Review Paper

The biopsy of the undescended testis: yes or no?

Abstract

Undescended testis is the most common disorder of the urogenital system. It has been shown that spermatogenesis is affected in cryptorchid boys after the 9 months of age when spermatogenic index decreases rapidly. There are many studies about possible consequences of this condition such as infertility or testicular cancer. Although orchidopexy before puberty decreases the risk of testicular cancer it does not completely eliminate it. If the child underwent bilateral orchidopexy it will carry 6-fold greater risk of being infertile when compared with unilaterally cryptorchid men and general population. There is still a debate if the biopsy should be taken during orchidopexy. The result of biopsy should give us an idea of the number of germ cells and AdS cells which hold a high predictive value of future spermatogenesis. Scientists still have many questions that require answer such as if there is any less invasive way to find out about the level of AdS at the time of orchidopexy such as measurement of testicular volume? Although testicular biopsy is not a standard part of the protocol for orchidopexy is it possible that detecting low AdS at the histopathological examination can point out the patients for postorchidopexy hormonal therapy?

Undescended testis or cryptorchidism is the most common disorder of the urogenital system that predominately affects preterm infants. Up to one third of preterm infants have undescended testis at the time of birth [1]. The reason for a high number of cryptorchid preterm boys is explained by the mechanism of the testicular descent which occurs in two phases. The first phase that occurs between 8 and 15 weeks of gestation is abdominal phase, and the second one is inguinoscrotal phase. In the second phase testis migrates from the inguinal area to the scrotum and this phase is usually completed by the time of birth [2]. In preterm infants this phase is interrupted, which explains the high incidence of undescended testis in preterm infants. In a large population-based study of 819111 non-syndromic boys in Denmark, Jensen and colleagues analyzed associations between birth weight, prematurity and cryptorchidism, which occurred in 14.1 cases out of 1000 boys [3]. The incidence of cryptorchidism in a full term male infants is between 1.8-8.4% [2]. Although there are many risk factors for cryptorchidism the exact etiology is still unknown.

It is well known that the possibility of spontaneous descent of testis after first six months of life is poor [4]. This fact together with the fact that spermatogenesis decreases over time led to the new suggestion that the therapy of undescended testes should start at 4 months of age in a full-term baby and at 6 months of age in a pre-term baby [4].

What happens with the process of spermatogenesis in an undescended testis? The testis contains three types of cells: germ cells, Sertoli and Leydig cells. Spermatogenesis takes place in the seminiferous tubules. The transformation of gonocytes into adult dark spermatogonia (AdS) occurs at around 3 months of age and it appears to be under control of a surge of gonadotropins and androgens in a so-called “mini-puberty” phase [5]. By the 5 years of age, the AdS will

further differentiate into primary spermatocytes as they will remain until puberty and the onset of spermatogenesis [6-9]. For the physiological functioning of the process of spermatogenesis it is essential that gonocytes transform into AdS as they represent future stem cells for spermatogenesis. This particular process is affected in children with undescended testis [10], and it implies that they might have future problem with lower sperm counts and subsequent infertility.

The results of the biopsies of the undescended testis in adult men showed a high rate of Sertoli cell-only (SCO) syndrome in one study recently conducted in Turkey [11]. SCO syndrome, also called germ cell aplasia, describes a condition of the testes in which only Sertoli cells line the seminiferous tubules. Typically, men with SCO syndrome are found to be azoospermic. As an example, Klinefelter syndrome is characterized by SCO and Leydig cell hyperplasia. Apart from SCO syndrome a high rate of maturation arrest on testicular biopsies were noted where numerous spermatogonia, few spermatocytes and no spermatides were reported. Hypospermatogenesis was defined as presence of all cell types (Sertoli cells, spermatogonia, spermatocytes and spermatides) with a low level of cellularity within the seminiferous tubules and was noted in 5 out of 244 patients [11]. The risk for azoospermia in cryptorchid boys is 10 times more likely than in general population and it raises up to 98% in untreated bilateral cryptorchid adult men.

It is clear that the biopsy should be done in adult patients with cryptorchidism as the incidence of testicular cancer is higher than in general population. Men with a history of undescended testis have an increased risk of developing testicular cancer compared with men in the general population in whom the age adjusted incidence is approximately 5.7 per 100000 [12]. It shows an increasing trend over the years [12]. However, the magnitude of increased risk is poorly quantified [13].

In a 2013 meta-analysis of nine case-control studies (including a total of 2281 cases) and three cohort studies (including more than 2 million boys), the pooled relative risk (RR) of testicular cancer in men with isolated cryptorchidism was 2.9 (95% CI 2.2-3.8) but there was significant heterogeneity between studies (with individual RRs ranging from 3 to 50), risk of publication bias, and overall lack of high-quality evidence [14]. The risk of developing testicular cancer is further increased in men with bilateral cryptorchidism (which may be associated with endocrinologic abnormalities or abnormal karyotype) and intra-abdominal undescended testes [15-17].

A history of cryptorchidism is also a risk factor for developing germ cell neoplasia in situ (formerly called intratubular germ cell neoplasia of unclassified type [18]), a premalignant condition. The most recent study published in 2017 by Osterballe et al. included a cohort of 1403 boys operated on cryptorchidism between 1971 and 2003. The standardized incidence ratio of testicular cancer in this study was 2.7 (95% CI, 1.5-4.3). For bilateral cryptorchidism this ratio was 4.1 (95% CI, 1.8-8.1), compared to 2.0 (95% CI, 0.8-3.9) in unilateral cases [19]. Intratubular germ cell neoplasia is predominantly observed prepubertally in boys who had associated congenital anomalies, chromosomal and/or genetic disorders and syndromes [20]. It has been recommended that testicular biopsy should be performed at time of orchidopexy in intraabdominal testes, abnormal external genitalia or known abnormal karyotype [21]. The biopsy that shows Oct3/4 or D2-40 immunopositive germ cells in seminiferous tubules of prepubertal cryptorchid testes may predict development of later testicular cancer especially if cryptorchidism is associated with other congenital anomalies, chromosomal and/or genetic disorders and syndromes [20].

Surgical repositioning of the testis (orchiopexy) before puberty appears to decrease the risk of testicular cancer but does not completely eliminate it [22, 23]. In a cohort of 16983 men who underwent orchiopexy between 1964 and 1999 and were followed for a total of 209984 person-years, 56 cases of testicular cancer were identified [22]. Among those who were treated before 13 years of age, the RR of testicular cancer compared with the general population was 2.2 (95% CI 1.6-3.1). Among those who were treated at ≥13 years of age, the RR was 5.4 (95% CI 3.2-8.6). These findings support those of several smaller case-control and cohort studies [15, 24-26].

About 10% of infertile men have a history of cryptorchidism and orchidopexy. If the child underwent bilateral orchidopexy it will carry 6-fold greater risk of being infertile when compared with unilaterally cryptorchid men and general population [27]. It has been shown that spermatogenesis is highly affected in cryptorchid boys after the 9 months of age when spermatogenic index decreases rapidly. If the descent of testis is stopped in the abdomen this testis would be affected with a greater germ cell loss than testis located in inguinal canal. As already mentioned earlier, the time for the orchidopexy had moved to 6 months of age. The study of Hadziselimovic and Herzog published in Lancet 2001 had demonstrated that biopsies taken from the undescended testis at the time of surgery performed before 6 months of age showed normal number of germ cells per tubule compared to boys having surgery after 6 months of age [28]. Unfortunately a long term follow up showed that there was no association between germ cell counts on biopsy and the total sperm count on semen analysis, but this association was found for the number of AdS and future fertility. Hadziselimovic suggests that the biopsy should be performed during orhidopexy in boys with undesended testes who had no response to LHRH therapy [29]. The result of such biopsy should give us a clear idea of the number of germ cells and AdS cells which hold a high predictive value of future spermatogenesis.

Mechlin et al. in their review article from 2014 concluded that biopsy specimens from cryptorchid testes should be analyzed for total germ cell concentration, presence of AdS, AdS/tubule ratio, presence of gonocytes (placental alkaline phosphatase positive cells), presence of primary spermatocytes (in boys older than 3 years of age) and the degree of fibrosis [30]. These findings have significant prognostic value for future fertility potential in cryptorchid boys.

Literature debates about the possible effect of neoadjuvant hormonal therapy before orchidopexy. In a randomized, double-blinded, placebo-controlled study buserelin (GnRH agonist) was shown to be capable of inducing testicular descent in addition to increasing simultaneously the number of germ cells and provoking further development of the epididymis [31].

Accepting the above mentioned correlation between low number of AdS at the time of orchidopexy and future problems with fertility can we do anything after orchidopexy at the age of 6 months in patients with low AdS to prevent future fertility problems? Hadziselimovic observed that GnRH administration after orchidopexy might result in improved fertility [32].

Is there any less invasive way to find out about the level of AdS at the time of orchidopexy?

If 80-90% of the testicular mass consists of seminiferous tubules containing germinal and Sertoli's cell [33] it means that testicular volume is largely a reflection of spermatogenesis [34]. Is it possible that only measurement of testicular volume could predispose the hypospermatogenesis in the cryptorchid boys with no need for biopsy? Apart of the higher possibilities of the decrease of spermatogenesis in cryptorchid boys with intraabdominal and nonpalpable testis with low testicular volume, there are no high evidence studies that suggest this association with only testicular volume.

But what about the risks of the biopsies performed? Why does the number of reported azoospermia and oligospermia increases up to 83% after the testicular biopsy taken during orchidopexy [35]? And is it really so, if we know that biopsies are usually taken in patients who have higher chance of being infertile [29]?

For now, apart from biopsy there are no other ways of measuring AdS and detecting future fertility problems in boys with undescended testis that might benefit from postorchidopexy hormonal therapy and prevent future fertility problems. Although testicular biopsy is not a standard part of the protocol for orchidopexy, is it possible that detecting low AdS at the histopathological examination can point out the patients for postorchidopexy hormonal therapy? Is this a way to stop this increasing trend of fertility problems? Future research in this field will give us an answer.

References:

1. Chung E, Brock GB. Cryptorchidism and its impact on male fertility: a state of art review of current literature. Can Urol Assoc J. 2011;5:210–4.

2. Virtanen H, Toppari J. Epidemiology and pathogenesis of cryptorchidism. Hum Reprod Update. 2008;14:49-58.

3. Jensen MS, Wilcox AJ, Olsen J, Bonde JP, Thulstrup AM, Høst C, et al. Cryptorchidism and hypospadias in a cohort of 934 538 Danish boys: the role of birth weight, gestational age, body dimensions, and fetal growth. Am J Epidemiol. 2012;175:917.

4. Hamza AF, Elrahim M, Elnagar, Maaty SA, Bassiouny E, Jehannin B. Testicular descent: when to interfere? Eur J Pediatr Surg. 2001;11:173-6.

5. Živković D, Fratrić I. Disturbances of Sperm Maturation and Minipuberty: Is there a Connection? BioMed Research International, vol. 2014, 2014. doi: 10.1155/2014/912746.

6. Huff DS, Fenig DM, Canning DA, Carr MG, Zderic SA, Snyder HM. Abnormal germ cell development in cryptorchidism. Horm Res. 2001;55:11-7.

7. Hutson JM. When to operate and when to investigate. Dialogues Pediatr Urol. 2005;26:2-3.

8. Hadziselimović F, Thommen L, Girard J, Herzog B. The significance of postnatal gonadotropin surge for testicular development in normal and cryptorchid testes. J Urol. 1986;136:274-6.

9. 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. J Urol. 2013;190:1566-71.

10. Huff DS, Hadziselimović F, Snyder HM 3rd, Blyth B, Duckett JW. Early postnatal testicular maldevelopment in cryptorchidism. J Urol. 1991;146:624-6.

11. Ates F, Soydan H, Okcelik S, Cirakoglu A, Yilmaz I, Malkoc E, et al. Clinical and histopathological results of the adult patients with unilateral cryptorchidism. Turk J Urol. 2016;42:74-9.

12. SEER Stat Fact Sheets: Testis. Available from: http://seer.cancer.gov/statfacts/html/testis.html, Accessed on September 4th, 2017.

13. Wood HM, Elder JS. Cryptorchidism and testicular cancer: separating fact from fiction. J Urol. 2009;181:452.

14. Lip SZ, Murchison LE, Cullis PS, Govan L, Carachi R. A meta-analysis of the risk of boys with isolated cryptorchidism developing testicular cancer in later life. Arch Dis Child. 2013;98:20-6.

15. Aetiology of testicular cancer: association with congenital abnormalities, age at puberty, infertility, and exercise. United Kingdom Testicular Cancer Study Group. BMJ. 1994;308:1393.

16. Batata MA, Chu FC, Hilaris BS, Whitmore WF, Golbey RB. Testicular cancer in cryptorchids. Cancer. 1982;49:1023.

17. Cortes D, Thorup J, Petersen BL. Testicular neoplasia in undescended testes of cryptorchid boys-does surgical strategy have an impact on the risk of invasive testicular neoplasia? Turk J Pediatr. 2004;46 Suppl:35.

18. Moch H, Humphrey PA, Ulbright TM, Reuter VE. WHO Classification of Tumours of the Urinary System and Male Genital Organs, 4.

19. Osterballe L, Clasen-Linde E, Cortes D, Engholm G, Hertzum-Larsen R, Reinhardt S, et al. The diagnostic impact of testicular biopsies for intratubular germ cell neoplasia in cryptorchid boys and the subsequent risk of testicular cancer in men with prepubertal surgery for syndromic or non-syndromic cryptorchidism. J Pediatr Surg. 2017;52:587-92.

20. Honecker F, Stoop H, De-Krijger RR, Chris Lau YF, Bokemeyer C, Looijenga LH. Pathobiological implications of the expression of markers of testicular carcinoma in situ by fetal germ cells. J Pathol. 2004;203:849-57.

21. Cortes D, Thorup J, Visfeldt J. Cryptorchidism: aspects of fertility and neoplasms. A study including data of 1335 cosecutive boys who underwent testicular biopsy simultaneously with surgery for cryptorchidism. Horm Res. 2001;55:21-7.

22. Pettersson A, Richiardi L, Nordenskjold A, Kaijser M, Akre O. Age at surgery for undescended testis and risk of testicular cancer. N Engl J Med. 2007;356:1835.

23. Walsh TJ, Dall'Era MA, Croughan MS, Carroll PR, Turek PJ. Prepubertal orchiopexy for cryptorchidism may be associated with lower risk of testicular cancer. J Urol. 2007;178:1440-6.

24. Herrinton LJ, Zhao W, Husson G. Management of cryptorchism and risk of testicular cancer. Am J Epidemiol. 2003;157:602.

25. Pottern LM, Brown LM, Hoover RN, Javadpour N, O'Connell KJ, Stutzman RE, et al. Testicular cancer risk among young men: role of cryptorchidism and inguinal hernia. J Natl Cancer Inst. 1985;74:377.

26. Pike MC, Chilvers C, Peckham MJ. Effect of age at orchidopexy on risk of testicular cancer. Lancet. 1986;1:1246.

27. Lee P. Fertility in cryptorchidism: does treatment make a difference? Endocrinol Metabol Clin North A. 1993;22:47.

28. Hadziselimovic F, Herzog B. The importance of both an early orchidopexy and germ cell maturation for fertility. Lancet. 2001;358:1156-7.

29. Hadziselimovic F. Cryptochidism, its impact on male fertility. Eur Urol. 2002;41:121-3.

30. Mechlin CW, Kogan BA. What lessons can be learned from testicular histology in undescended testes? Transl Androl Urol. 2014;3:365-9.

31. Bica DT, Hadziselimovic F. Buserelin treatment of cryptorchidism: a randomized, double-blind, placebo-controlled study. J Urol. 1992;148:617–21.

32. Hadziselimovic F, Herzog B. Treatment with a luteinizing hormone-releasing hormone analogue after successful orchiopexy markedly improves the chance of fertility later in life. J Urol. 1997;158:1193–5.

33. Tahikara H, Cosentino MJ, Sakatoku J, Cockett ATK. Significance of testicular size in andrology: II. Corelation of testicular size with testicular function. J Urol. 1987;137:416-9.

34. Bahk JY, Jung JH, Jin LM, Min SK. Cut-off value of testicles volume in young adults and correlation among testicles volume, body mass index, hormonal level, and seminal profiles. Urology. 2010;75:1318-23.

35. Grasso M, Bounaguidi A, Lania C, Bergamaschi F, Castelli M, Rigatti P. Postpubertal cryptorchidism: review and evaluation of the fertility. Eur Urol. 1991;20:126-8.