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**Faruk Hadziselimovic**

Institute for Cryptorchidism Research,
Kindermedizinisches Zentrum Liestal,
Liestal, Switzerland

# Opinion: Comment on Evaluation and Treatment of Cryptorchidism: AUA/AAP and Nordic Consensus Guidelines

**Key Words**

Cryptorchidism · Orchidipexy · Hormonal treatment · Pathophysiology

**Abstract**

The ultimate goal in the treatment of cryptorchidism is to achieve normal fertility. However, in a substantial number of cryptorchid males, early and apparently successful orchidopexy does not improve fertility as it does not address the underlying pathophysiological cause, namely, the impaired transformation of gonocytes into Ad spermatogonia. It is important to realize that over half the patients presenting with unilateral cryptorchidism and the majority of those presenting with bilateral cryptorchidism have abnormal spermiogram which indicates that unilateral cryptorchidism is in fact a bilateral disease and therefore a serious andrological problem. More importantly, only testicular biopsy can nowadays determine which patient should benefit from hormonal therapy. This means that the rationale behind testicular biopsy is both diagnostic and therapeutic, particularly since LH-RHa hormonal therapy is a worthwhile solution to this andrological problem. In boys with a high risk of azoospermia development, adequate treatment with low doses of LH-RHa allowed 86% of subjects to achieve a normal sperm count. This strongly contrasts with the results of the 'surgery-only' group where not a single patient had a normal spermiogram and 20% suffered from azoospermia. Testicular biopsy is all the more justified that it allowed the detection of in situ carcinoma in 0.6% of all the cryptorchid boys studied. Even if hormonal pre-treatment only achieves successful epididymo-testicular descent in 20% of cases, this treatment should remain the first therapeutic choice because it may avoid resorting to surgery. In addition, it has no adverse effect on fertility and, in unsuccessful cases, facilitates orchidopexy and considerably helps reduce the incidence of post-surgical testicular atrophy, whether unilateral or, and this is a much more serious event, bilateral.



## Challenge

The greatest challenge in any discussion on undescended testicles is to exclude the retractile testis, for which no treatment is required except categorical reassurance.

Inadequate examination has certainly fooled many doctors and even experienced surgeons many times. Over half of the patients sent for treatment are in this category [1]. If the retractile testis is 'treated', the 'results' are bound to be good. It is vital to exclude such cases from the discussion [1]. Importantly, only histological examination of the testicular biopsy can distinguish a true cryptorchid

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E-Mail karger@karger.com
www.karger.com/uin



Faruk Hadziselimovic, MD
Professor of Pediatrics University Basel
Institute for Cryptorchidism Research
Kindermedizinisches Zentrum, CH–4410 Liestal (Switzerland)
E-Mail info@kindermedizin-zentrum.ch

testis from a retractile one. Therefore, to conclude that only congenital cryptorchid testes were treated because these boys had surgery is inappropriate. Upon analyses of testicular biopsies, significant differences were observed between 3 pediatric surgical centers regarding the quality of testicular histology and infertility risk, supporting the above statement [2]. In the absence of histological analysis at the time of surgery, an increase in testicular volume of cryptorchid boys who had orchidopexy before their second birthday could be due to an inappropriate diagnosis of undescended testis.

## Crucial Role for Testicular Biopsy

The main issue of the guidances is the statement that current knowledge supports undoubtedly the idea that surgical intervention in cryptorchidism within the first year of life will preserve fertility; this is misleading [3, 4].

Early and successful orchidopexy (before 9 months of age) could not prevent infertility development in 36% of cryptorchid males [5]. Furthermore, no influence of early age at orchidopexy on fertility parameters was observed [6]. The first prospective study, with a follow-up period of over 20 years showed correlations between testicular histology and postpubertal hormone levels, underscoring a relative gonadotropin deficiency in the majority of males with cryptorchidism. In our opinion, the most critical factor in development of infertility is the finding that gonadotropin levels show more significant correlation with the presence or absence of Ad spermatogonia in both gonads than with the unilaterality or bilaterality of undescended testes. Patients with the greatest impairments to mini-puberty who completely lacked gonocytes transformation into Ad spermatogonia in both testes were those with the most severe infertility [7]. Therefore, studies designed to analyze the fertility outcome with respect to unilaterality or bilaterality of undescended testes cannot address the question of the prognostic importance of testicular biopsy reported in the recent literature that endocrinopathy affects both testes irrespective of unilaterality or bilaterality of descent. Analysis of the contralateral descended testis in unilateral cryptorchidism demonstrated that cryptorchidism is a bilateral disease [8–12]. Furthermore, testicular biopsy can also help in diagnosing carcinoma in situ, as it is found in 0.6% of all cryptorchid boys [13, 14]. Finally, it has been shown conclusively that performing biopsy in prepubertal testes does not cause any damage to the developing gonad [15]. In the absence of testicular biopsy, parents cannot be given accurate information regarding their child's prospects for future fertility. Not to mention the fact that in patients at increased risk of infertility, a simple hormonal therapy would fail to diminish this risk.

## Hormonal Treatment for Descent and Fertility

In the guidances, the use of hormones in cryptorchid boys was not recommended because the paternity rate is normal in men with unilateral undescended testes treated with surgery alone and there are potential adverse effects associated with treatment. However, despite successful surgery, azoospermia is 25 times more common in unilateral and 80 times more common in bilateral cryptorchidism in comparison with the control population [7]. Thus, cryptorchidism is one of the main etiologic causes of non-obstructive azoospermia in man [16]. Interestingly enough, in unilateral cryptorchid males, no significant differences in the frequency of azoospermia were observed irrespective of the treatment modalities used (untreated, 12% (16/134); human chorionic gonadotropin (HCG) treated, 12.6% (25/198); surgically treated, 10.3% (198/1,773) [17]. Moreover, more than one third of males in the high-infertility risk group will develop azoospermia (8/21) (10), (20/61) [18] while none (0/50) ($p < 0.000001$) of the males with identical testicular pathology at surgery who received treatment with luteinizing hormone (LH)-RHa following orchidopexy developed azoospermia. Notably, if patients who were at increased risk of infertility (those lacking Ad spermatogonia in their testes) received treatment with LH-RHa, normal sperm count were observed in 86% of subjects [19]. Thus, the effect of LH-RHa treatment persisted into adulthood. All males in the untreated group (surgery only) were severely oligospermic, with 20% being azoospermic [20]. Furthermore, neoadjuvant gonadotropin releasing hormone treatment was found to improve the fertility index [20, 21]. This profoundly changes our current concept of cryptorchidism treatment. For the first time, it is possible to demonstrate that azoospermia caused by cryptorchidism, which is believed to be a congenital malformation, can be successfully corrected if adequately treated. Biers and Malone [22] performed a critical appraisal of the key papers in the world literature in order to evaluate the level of evidence for improved fertility indices, semen analysis and paternity rates following hormone therapy in undescended testes. They suggest that the evidence is sufficiently strong to recommend a change in clinical practice [22].

## Role of Temperature

Some authors argue that exposure of the cryptorchid human testis to abnormally high temperatures induce germ cell apoptosis [23]. However, this premise does not explain some histological findings of changes that were not confounded by increased temperature. For example, in boys with unilateral cryptorchidism and impaired mini-puberty, gonocytes in the contralateral testis completely lacked transformation into Ad spermatogonia [12]. Furthermore, it is unlikely that increased temperature alone could explain the massive germ cell loss, because boys with bilateral cryptorchidism that were also deficient in SRD5A2 exhibited normal spermatogonia numbers and differentiation during the entire pre-pubertal period, in contrast to boys with isolated bilateral cryptorchidism [24]. An alternative explanation might be that massive germ cell death was due to an insufficient endogenous defense system against transposons. For example, a group of boys with cryptorchidism that were at high risk of infertility exhibited impaired expression of genes that are important for transposon silencing, including *DDX4*, *MAEL*, *MOV10L1*, *PIWIL2*, *PIWIL4*, and TDRD-family members, GTSF1 and MORC1. This suggests that gene instability induced by impaired expression of transposon-silencing genes may have contributed to the development of azoospermia. Intact mini-puberty appeared to be essential for the development of the endogenous defense system mediated by transposon silencing [25].

## Nordic Consensus

The Nordic consensus on the treatment of undescended testis relied greatly on observations reported by Ritzén et al. [4]. Swedish researchers examined endocrine, volumetric, and morphometric data on testicular function before and after orchidopexy, at 9 months and at 3 years. The key message was that the observed germ cell loss was caused solely by the position of the undescended testes, and that the preoperative position of the testes was of lesser importance when surgery was performed early. However, this conclusion was incorrect. Despite the technical adequacy in histological tissue preparations, the responsible histologist clearly did not differentiate between gonocytes and spermatogonia in the germ cell population. This differentiation is important, because between 9 months and 3 years, in the normal testis, 40% of germ cells are lost due to the transformation of gonocytes into spermatogonia, and this is not induced by the cryptorchid position [26]. Therefore, the key message was based on incorrect histological data assessments. Alternatively, the occurrence of Ad spermatogonia indicates completion of mini-puberty, and it is an excellent parameter for predicting fertility outcome in cryptorchid boys [7, 27]. Cryptorchid boys that lack Ad spermatogonia in both testes will develop infertility, despite early orchidopexy, and irrespective of unilateral or bilateral cryptorchidism [7]. However, the differential count of Ad spermatogonia was not performed. Furthermore, over the last 30 years, it has been convincingly shown that 3-year-old, unilateral cryptorchid boys have an average germ cell count of 0.32 germ cells per tubular cross-section [9, 10]. Noticeably, in this study, 3-year-old, cryptorchid boys had an average germ cell count that was 320% lower than expected. This suggested either a selection bias or an invalid histological analysis. Finally, only a comparison between groups of cryptorchid boys that lack Ad spermatogonia in both testes with a group of cryptorchid boys that have Ad spermatogonia in both testes could confirm previously reported observations that cryptorchid boys that lacked Ad spermatogonia had hypogonadotropic hypogonadism who should be treated with LH-RHa following orchidopexy to escape infertility development. This comparison, however, was not performed by Ritzén et al. in this paper. Due to the inexperience of the histologist, the analysis of testicular tissue was inadequate in this study; this resulted in unsubstantiated and, to a great extent, misleading conclusions. In contrast to the concerns raised by the Nordic consensus group, the results of our study showed that hormonal treatment for undescended testis improved the histopathology of the contralateral testis without harming the germ cells [12, 28]. In addition, because testicular volume does not accurately predict the germ cell count in patients with undescended testes, this parameter cannot be used to select patients for post-orchidopexy hormonal therapy. Therefore, testicular volume cannot replace the predictive value of testicular biopsy in the modern management of cryptorchidism.

Furthermore, a Nordic consensus on the treatment of undescended testis prohibited the use of hormones because of possible long-term adverse effects on spermatogenesis. Even if excessive high doses of HCG treatment used may have induced increased apoptosis of the germ cells, it is still irrelevant for subsequent fertility outcome because the follow-up spermiogram performed in these patients showed no significant difference in fertility outcome between the treated and untreated groups [29]. In contrast, a recent study found no adverse effect of prepubertal LH-RH treatment on spermiogram [6]. The second reason was the observation of decreased numbers of germ

cells in cryptorchid boys aged 1–3 who were previously unsuccessfully treated with HCG in comparison to the untreated group [30]. These results, although statistically significant, are again irrelevant for the fertility outcome because the germ cell count in both groups was below 0.2 germ cells per tubular cross-section. If the germ cell count is <0.2, a majority of patients will develop infertility irrespective of whether they had only surgery or hormonal pre-treatment in addition to orchidopexy.

## Back to the Root

*The Physiological Meaning of Mini-Puberty and Molecular Pathology of Cryptorchidism Induced Infertility*

Eleven years ago we found that the potential for male fertility is established in infancy between 30 and 90 postnatal days, a period we designated as mini-puberty [27, 31]. Due to a transient increase in gonadotropins and testosterone during mini-puberty, gonocytes differentiate into Ad spermatogonia, which establish male germ cell memory and male-specific DNA methylation pathways [32].

The question as to whether impaired testosterone secretion is a result of defective mini-puberty is controversial. Two studies have indicated that cryptorchid boys may have a mild primary testicular dysfunction. Pierik et al. [33] found testosterone and free-androgens deficiency in cryptorchid infants, indicating disturbed testicular function evident early after birth. Scandinavian results support the hypothesis that cryptorchidism is associated with a primary testicular disorder, which could be a cause or consequence of cryptorchidism. In a Finnish cohort, hormonal malfunction in 3-month-old boys was found to be reflected in low inhibin B production; and in Finnish and Danish cohorts, high gonadotropin levels [34]. However, cryptorchid boys have low or even undetectable levels of LH and testosterone surges [35], atrophic Leydig cells, and abrogated differentiation of gonocytes into Ad spermatogonia [36]. A vast majority of data available supports the conclusion that in many children with undescended testes, the response of Leydig cells to HCG is diminished as compared to normal boys [37]. Nevertheless, some cryptorchid boys show a normal response, with a higher incidence among those with unilateral cryptorchidism. Except for a blunted testosterone response to HCG, there is no evidence of altered steroidogenesis in cryptorchid testes prior to puberty [37]. Pre-treatment of cryptorchid boys with HCG cancelled out the differences in their response to a stimulation test as compared to a control population [38]. Thus, the cause of the lower testosterone response seems to be at the pituitary or hypothalamic level, and may be a result of insufficient Leydig cell stimulation. Numerous LH-RH tests have demonstrated a lower LH response by gonadotropin-releasing hormone [35, 39–42]. During the last 40 years, histology has contributed the most to helping us better understand the etiology of cryptorchidism. In 1975, we proposed pronounced Leydig cell atrophy starting in early infancy as evidence to support endocrinopathy as an etiological factor in cryptorchidism [43]. Development of Ad spermatogonia from gonocytes, which occurs during the first months of life, has been shown to be testosterone-dependent and is disturbed in cryptorchid boys [12, 31]. Semithin section analysis of the contralateral descended testis in unilateral cryptorchidism confirmed several studies from the late 1960s suggesting that cryptorchidism is a bilateral disease [8–10]. The high azoospermia risk group has significantly lower basal plasma LH levels compared to the low azoospermia risk group, indicating hypogonadotropic hypogonadism [26, 44]. Our observation explains the findings of Gilhooly et al. [45] that were published over 30 years ago of 2 different subsets of unilaterally cryptorchid boys: one with normal spermatogenic potential and other exhibiting germinal deficiency unresponsive to surgical treatment in both testes. Correlations between testicular histology and postpubertal hormone levels confirmed a relative gonadotropin deficiency in a majority of adult cryptorchid men [7]. A recent study estimated that the incidence of defective mini-puberty in cryptorchid boys is as high as 50% [46].

## Conclusion

Hormonal treatment as a first choice of treatment has a long tradition in Europe [47, 48]. It abrogates the necessity of subsequent surgery and in case of non-responders it facilitates orchidopexy and contributes considerably to a reduced incidence of unilateral and more serious bilateral complete post-surgical testicular atrophy. Therefore, hormonal treatment remains the first choice of cryptorchidism treatment. Since abnormal mini-puberty is responsible for adult onset infertility in cryptorchidism, post-surgical hormonal treatment is highly recommended in high infertility and azoospermia risk group of cryptorchid boys who underwent successful early orchidopexy.

Whole genome expression analysis strongly supports the theory that impaired mini-puberty is responsible for

azoospermia and adult infertility in cryptorchidism [49]. Multiple differences in gene expression between high- and low-infertility risk groups underscore the importance of an intact hypothalamus-pituitary-testicular axis in fertility development. Molecular biological observations support LH deficiency, with EGR4 as a master gene over Leydig cell dysgenesis as the reason for impaired mini-puberty [49].

In contrast to the general belief that temperature-dependent effects on non-descent damages testes before sexual maturation is complete, recent evidence is consistent with the idea that infertility in cryptorchidism is a consequence of alterations in the Piwi pathway and transposon de-repression. Thus, abnormal germ cell development in cryptorchidism is preceded by a hormone imbalance and perturbation in germ cell-specific gene expression during mini-puberty. In addition, the intact function of P-bodies during mini-puberty contributes to the establishment of germ cell memory and male-specific DNA methylation pathways.

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