

Undescended testis and infertility—Is hormonal therapy indicated?

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Purpose: The purpose of this chapter is to review hormonal therapy in cryptorchidism in boys to improve fertility.

Methods: Multiple searches, primarily in PubMed, were performed using various combinations of the terms: cryptorchidism, undescended testis (UDT), hormonal therapy, fertility, infertility, germ cell numbers, spermatogonia and semen analyses. In addition the pertinent articles from the reference lists in these papers were also obtained and reviewed.

Results: Data on fertility in unilateral cryptorchidism does not reveal a significant risk for infertility. Testes biopsies in childhood do not correlate with fertility parameters in adulthood. In bilateral cryptorchidism there is a significant risk of infertility. Results of hormonal treatment were not reported separately for bilateral cryptorchidism. Current data is insufficient to know if hormonal therapy is efficacious in bilateral UDT.

Conclusions: Hormonal therapy should not be used in childhood to improve fertility in cases of unilateral cryptorchidism. Testes biopsies in childhood to identify those at risk for infertility should not be performed in unilateral cryptorchidism. More data are needed to answer whether hormonal therapy is beneficial in bilateral UDT. There is insufficient data to establish that testis biopsies are helpful in bilateral cryptorchidism in identifying the subgroup with risk for infertility. They should not be performed in the routine clinical setting but may have a role in a research protocol.

Keywords: Undescended testis (UDT); hormonal therapy; infertility; cryptorchidism; testis biopsy in childhood

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Introduction

One to two percent of males have an undescended testis(s) (UDT) that does not spontaneously descend by six months of age and requires treatment. In approximately 30% of cases of cryptorchidism the problem is bilateral. An association between UDT in childhood and infertility in men has been observed (1,2). Some researchers advocate use of hormonal therapy in boys with UDT to improve fertility (3). The consensus of opinion reported at the European Society of Pediatric Urologists (ESPU) workshops in 2008 and 2009 favored hormonal therapy to improve fertility (3). The Nordic consensus on treatment of UDT, from a group including experts in the fields of testicular physiology, pediatric surgery, pediatric urology, pediatric endocrinology,

andrology, pathology and anesthesiology, did not support use of hormonal treatment (4).

This chapter will review the incidence of infertility in men with history of UDT, the biological basis for using hormonal therapy and the studies assessing efficacy of hormonal therapy in boys with cryptorchidism.

Association of UDT and infertility

Unilateral UDT does not appear to present a significant risk for infertility. In 1989, Cendren *et al.* contacted 40 men who had undergone orchiopexy in childhood. Of the 23 men who had unilateral UDT and later attempted to have children, 20 (87%) were successful (5). In 2002 Lee and Coughlin reported a similar result in a much larger

study population: 313 of 349 (89.7%) men with unilateral cryptorchidism reported success after attempting paternity. This was not a statistically significant difference from the normal control group in which 412 of 442 (93.2%) reported successful parenting. In this study 349 of 593 (59%) completed the questionnaire (2). Follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone and sperm density, motility and morphology are similar in men with history of unilateral orchiopexy and normal controls (6).

Bilateral UDT is associated with significant risk for infertility. In the study by Cendren *et al.*, 6 of 9 (67%) men with a history of bilateral orchiopexy reported inability to father a child (5). Lee *et al.* found that 38.5% of 39 men with bilateral cryptorchidism failed when attempting paternity (7).

Review of descent of the testis and development of sperm

Testicular descent is dependent on androgens. There are two phases of testis descent during gestation. The abdominal phase, the testis moving from the mid abdomen to the internal inguinal ring is mediated by the gubernaculum. The second phase is the testis moving from the internal ring, through the inguinal canal to the scrotum. This phase is mediated by androgens (8).

An understanding of the different types of germ cells observed in the process of spermatogonia in the fetus eventually transforming to mature sperm in the adult is essential to evaluate the studies on efficacy of hormonal therapy. When the gonad differentiates into a testis, gonocytes develop and move to the periphery of the seminiferous tubules. It is probably somewhere between 2-9 months of age that gonocytes develop into spermatogonia, dark type A, “Ad spermatogonia”, thought to be the stem cells crucial to having normal numbers and quality of sperm in the adult. The transformation is thought to be stimulated by gonadotropins and androgens, although not directly proven. Pale type A spermatogonia (Ap) produce type B spermatogonia, the cell type that is committed to become spermatocytes. This process is thought to occur around 4-5 years of age. Mature spermatocytes are the first type of germ cell to undergo meiotic division, beginning the transformation process to mature sperm in the adult male (8-10).

FSH stimulates Sertoli cells that support spermatogenesis and LH stimulates Leydig cells to produce testosterone. FSH and LH are produced by the pituitary gland and

regulated by gonadotropin releasing hormone (GnRH) produced by the hypothalamus gland (10).

Studies assessing efficacy of hormonal therapy in boys with cryptorchidism to improve fertility

In the past beta human chorionic gonadotropin (hCG) and/or LH releasing hormone analogues (GnRH) were used to treat cryptorchidism in some cases (or some centers) and if not successful orchiopexy was performed. When biopsies of the testis(s) were performed at time of orchiopexy, it was observed that boys who tried hormonal therapy had greater number of germ cells than boys who had gone straight to surgery (11). These findings led to the hypothesis that hormonal therapy given during childhood could potentially improve fertility in adulthood. A number of studies followed over the next two decades to evaluate efficacy of hormonal therapy in cryptorchidism to improve fertility.

I initially searched this subject in 2012 and again in preparation for this chapter. The meta-analysis published by Beirs and Malone in 2010 is still the most thorough review on this subject. However, their conclusion that there is “growing evidence” to support use of GnRH therapy to improve fertility is arguable (3). Hutson wrote a commentary to their review stating that there is not sufficient evidence to start recommending hormonal therapy. His primary concern was that lack of a randomized controlled trial showing that GnRH is effective in preventing infertility (12).

Biers and Malone found six papers that concluded benefit to hormonal therapy given prior to orchiopexy (11,13-17), compared to only one study that reported superior results on testis biopsy in the group with no hormonal therapy (18). In the majority of these studies the researchers employed one of several products that are analogs of LH releasing hormone (GnRH) given intranasally (Buserelin, Gonadorelin, Nafarelin) and some employed intramuscular hCG in addition to the GnRH analogue. The doses of GnRH and hCG varied among the studies.

None of these seven studies compared the results of hormonal therapy to orchiopexy alone; the biopsies were carried out at the same time orchiopexy was performed. The studies did not provide results for bilateral cryptorchidism separately from unilateral cryptorchidism.

All of these studies measured efficacy of hormonal therapy by results on biopsy (number of germ cells) performed at time of orchiopexy. A variety of terms for measurement of fertility on testis biopsies was noted (“mean

spermatogonia/tubule”, “normal” spermatogonia, “number of germ cells”, etc.) but overall the studies did not clarify if the cells counted were dark type A (Ad spermatogonia). This is important because these cells are thought to form the stem cells crucial to having normal number of sperm in the adult. No study to date has data to assess whether the increased number of germ cells observed on childhood biopsy is only a transient response to hormone treatment or a response lasting into adulthood. Hutson pointed out that the use of testis biopsy results in childhood has never been validated as a measure of subsequent fertility (12).

Since the review by Biers and Malone, a long term study was published by Kraft *et al.* concluding that testis biopsy in childhood was not a valid measure for fertility. They performed hormonal testing and semen analyses on men after 18 years of age with history of cryptorchidism who had orchiopexy in childhood, 91 with unilateral cryptorchidism and 19 with bilateral cryptorchidism. All boys had undergone bilateral testis biopsies at time of orchiopexy. They grouped the patients by germ cell histology (mild, moderate and severe) and by Ad spermatogonia histology (normal or abnormal). No significant differences were seen in semen analysis parameters across the different germ cell histology groups. Some semen analysis parameters were decreased in the group who had abnormal Ad spermatogonia compared to the group with normal Ad spermatogonia but, except for one parameter, all results were still in the normal range or the difference between the groups was not statistically significant. These authors concluded that total germ cell histology at unilateral orchiopexy was not a valid measure for fertility potential (19).

Biers and Malone reviewed three studies that used semen analysis results in adulthood to evaluate efficacy of childhood hormonal therapy, two concluding benefit and one showing a negative impact of hormonal treatment. Both of the studies reporting superior semen analysis parameters were from Hadziselimović and both studies evaluated post orchiopexy hormonal therapy (20,21). In 2001, Vinardi *et al.* reported that a significantly higher proportion of men who had orchiopexy alone in childhood had a normal sperm count ($>20 \times 10^6$ per mL) in adulthood compared to the group who had GnRH and hCG prior to orchiopexy (22). Neither of these studies were randomized controlled trials so recruitment bias cannot be excluded.

Several points should be noted about the papers reviewed by Biers and Malone (3). The only study reviewed comparing hormonal therapy to orchiopexy alone was the

one by Vinardi evaluating semen analyses in adulthood to assess efficacy of pre-orchioepexy hormonal treatment. Across all of these studies there was a wide range in age at time of hormonal treatment, multiple regimens of different hormones were employed and most of the treatment groups were small. Most studies included unilateral and bilateral cryptorchidism and did not stratify the results separately for bilateral UDT and two studies were on unilateral UDT only.

Several findings in unilateral cryptorchidism add to the evidence that childhood testis biopsies are not helpful. Abnormalities in the unilateral UDT and the contralateral normally descended testis were well documented by Huff *et al.* They reported on 767 boys with unilateral cryptorchidism who underwent orchiopexy between birth and 9 years old. They found abnormal histology with respect to germ cell number and Ad spermatogonia in the cryptorchid testes and in the normally descended contralateral testes, although less severe on the normal side (23). However, studies have not demonstrated a significant incidence of infertility in men with history of unilateral orchiopexy in childhood. This suggests that the findings on childhood testis biopsies are indeed not valid for measuring fertility or suggests that childhood orchiopexy alone is an effective treatment for fertility in unilateral cryptorchidism. In either case performing biopsy at time of orchiopexy does not appear to have value for diagnosing or treating fertility in this patient population.

The AUA Guideline published in August 2014 noted that no studies on long term fertility outcomes following hormonal therapy alone were found (24). This guideline did not recommend hormonal treatment to improve fertility in boys with cryptorchidism. However, I would call attention to two statements in this guideline for which I believe there is not adequate supporting data when the study by Kraft *et al.* is taken into account. They stated that GnRH or hCG prior to orchiopexy “has been shown to improve the fertility index on biopsies obtained at the time of orchiopexy”. The study by Kraft *et al.* demonstrated that childhood biopsy is not a valid measure of fertility. In another section of the guideline they stated that childhood testis biopsy may predict fertility in bilateral cryptorchidism. The study from Kraft *et al.* lends only minimal support for this statement. They compared semen analysis parameters (sperm density, count and motility) and hormone levels (FSH, LH, testosterone, and inhibin B) in adulthood between a group with childhood testis biopsy revealing normal number of Ad spermatogonia and a group with abnormal

number of Ad spermatogonia. In the boys who had bilateral cryptorchidism, they found that the group with abnormal Ad spermatogonia in childhood had sperm density in the abnormal range and lower than the group with normal Ad spermatogonia to a statistically significant degree. For the other two parameters on semen analysis and for all hormone levels there was not a significant difference between those with abnormal *vs.* normal number Ad spermatogonia in childhood (19).

When recommending a medication risk as well as benefit should be considered. There is mention in some of the papers that no significant side effects have been demonstrated but there is not sufficient long term data to be certain of that.

Correlating a problem and/or treatment in early childhood to results in adulthood is difficult. It is challenging to obtain follow up on adequate numbers given how frequently people move and with no central data base (in countries without a national health services). The researchers who have published on this subject deserve much credit for trying to find a test in childhood that is a valid measure of fertility in adulthood. It is especially commendable that several researchers have been able to follow a fair number of children into adulthood and get them back in for blood draw and semen analyses. Putting all the data together, much valuable information has been gained.

Conclusions

Childhood testis biopsy is not a valid measure of fertility potential. There is not a role for childhood testis biopsy in unilateral cryptorchidism. In bilateral cryptorchidism there is minimal data to support that one parameter on childhood testis biopsy (number of Ad spermatogonia) may identify a group with abnormal sperm density in the adult. This parameter did not correlate with any of the other measurements of infertility. The predictive value for paternity from this one parameter on childhood biopsy has not been established. Testis biopsies in cases of bilateral orchiopexy may be appropriate in research protocols but the data do not justify routine testis biopsies in bilateral cryptorchidism.

I believe there is adequate data to conclude that hormonal therapy is not useful in unilateral cryptorchidism. Orchiopexy alone in early childhood results in fertility potential about the same as the general population. Thus, experimenting with hormonal therapy in this population to improve germ cell counts on biopsies in childhood or semen

analyses in adulthood does not seem reasonable.

In bilateral cryptorchidism, there is a significant risk of infertility and a prospective randomized controlled trial to evaluate hormonal treatment or other treatment is needed.

Review of the past studies will help in designing future studies. Areas identified that need attention in future studies to be able to conclude whether or not to recommend hormonal therapy in bilateral cryptorchidism include: (I) outcome data should be validated measures of fertility; (II) outcome of hormonal therapy should be compared to orchiopexy alone; (III) the interventions, hormones and/or orchiopexy, should be administered at the same age (or reasonable range of age); and (IV) the study population needs to be powered sufficiently to yield statistically significant results. A multi-institutional study may be helpful in achieving sufficient numbers and long term follow up especially as bilateral cryptorchidism is less common.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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