classified as Tanner's stage 1).

After collection of data including patient-demographics we proceed with the assessment of the undescended testis position using abdominal-inguino-scrotal palpation. The sonographically estimated testicular volume follows the volume formula for an ellipsoid (π/6 x length x width x height) and is compared to a reference value of testicular volume for age measured sonographically by Goede et al. [15],. We employ TAI and TAIn respectively for unilateral and bilateral UDT. These two parameters are objective tools for qualifying patient for surgery and for monitoring the results of treatment. TAI and TAIn value ≥ of 20% should be considered an indication for surgery in boys with retractile testes [7,14].

At the end of physical examination, the necessity of surgical treatment is discussed and established. Before surgical treatment the patients are tested for serum *Luteinizing Hormone* (LH), *Follicle-Stimulating Hormone* (FSH), Inhibin B, *Lactate Dehydrogenase* (LDH), Free Testosterone and Dihydroepiandrosterone (DHEA).

Surgical Management

In case of palpable testes located in the proximal tract of the inguinal canal orchidopexy according to Shoemakers procedure was performed [16,17]. In presence of palpable testes located in the distal tract of the inguinal canal, or in case of the retractile testes which have volume reduction transscrotal orchidopexy is the choice, especially following Spinelli's technique.

Shoemaker procedure provides a transverse inguinal incision over the internal ring. The external oblique aponeurosis is incised. The testis is dissected from the canal. The tunica vaginalis is then dissected away from the vas deferens and the vessels and divided. The proximal sac is suture-ligated and amputated. A tunnel is created from the inguinal canal into the scrotum and it is enlarged. A subdartos pouch is created by placing the finger through the tunnel and stretching the skin in a dependent portion of the scrotum. A incision is made in the skin over the finger. Then the testis is placed in the dartos pouch and fixed. The scrotal skin incision is closed. [17].

During Spinelli's procedure an unique transversal incision of the hemiscrotum of the affected testis is made. The access is at the level of the middle part of the scrotum, through an incision about one centimeter. The testis is exposed and delivered through the wound. Then an accurate funicololisis until reaching the external inguinal ring is carried out: vas and vessels are identified and preserved intact. The vaginal tunic of the testicle is open and, if present, the peritoneum-vaginal duct is removed and sutured.

The prescrotal adipose tissue is prepared: an adipose fan of trapezoidal shape it is created and is perforated in the middle. A pull-through of the testis across adipose fan is made and at last the testis is anchored to adipose tissue. The operation ends with the scrotal skin closed with subcuticular suture using absorbable stitches.

In both cases during surgery, in order to assess the histological findings, a biopsy is performed through an incision of 2-3 mm in the a vascular zone. The pressure applied on the rear surface of the testis facilitates evagination of a 2X2X2 mm portion of testicular parenchyma which is cleaved with a sharp pair of scissors and soaked, using the method non-touch.

Using light microscopy at 400X magnification and in each biopsy 50 seminiferous tubules, at a minimum, are examined.

Post-Operative Management

Each patient is undergone a physical examination and an abdominal and inguino-scrotal ultrasound after three months, twelve months and then five years.

If a neo adiuvant hormonal treatment is made, this will be continued for one month after surgery. Six months after surgery serum level of hormones, including LH, FSH, Inhibin B, LDH, Testosterone and DHEA, are assessed for all patients included in the study.

In order to establish the correlation among testicular volume and histological findings, obtained by biopsy, statistical analysis was performed using the SPSS software version 21 (SPSS, Chicago, Illinois, USA). Comparisons between groups were made using Student's t-test and Fisher's exact test accordingly. Differences were considered statistically significant for p-values < 0.05.

RESULTS

In patients treated with hormonal therapy, we found a slight

accentuation of secondary sex characteristics. These alterations regressed after discontinuation of the treatment one month post-surgery.

In our experience immediate and delayed post-surgery complications did not occurr. There has been no recurrences of the fixed testes by orchidopexy. We have demonstrated that various grades of histological damage were present in all patients. One third of patients had severe damage such as fibrosis, thickening of the basement membrane and anisometry or reduction of Tubular Fertility Index (TFI) and Sertoli cell index.

DISCUSSION

Sub fertility and testicular hypotrophy are considered the principal long-term consequences of undescended testis [18]. Indeed detecting and identifying cryptorchid condition is crucial above all to forecast the future fertility and to decrease the infertility risk.

In the pediatric age group several factors have been used as predictors of future fertility including: testicular volume, histology and serum hormone levels [5,10].

In unilateral UDT, the u testis is typically smaller than the normally positioned one, which typically hypertrophies to compensate for the reduced function of the contra lateral testis [19,20]. Testicular volume has been estimated by various tools: the orchidometer of Prader and Rochester, rulers, and ultrasound examination [21].

Accordingly a testicular biopsy could serve as an objective means by which future fertility could be assessed. Biopsy allow us to identify the architectural damage which is characterized by fibrosis, thickening of the basement membrane and anisometry. It can also permit to analyze the histological findings such as: Main Tubular Diameter (MTD), Germ cell count (germ cell count /tubule, GCC), Sertoli cell index (SCI), Interstitial fibrosis index (IFI) and Tubular Fertility Index (TFI). This last one has been particularly found to correlate significantly with future fertility potential [22,23].

However, routine testicular biopsy for children with UDT remains controversial, due to the fear of injuring the testis, but it has been shown conclusively that performing a biopsy in prepubertal testes does not cause any damage to the developing gonad with respect to future fertility [24].

Testicular biopsy analysis is currently the most effective method for identifying boys at risk of infertility after successful surgery for cryptorchidism, because a positive correlation exists between testicular histopathology at orchidopexy and future fertility in patients with cryptorchidism [25].

Moreover, testicular biopsy is the only diagnostic procedure capable of identifying patients who need to be treated with LH-RH following successful orchidopexy and should therefore be routinely performed during surgery [26].

Our practice has shown that the degree of reduction in the volume of an undescended testis does not seem to significantly correlate with the severity of histological changes that accompany UDT, nor does it accurately reflect potential future fertility [27].

The importance of a hormonal evaluation is related to the correlation between the levels of gonadotropins (LH and FSH) and inhibin B with spermatogenesis. Cryptorchid individuals have been found to have higher levels of gonadotropins and lower levels of inhibin B [5,19,28-31].

Adjuvant hormonal therapy, given one month before surgery, may reduce the outstanding surgical difficulties that can occur when the scrotum is underdeveloped or when the testis is malformed, small or associated with short vessels; GnRHa, in fact, is known to elongate the cord structures and enlarge the inguinal canal by stimulating the natural process of growth [32].

Moreover, potential disadvantages of HT are its cost, the necessity of delay surgical procedure and its side effects, as accelerated secondary sexual characteristic, premature epiphyseal closure and an aggressive behavior of the child during the treatment (that usually recedes after cessation of therapy). Current reports [33,34] suggest that the cases of UDT that may benefit from supplementary gonadotropin treatment are those with bilateral UDT, normal LH and FSH levels and those with a decreased germ cell number in the biopsy.

In our study, to discern the presence of an effect of HT we decided to consider the Testicular Atrophy Index (TAI), introduced by Niedzielski et al. and defined as: (contra lateral testis volume - affected testis volume)/contra lateral testis volume X 100, expressed as a percent [14].

However, this parameter is applicable only in unilateral UDT. Due to the necessity to consider also the case of bilateral UDT, we have introduced a new parameter, the normalized Testicular Atrophy Index (TAIn), based on the difference between the mean volume of normally descended testis from the literature for age [15] and the mean volume of the two affected testes [7].

CONCLUSION

In our experience, TAIn turned out to be a useful parameter to monitor the results of HT in testicular growth, especially in case of bilateral UDT. Our results indicate that patients with a TAIn ≥ 20 % treated with preoperative and post-operative GnRHa therapy have a significant increase in TV after 5 years of follow-up, as shown by the relative reduction of TAIn values.

Our data show that connection between histopathological findings and testis size exists, and this evidence alighted that a more reduced testicular volume is not strictly correlated with a worst histopathological damage and, conversely, a less reduced testicular volume does not necessarily correspond to an alteration of minor grade. Throughout these data and the statistical study we realized that biopsy, conducted during orchidopexy, remains the more predictive method about future potential fertility.

REFERENCES

1. Penson DF KS, Jules A. Evaluation and Treatment of Cryptorchidism. Comparative Effectiveness Reviews. 2012; 88.

2. Niedzielski JK, Oszukowska E, Słowikowska-Hilczer J. Undescended testis - current trends and guidelines: a review of the literature. Arch Med Sci. 2016; 12: 667-677.

3. Park K, Choi H. An evolution of orchiopexy: historical aspect. Korean J Urol. 2010; 51: 155-160.

4. Editors Penson DF, Krishnaswami S, Jules A, Seroogy JC, McPheeters ML. Evaluation and Treatment of Cryptorchidism

5. Trsinar B, Muravec UR. Fertility potential after unilateral and bilateral orchidopexy for cryptorchidism. World J Urol. 2009; 27: 513-519.

6. Hutson JM, Southwell BR, Li R, Lie G, Ismail K, Harisis G, et al. The regulation of testicular descent and the effects of cryptorchidism. Endocr Rev. 2013; 34: 725-752.

7. Spinelli C, Strambi S, Busetto M, Pucci V, Bianco F. Effects on normalized testicular atrophy index (TAIn) in cryptorchid infants treated with GnRHa pre and post-operative vs surgery alone: a prospective randomized trial and long-term follow-up on 62 cases. Pediatric surgery international. 2014; 30: 1061-1067.

8. Lee PA, Coughlin MT, Bellinger MF. Paternity and hormone levels after unilateral cryptorchidism: association with pretreatment testicular location. J Urol. 2000; 164: 1697-1701.

9. van Brakel J, Kranse R, de Muinck Keizer-Schrama SM, Hendriks AE, de Jong FH, Hack WW, et al. Fertility potential in a cohort of 65 men with previously acquired undescended testes. Journal of pediatric surgery. 2014; 49: 599-605.

10. Varela-Cives R, Mendez-Gallart R, Estevez-Martinez E, Rodriguez-Barca P, Bautista-Casasnovas A, Pombo-Arias M, et al. A cross-sectional study of cryptorchidism in children: testicular volume and hormonal function at 18 years of age. International braz j urol: official journal of the Brazilian Society of Urology. 2015; 41: 57-66.

11. Goel P, Rawat JD, Wakhlu A, Kureel SN. Undescended testicle: An update on fertility in cryptorchid men. Indian J Med Res. 2015; 141: 163-171.

12. Chan E, Wayne C, Nasr A. FRCSC for Canadian Association of Pediatric Surgeon Evidence-Based Resource. Ideal timing of orchiopexy: a systematic review. Pediatr Surg Int. 2014; 30: 87-97.

13. Hadziselimovic F. Successful treatment of unilateral cryptorchid boys risking infertility with LH-RH analogue. International braz j urol: official journal of the Brazilian Society of Urology. 2008; 34: 319-326.

14. Niedzielski J, Pisarska K, Przewratil P. The usefulness of testicular atrophy index in the assessment of undescended testicle--preliminary report. Roczniki Akademii Medycznej w Bialymstoku. 2003; 48: 112-114.

15. Goede J, Hack WW, Sijstermans K, van der Voort-Doedens LM, Van der Ploeg T, Meij-de Vries A, et al. Normative values for testicular volume measured by ultrasonography in a normal population from infancy to adolescence. Horm Res Paediatr. 2011; 76: 56-64.

16. Thorup J, Haugen S, Kollin C, Lindahl S, Läckgren G, Nordenskjold A, et al. Surgical treatment of undescended testes. Acta Paediatr. 2007; 96: 631-637.

17. Thorup J, Cortes D. Surgical treatment and follow up on undescended testis. Pediatric endocrinology reviews: PER. 2009; 7: 38-43.

18. Virtanen HE, Bjerknes R, Cortes D, Jorgensen N, Rajpert-De Meyts E, Thorsson AV, et al. Cryptorchidism: classification, prevalence and long-term consequences. Acta paediatrica (Oslo, Norway : 1992). 2007; 96: 611-616.

19. Gaudino R, Cavarzere P, Camilot M, Teofoli F, Zampieri N, Tatò L. Prepubertal serum inhibin B in cryptorchid infants and in monorchid boys with compensatory testicular hypertrophy. Fertil Steril. 2008; 90: 2217-2221.

20. Lee PA, Coughlin MT, Bellinger MF. No relationship of testicular size at orchiopexy with fertility in men who previously had unilateral cryptorchidism. J Urol. 2001; 166: 236-239.

21. Zvizdic Z, Milisic E, Halimic A, Zvizdic D, Zubovic SV. Testicular volume and testicular atrophy index as predictors of functionality of unilaterally cryptorchid testis. Medical archives (Sarajevo, Bosnia and Herzegovina). 2014; 68: 79-82.

22. Cortes D, Thorup JM, Lindenberg S. Fertility potential after unilateral orchiopexy: an age independent risk of subsequent infertility when biopsies at surgery lack germ cells. J Urol. 1996; 156: 217-220.

23. Kraft KH, Mucksavage P, Canning DA, Snyder HM, 3rd, Kolon TF. Histological findings in patients with cryptorchidism and testis-epididymis nonfusion. The Journal of urology. 2011; 186: 2045-2049.

24. AbouZeid AA, Mousa MH, Soliman HA, Hamza AF, Hay SA. Intra-abdominal testis: histological alterations and significance of biopsy. J Urol. 2011; 185: 269-274.

25. Cerilli LA, Kuang W, Rogers D. A practical approach to testicular biopsy interpretation for male infertility. Archives of pathology & laboratory medicine. 2010; 134: 1197-1204.

26. Hadziselimovic F, Hoecht B. Testicular histology related to fertility outcome and postpubertal hormone status in cryptorchidism. Klin Padiatr. 2008; 220: 302-307.

27. Spinelli C BS, Strambi S, Piscioneri J, Pucci A, Bianco F, Liloia C, et al. An assessment of the correlation between testicular volume and histological findings, and its potential impact on future fertility in patients with unilateral cryptorchidism. Pediatric surgery international. 2016.

28. Cortes D, Thorup JM, Lindenberg S. Fertility potential after unilateral orchiopexy: simultaneous testicular biopsy and orchiopexy in a cohort of 87 patients. The Journal of urology. 1996; 155:1061-1065.

29. Thorup J, Petersen BL, Kvist K, Cortes D. Bilateral undescended testes classified according to preoperative and postoperative status of gonadotropins and inhibin B in relation to testicular histopathology at bilateral orchiopexy in infant boys. J Urol. 2012; 188: 1436-1442.

30. Thorup J, Clasen-Linde E, Thorup SC, Cortes D. Pre- and postoperative status of gonadotropins (FSH and LH) and inhibin-B in relation to testicular histopathology at orchiopexy in infant boys with unilateral undescended testes. Journal of pediatric urology. 2015; 11: 1-5.

31. Irkilata HC, Kibar Y, Basal S, Kurt B, Gunal A, Alp BF, et al. The impact of simple orchiectomy on semen quality and endocrine parameters in postpubertal cryptorchid men. International urology and nephrology. 2012; 44: 1617-1622.

32. Schwentner C, Oswald J, Kreczy A, Lunacek A, Bartsch G, Deibl M, et al. Neoadjuvant gonadotropin-releasing hormone therapy before surgery may improve the fertility index in undescended testes: a prospective randomized t. J Urol. 2005; 173: 974-977.

33. Kim SO1, Hwang EC, Hwang IS, Oh KJ, Jung SI, Kang TW, et al. Testicular catch up growth: the impact of orchiopexy age. Urology. 2011; 78: 886-889.

34. Thorup J, Kvist K, Clasen-Linde E, Petersen BL, Cortes D. The relation between adult dark spermatogonia and other parameters of fertility potential in cryptorchid testes. The Journal of urology. 2013; 190: 1566-1571.

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