Fertility Potential is Compromised in 20% to 25% of Boys with Nonsyndromic Cryptorchidism despite Orchiopexy within the First Year of Life

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Abbreviations and Acronyms

Ad = type A dark

AdS/T = number of type A dark spermatogonia per seminiferous tubule cross-section

FSH = follicle-stimulating hormone

G/T = number of germ cells (gonocytes, spermatogonia and type A dark spermatogonia) per seminiferous tubule cross-section

LH = luteinizing hormone

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Study received Institutional Review Board approval (IRB No. KF-01299830) and Regional Ethics Committee of Copenhagen approval (No. H-18063061).

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See Editorial on page 672.

Purpose: One of the concerns surrounding cryptorchidism is the risk of impaired fertility. Current guidelines recommend orchiopexy at age 6 to 12 months to optimize fertility outcome. We evaluated the fertility potential of boys with nonsyndromic cryptorchidism who underwent orchiopexy within the recommended age range to clarify the need for eventual supplemental treatment modalities.

Materials and Methods: We retrospectively evaluated mini-puberty hormones (follicle-stimulating hormone, luteinizing hormone and inhibin B) and testicular biopsies from boys with cryptorchidism who underwent orchiopexy within the first year of life between 2010 and 2019. We histologically analyzed germ cell number and type A dark spermatogonia number per seminiferous tubule cross-section in relation to normal values.

Results: Of the 333 boys with nonsyndromic cryptorchidism 83 (25%, 21% with bilateral cryptorchidism) had a reduced number of germ cells. A total of 70 boys (21%) had low serum inhibin B, of whom 32 (46%) had a decreased number of germ cells and 23 (33%) had a decreased number of type A dark spermatogonia ($p < 0.01$). Overall, 75 boys (23%) had no type A dark spermatogonia present.

Conclusions: Despite early and successful orchiopexy, 20% to 25% of boys with cryptorchidism may be at risk for infertility based on hormonal and histological data. Blood test and testicular biopsy are mandatory to identify boys at high risk for infertility, in whom additional treatment modalities and followup may be needed.

Key Words: spermatogonia; cryptorchidism; germ cells; infertility, male; testis

EUROPEAN and U.S. guidelines recommended corrective surgery for congenital cryptorchidism within the first 18 months of life,[1,2] while the Nordic consensus is that orchiopexy should be performed at age 6 to 12 months.[3] The main argument for this strategy regarding future fertility potential is severe deterioration of the germinal epithelium already described at age 1 year compared to normal. Orchiopexy seems rational to perform while there are likely still germ cells present in the cryptorchid testes.[4] In an epidemiological cohort study of 350,835 males Schneuer et al recently showed that even boys undergoing orchiopexy within the first 18 months of life are at increased risk in adulthood for needing assisted reproductive technologies to father children.[5] They report that for every

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6 months of delay in orchiopexy there is a 5% increased risk of future use of assisted reproductive technologies and a 1% reduction in paternity.

Histological evaluation of G/T has been a standard way of determining fertility potential in boys with cryptorchid testes.[6–8] Subsequently it has been claimed that the most important event for later fertility is the first postnatal maturational step of germ cells, which is the transformation of gonocytes into Ad spermatogonia. Hadziselimovic and Herzog matched histological findings of the testes at early orchiopexy from 31 patients with a later spermiogram.[9] Ad spermatogonia were present at early orchiopexy in 17 of 18 men (94%), who had a mean total sperm count of 40 million or greater per ejaculate. By contrast, despite successful early surgery, Ad spermatogonia were absent in 12 of 13 patients (92%) with abnormal spermiograms.

Inhibin B is produced by Sertoli cells and the serum level partly reflects the histological state of seminiferous tubules. During the last decade measurement of serum inhibin B in boys with cryptorchidism has become increasingly useful when evaluating fertility potential.[10–13] We assessed the fertility potential of boys with nonsyndromic cryptorchidism who were operated on during the first year of life using the aforementioned histopathological and hormonal parameters to clarify the need for eventual supplementary treatment modalities. Even when infants with cryptorchidism were operated on early according to guidelines, we hypothesized that a significant number of boys were at risk for later infertility.

MATERIALS AND METHODS

A total of 446 consecutive boys younger than 1 year old underwent surgery for cryptorchidism between 2010 and April 2019. If surgery was scheduled during the 1-year birthday month, the case was included. Only patients with congenital cryptorchidism were included in the study. Boys with syndromic cryptorchidism or associated anomalies (27) were excluded, as were those with vanished testes (48), those who had undergone orchiopexy with primary repair of symptomatic inguinal hernia (3) and those for whom the hormonal profile was unavailable (22). Cases where the biopsy samples were inaccessibly stored off-site or biopsy was inconclusive (13) were also excluded. Thus, 333 boys with nonsyndromic cryptorchidism (median age 274 days, range 34 to 390) were retrospectively included for evaluation of fertility potential. Of these patients 69 (21%) had bilateral cryptorchidism and 264 had unilateral cryptorchidism (139 on right and 125 on left side). Among 82 nonpalpable testes 21 intra-abdominal testes were verified by laparoscopy.

The study was conducted according to the Helsinki II Declaration, and informed consent for blood samples and surgery with biopsies for clinical and research use was obtained from the parents. The study received Institutional Review Board approval (IRB No. KF-01299830) and Regional Ethics Committee of Copenhagen approval (No. H-18063061).

Hormonal Assays

Blood samples were obtained by venipuncture between 8:00 and 11:00 a.m. After 10 minutes of centrifugation at 2,000 G the serum samples were stored between −20C and −80C until analysis. Serum inhibin B was measured using a commercially available ELISA with research kit as recommended by the manufacturer (Serotec Ltd., Oxford, United Kingdom). The lower detection limit was 5 pg/ml and measurements were made in duplicate. This kit has been used in previous studies in normal boys and those with cryptorchidism.[14] Serum LH and FSH levels were measured with Delfia®, a sandwich electrochemiluminescence immunoassay. The limit of detection of FSH and LH was 0.05 IU/l. Normal reference serum levels of inhibin B, LH and FSH were defined as described by Andersson et al.[14]

Testicular Biopsies

A total of 402 testicular biopsies from 333 boys with cryptorchidism were evaluated. There were no surgical complications related to performance of testicular biopsies. All 2 to 5 mm^3 specimens were fixed in Stieve solution, embedded in paraffin and cut into serial sections of 2 μm. Sections were stained with hematoxylin and eosin, M3619 (monoclonal mouse anti-human podoplanin, clone D2-40, 1:25 concentration; Dako, Glostrup, Denmark), 12E7 (antibody CD99/MIC2, 1:100 concentration; Dako) and anti-placental alkaline phosphatase (clone PL8-F6, 1:200 concentration; BioGenex, Fremont, California). In blinded fashion G/T, including gonocytes and Ad spermatogonia, and AdS/T were measured from at least 100 tubular cross-sections, and mean AdS/T and G/T were calculated. G/T was considered normal when the value was above the lower range interval established by our 2 previously published normal materials (n=72).[4,15] Mean AdS/T was considered normal (0.01 or greater) or decreased (less than 0.01) based on previously published studies.[16,17] All biopsy specimens were reviewed by a single pathologist (EC-L).

Statistical Analyses

Nonparametric statistics were used for analyses as data were not normally distributed. Mann-Whitney U test was used for comparison of 2 independent groups. Spearman rank correlation was used to measure degree of association between 2 variables. For comparisons between categorical variables we used the Fisher exact test. A 2-sided p value of less than 0.05 was considered significant. Data were analyzed using GraphPad Prism®, version 8.1.1.

RESULTS

Serum inhibin B levels in boys with cryptorchidism are shown in figure 1 and table 1 according to age. Serum inhibin B significantly correlated with G/T ($p < 0.001$) and AdS/T ($p = 0.02$). A total of 70 boys (21%) had decreased serum inhibin B and 281 (84%) had levels below the median (fig. 1). Of patients with low serum inhibin B 32 (46%) also had reduced G/T.

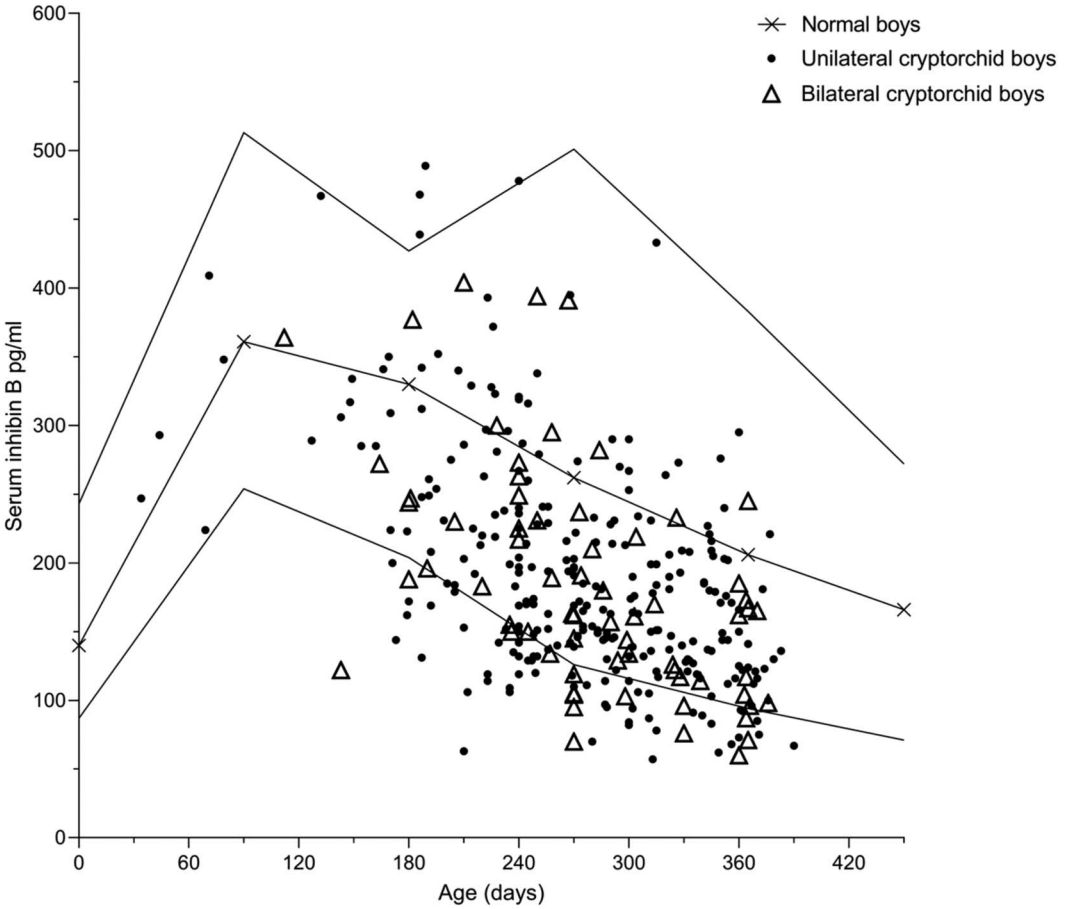

Figure 1. Serum inhibin B of boys with nonsyndromic cryptorchidism according to age compared to normal boys[14]

Median age was similar in bilateral and unilateral cases (273 vs 274 days, p = 0.34). As outlined in figure 1 and table 2, boys with bilateral and unilateral cryptorchidism had similar serum inhibin B levels and comparable rates below the normal range. Overall, 83 boys (25%) had reduced G/T (fig. 2, table 1). G/T was not lower in bilateral compared to unilateral cases (table 2). Furthermore, biopsy specimens revealed reduced AdS/T (range 0 to 0.0048) in 92 boys (28%) and the absence of Ad spermatogonia in 75 (23%; fig. 3 and tables 1 and 2). G/T was reduced in 62 of 92 cases (67%) with reduced AdS/T. Of the 70 boys with low serum inhibin B 23 (33%) had AdS/T less than 0.01.

Serum FSH was increased in 31 of 319 patients (10%) and was unavailable in 14 (fig. 4). Low serum inhibin B was observed in 13 of these cases (42%). Boys with bilateral cryptorchidism had higher median serum FSH (0.8 IU/l, range 0.2 to 4.0) than those with unilateral cryptorchidism (0.6 IU/l, range 0.1 to 3.5, p = 0.0009; table 2). Of boys with serum inhibin B and G/T below normal range 87% (60 of 69, FSH missing in 1) and 90% (71 of 79, FSH missing in 4), respectively, did not exhibit the expected feedback response with increased serum FSH.

Nonpalpable testes were located intra-abdominally in 21 cases (6%). These cases trended toward lower median serum inhibin B (150 pg/ml, range 84 to 309) compared to those involving more distally placed testes (173 pg/ml, range 57 to 489, p = 0.20). Two boys with unilateral cryptorchidism had no germ cells based on histological classification of the entire biopsy. One of these boys had impaired serum inhibin B.

DISCUSSION

Our study demonstrates that 20% to 25% of boys with nonsyndromic cryptorchidism probably already belong to a group at high risk for infertility even after undergoing orchiopexy during the first year of life. It has been demonstrated in males with bilateral cryptorchidism that if prepubertal G/T is reduced in both testes, azoospermia or severe abnormal spermiograms can be observed in adulthood.[7] In unilateral cases G/T in the prepubertal testicular biopsy also has prognostic value for fertility potential in adulthood.[18] Of men with persisting unilateral cryptorchidism 15% to 20% have azoospermia since the same pathological mechanism may affect both testes.[19] In other words, based on certain endocrine

Table 1

	Age		p Value
	Less than 9 Mos	9 Mos—Less than 12 Mos	
	Unilat cryptorchidism		
No. pts (%)	119 (45)	145 (55)	—
Median days age (range)	227 (34—269)	315 (270—390)	—
Serum inhibin B:			
Median pg/ml (range)	223 (63—489)	150 (57—433)	<0.0001 (Mann-Whitney U test)
No. below normal range (%)	27 (23)	26 (18)	0.34 (chi-square test)
Serum FSH:			
Median IU/l (range)	0.78 (0.06—3.54)	0.51 (0.05—2.40)	<0.005 (Mann-Whitney U test)
No. above normal range (%)	14 (12)	5 (3)	<0.01 (chi-square test)
G/T:			
Median (range)	1.29 (0.04—4.48)	0.620 (0—3.414)	<0.0001 (Mann-Whitney U test)
No. below normal range (%)	21 (18)	43 (30)	<0.05 (chi-square test)
AdS/T:			
Median (range)	0.023 (0—0.222)	0.009 (0—0.184)	<0.001 (Mann-Whitney U test)
No. less than 0.01 (%)	22 (18)	57 (39)	<0.0005 (chi-square test)
No. absence of Ad spermatogonia (%)	19 (16)	45 (31)	<0.005 (chi-square test)
No. intra-abdominal location (%)	4 (3)	11 (8)	0.14 (chi-square test)
	Bilat cryptorchidism		
No. pts (%)	27 (39)	42 (61)	—
Median days age (range)	236 (112—269)	325 (270—376)	—
Serum inhibin B:			
Median pg/ml (range)	231 (122—404)	132 (60—282)	<0.0001 (Mann-Whitney U test)
No. below normal range (%)	7 (26)	10 (24)	0.84 (chi-square test)
Serum FSH:			
Median IU/l (range)	0.87 (0.21—4.01)	0.70 (0.24—2.90)	0.41 (Mann-Whitney U test)
No. above normal range (%)	4 (15)	8 (19)	0.65 (chi-square test)
G/T:			
Median (range)	1.36 (0.06—2.97)	0.62 (0.06—4.14)	<0.005 (Mann-Whitney U test)
No. below normal range (%)	6 (22)	13 (31)	0.43 (chi-square test)
AdS/T:			
Median (range)	0.026 (0—0.148)	0.0185 (0—0.214)	0.23 (Mann-Whitney U test)
No. less than 0.01 (%)	3 (11)	10 (24)	0.19 (chi-square test)
No. absence of Ad spermatogonia (%)	3 (11)	8 (19)	0.38 (chi-square test)
No. intra-abdominal location (%)	2 (7)	4 (10)	0.76 (chi-square test)

According to normal material reference values, median values of serum inhibin B, serum FSH and G/T are expected to be significantly higher in younger age group.

insufficiency causing maldevelopment, which both testes are subject to, cryptorchidism may be a bilateral disease even if only 1 testis fails to descend properly. This concept is supported by the findings of Hadziselimovic and Hoecht, who describe reduced G/T and AdS/T of the scrotal testis in 70% of prepubertal boys with unilateral cryptorchidism.[16] However, some cases represent an isolated unilateral pathology. Nonetheless, a recent study of sperm retrieval rates for assisted reproductive technologies in 225 men with a history of cryptorchidism indicated similar outcomes in men with a history of unilateral cryptorchidism (80) compared to bilateral cryptorchidism (145), suggesting that unilateral cryptorchidism in boys could reflect bilateral testicular impairment.[20]

Table 2

	Unilat Cryptorchidism	Bilat Cryptorchidism	p Value
No. pts (%)	264 (79)	69 (21)	—
Median days age (range)	274 (34—390)	273 (112—376)	0.34
Serum inhibin B:			
Median pg/ml (range)	177 (57—489)	165 (60—404)	0.69 (Mann-Whitney U test)
No. below normal range (%)	53 (20)	17 (25)	0.41 (chi-square test)
Serum FSH:			
Median IU/l (range)	0.60 (0.05—3.54)	0.80 (0.21—4.01)	<0.001 (Mann-Whitney U test)
No. above normal range (%)	19 (7)	12 (17)	<0.01 (chi-square test)
G/T:			
Median (range)	0.90 (0—4.48)	0.75 (0.06—4.14)	0.69 (Mann-Whitney U test)
No. below normal range (%)	64 (24)	19 (28)	0.57 (chi-square test)
AdS/T:			
Median (range)	0.015 (0—0.222)	0.019 (0—0.214)	0.12 (Mann-Whitney U test)
No. less than 0.01 (%)	79 (30)	13 (19)	0.07 (chi-square test)
No. absence of Ad spermatogonia (%)	64 (24)	11 (16)	0.14 (chi-square test)
No. intra-abdominal location (%)	15 (6)	6 (7)	0.36 (chi-square test)

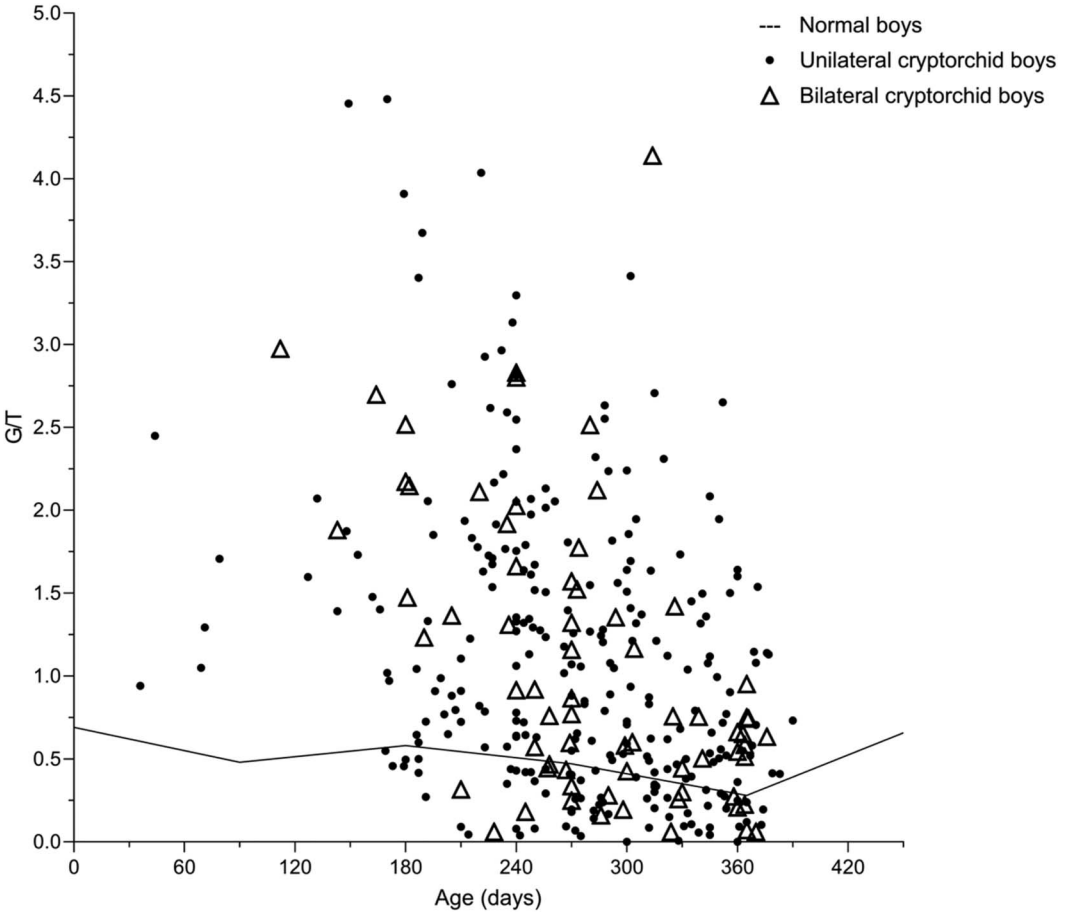

Figure 2. G/T of boys with nonsyndromic cryptorchidism according to age in reference to lower normal range of G/T values[4,15]

G/T and fertility index (percentage of tubular cross-sections with presence of germ cells) have been regarded as the gold standards for fertility prognosis in boys with cryptorchidism. We have previously observed that G/T is well correlated to AdS/T in testicular biopsy materials from boys with cryptorchidism after mini-puberty.[12] Other research groups have found that AdS/T in prepubertal cryptorchid testes is a more reliable parameter to evaluate the risk of infertility in adulthood.[9,16,21] Regardless of whether G/T or AdS/T is used, there is good evidence that at least 20% of boys with cryptorchidism operated on during the first year of life are at high risk for infertility based on hormonal findings.

It is noteworthy that up to 25% of boys in our study had severely decreased G/T. This finding is in accordance with previously published results indicating that about 25% of boys with congenital cryptorchidism are born with a reduced number of germ cells and the same percentage have a decreased number of germ cells at age 1 year.[4] However, early timing of surgery may have a positive impact on G/T and AdS/T, especially in unilateral cases, even in this young age group (table 1). Although germ cell numbers in some patients may improve following surgery, others may deteriorate further due to impaired hormonal stimulation in mini-puberty.[11,16,22,23] A recent study indicated that undescended testes grow faster relative to the scrotal testes when orchiopexy is conducted before age 1 year based on ultrasonographic measurement of the testes.[24] This finding is in accordance with a previous study from another research group.[25]

Understanding the hypothalamic-pituitary-gonadal axis and the effect on cryptorchidism is critical for assessment and treatment of infertility. The hormonal findings in the present study correspond well with the literature. It is noteworthy that 46% of boys with low serum inhibin B also had reduced G/T. In our analysis 2 boys with unilateral cryptorchidism completely lacked germ cells in the biopsy, of whom 1 had impaired serum inhibin B. As a prognostic parameter for fertility potential, the level of inhibin B, which is produced by Sertoli cells, is probably not as precise as G/T or AdS/T, although there is some correlation.[13]

We previously observed that Sertoli cell number per tubular cross-section is significantly associated with G/T and AdS/T in boys up to age 35 months with cryptorchidism, and that there is a significant correlation between serum inhibin B and G/T.[13]

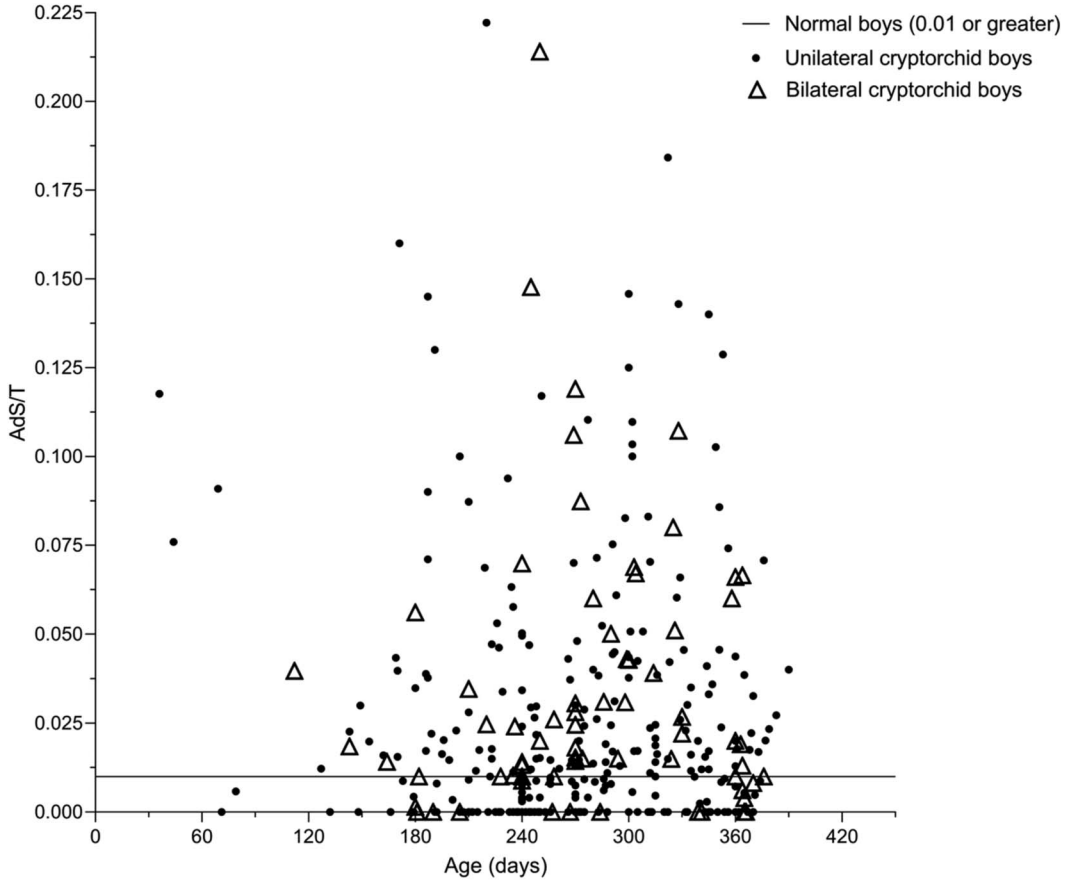

Figure 3. AdS/T according to age in reference to lower normal range of AdS/T values (greater than 0.01)

Serum inhibin B was not associated with AdS/T in that study, which is in accordance with the findings of Verkauskas et al, who evaluated males 7 to 65 months old with cryptorchidism.[26] However, our previous research in males 0.5 to 13 years old with cryptorchidism revealed a significant correlation between AdS/T and inhibin B.[27] Inhibin B has shown to be a promising marker of the competence of Sertoli cells and spermatogenesis in prepubertal and adult males.[28] Our hormonal findings indicating 2 significant groups having either hypergonadotropic hypogonadism or FSH insufficiency (hypogonadotropic hypogonadism) are in agreement with other studies.[11,16] Moreover, it is generally accepted that intra-abdominal testes impair the quality of the germinal epithelium compared to more distally placed cryptorchid testes.

The main strength of our study is the population, which is the largest series of males operated on for cryptorchidism with testicular biopsy in the first year of life. Limitations of our study include the retrospective nature and lack of paternity data, which are hard to gather because of the time span in such consecutive series. A specific weakness of our study is related to normal germ cell evaluation due to the sparse material available in the literature. However, the lower normal range of G/T in the first year of life seems evidence based, and we emphasize the importance of normal and cryptorchid germ cell counts performed in the same laboratory by a collaborating staff. In contrast, lower normal range of AdS/T is mainly defined according to clinical practice.

Another weakness of our study is related to the lack of bilateral biopsy specimens in boys with unilateral cryptorchidism, so the estimated risk of bilateral pathology relies on studies in the literature. However, despite this limitation, including interpretations of the predictive value of inhibin B, it seems well documented that there will still be a significant risk of infertility in adulthood for at least 20% of boys with congenital cryptorchid testes undergoing orchiopexy according to the guidelines. It may, of course, be questioned whether the latter limitations of the study allow such a definitive conclusion. However, we have no exact parameters to predict which of these boys at high risk for infertility will have sufficiently improved fertility potential following surgery, as described previously.[11,22] According to our prior studies, possibly a third of these cases will improve postoperatively. Therefore, these patients require regular followup with physical

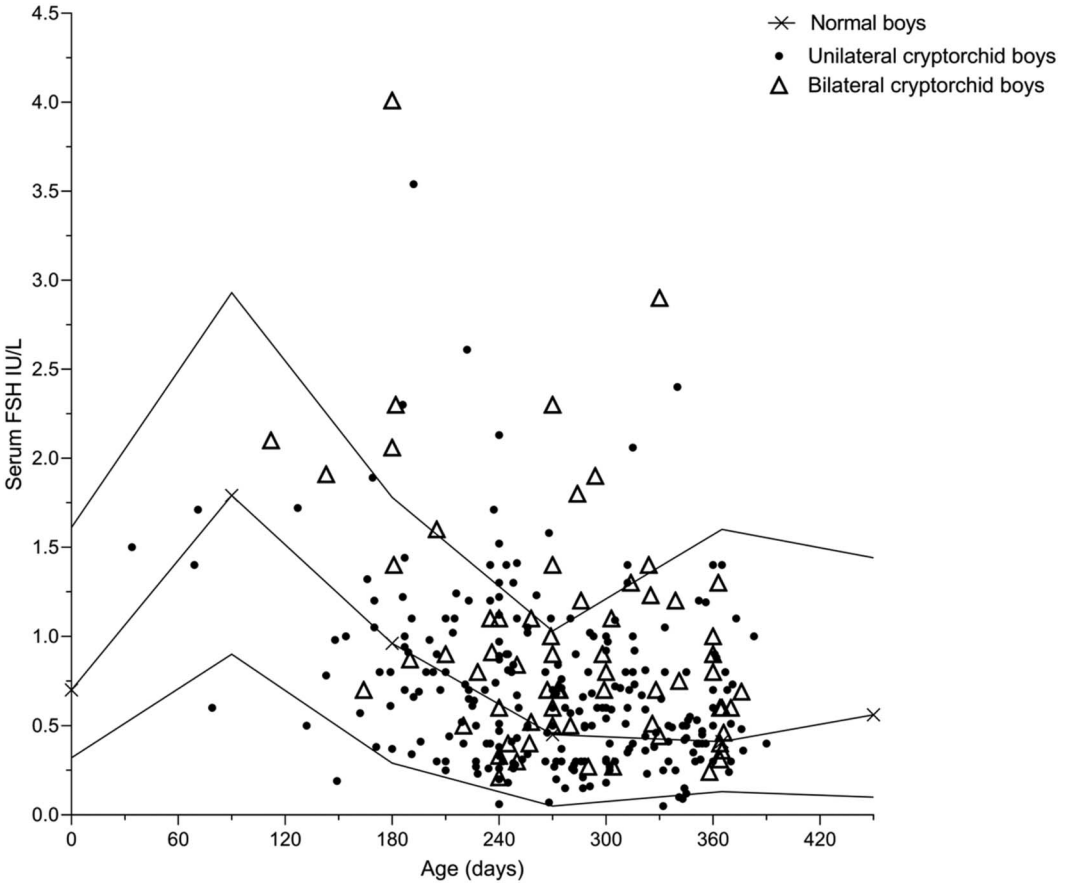

Figure 4. Serum FSH of boys with nonsyndromic cryptorchidism according to age in reference to normal median and upper and lower normal values.[14]

examination and hormonal blood samples during childhood.

Information regarding the fertility status of testicular tissue, eg G/T and AdS/T, in relation to hormonal profile can help clinicians determine fertility potential and clarify the need for supplementary treatment. Testicular biopsy is not typically used for prognostic purposes by American pediatric urologists. Recommendations to perform testicular biopsy need to be interpreted cautiously in clinical situations as the implications can be significant. A prospective study with good clinical correlation in individual patients can validate the information from this retrospective study. However, this will be difficult to achieve.

CONCLUSIONS

Based on the literature and the current results, we recommend considering adjuvant luteinizing hormone-releasing hormone treatment in boys with cryptorchidism who have insufficient genuine gonadotropin stimulation following surgery, culminating in impaired Ad spermatogonia maturation and decreased G/T.[29,30] Boys with serum inhibin B or G/T below normal range and no feedback response with increased FSH could be further evaluated at followup with a gonadotropin-releasing hormone stimulation test. Cryopreservation of testicular tissue for later fertility treatment could be an option in instances of failure of adjuvant treatment with luteinizing hormone-releasing hormone.[29] However, to avoid reoperation with biopsy, some parents may choose biopsy for cryopreservation at the initial bilateral orchiopexy, although they should be informed that the procedure may actually be indicated in less than 20% of the cases because some boys may have fertility potential improved sufficiently by surgery.[29]

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EDITORIAL COMMENTS

Combination of histological data and inhibin level provides relevant results. Around 20% of boys with cryptorchidism may have fertility compromised despite early surgery. Thus, early orchiopexy may not be the panacea for these patients—parents are actually aware that early surgery does not guarantee normal fertility—and the authors propose tailored hormonal treatment based on histology of the testis, FSH plasma level and gonadotropin-releasing hormone stimulation test in some instances.

These data are of concern but remain predictive. Other positive elements may be considered. The effect of early surgery may improve fertility potential in some cases with normalizing FSH (reference 22 in article). Biopsies performed in cases of unilateral orchiopexy only reflect the condition of that testis. Even if contralateral abnormalities are reported (and it is quite likely that undescended testis is a general disease of the testis itself and not only a defective migration), the opposite testis may at least partly compensate for this functional defect (reference 16 in article).

Long-term prospective studies focusing on paternity rate will be the next step in evaluating the actual fertility of these patients to specify the indications of testicular biopsies and to distinguish patients who will have improved fertility potential

following surgery from those who will require adjuvant hormonal treatment. Such studies are truly a methodological challenge (reference 5 in article).

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Testicular biopsies have implicated decreased germ cell count as the histological basis of subfertility in patients with undescended testis. Recently revised guidelines on management of cryptorchidism recommend orchiopexy in infancy to preserve fertility, with the Nordic consensus suggesting earliest intervention at age 6 to 12 months (reference 3 in article). The authors retrospectively reviewed hormonal and testis biopsy results in a cohort undergoing early orchiopexy in compliance with these guidelines. What is most striking about their findings is the percentage of patients who despite early intervention had a reduced number of germs cells and type A dark spermatogonia. Differences in histology were more significantly pronounced in those undergoing relatively delayed orchiopexy (age 9 to 12 months), arguing all the more for early intervention.

The authors conclude that at least 20% of boys with unilateral undescended testis may struggle with infertility in adulthood. Paternity remains the gold standard for assessing fertility, and the data of Lee et al in men who formerly had unilateral cryptorchidism is reassuring in that the paternity rate reaches 89.5%, approaching the 94% paternity rate found in the general population.[1] The authors recognize that testicular biopsy during orchiopexy is not routinely performed in the U.S. to provide prognostic information, and despite their robust data, this practice is unlikely to change soon. However, what these results emphasize is our obligation to adhere to all American Urological Association guidelines for cryptorchidism (reference 2 in article), not only treating with surgical intervention, but also providing appropriate counseling regarding long-term fertility.

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REPLY BY AUTHORS

Our data indeed support stressing early orchiopexy in boys with congenital cryptorchidism, as soon as it is apparent that mini-puberty is unlikely to lead to testicular descent. We previously evaluated followup of 65 men who had undergone unilateral orchiopexy before puberty.[1] Our findings support those of Lee et al (reference 1 in comment by Kraft), that probably only about 10% would struggle with infertility. However, our previous study also indicated that almost all of these patients had gonadotropin insufficiency and, therefore, may have benefited from adjuvant hormonal treatment in childhood. Gonadotropin insufficiency is found in a much larger proportion of individuals with bilateral cryptorchidism.

We agree that further investigations are needed to specify the prognostic value of testicular biopsy and to distinguish patients who will have improved fertility potential following surgery from those who will require additional treatment modalities. Solid phase IV pharmaceutical studies on hormonal therapy are also still required. However, we strongly believe that cryptorchidism is a complex condition. As such, before orchiopexy it is important to involve the parents in decisions that address the potential risk of future need for additional fertility preserving techniques, whether via adjuvant hormonal treatment, cryopreservation of testicular tissue in infancy or assisted reproductive technologies, including for instance surgical sperm retrieval in adulthood.

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