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# Review Article

# THE EPIDEMIOLOGY OF CONGENITAL CRYPTORCHIDISM, TESTICULAR ASCENT AND ORCHIOPEXY

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ABSTRACT

Purpose: The frequency, significance and possible etiology of testicular ascent (acquired cryptorchidism) are characterized in light of the known incidence and natural history of congenital cryptorchidism, and data provided by longitudinal and epidemiological studies of ascended testes and orchiopexy rates.

Materials and Methods: We comprehensively reviewed the literature addressing the epidemiology of congenital and acquired cryptorchidism and orchiopexy.

Results: The incidence of congenital cryptorchidism in full-term males at birth (2% to 4%) and at age 1 year (approximately 1%) has not increased in the last few decades. The risk of ascent may be as high as 50% in cases where 1 testis is significantly retractile. Ascended testes are typically unilateral (77%), identified in mid childhood and located distal to the inguinal canal (77%). Ascended and significantly retractile testes may be prone to the same germ cell maldevelopment seen in congenital cryptorchidism. Cumulative orchiopexy rates in defined populations are 2% to 4%, and mean age at orchiopexy remains higher than expected (greater than 4 years), despite a long held standard of care that includes recommendation for surgery by age 2. These data suggest that cryptorchidism may be acquired in a significant subset of cases.

Conclusions: With close monitoring of young boys spontaneous ascent of testes from a scrotal to a suprascrotal position may be observed with time, due to either true or apparent testicular ascent, with possible adverse effects on germ cell development and fertility potential. Patients with significant testicular retractility appear to be at highest risk for acquired cryptorchidism, and should be followed closely at yearly intervals until puberty.

KEY WORDS: cryptorchidism/epidemiology, testis/abnormalities, testis/surgery

Cryptorchidism, or undescended testis, is the most common genital anomaly identified at birth in males. In 1964 Scorer reported an incidence of cryptorchidism in newborns 2,500 gm or greater and at age 1 year of 2.8% and 0.7%, respectively.[1] Studies of military recruits in adulthood confirmed no change in the 0.8% prevalence seen at age 1 year, with the implication that changes in testicular position beyond infancy do not occur.[2] During the last 30 years many reports have suggested that this paradigm is incorrect. Increasing childhood orchiopexy rates several times higher than expected based on the prevalence of the disease are noted and attributed to inappropriate surgery for retractile testes.[3] However, longitudinal studies of individuals and groups of patients indicate that many patients continue to be diagnosed and treated later in childhood, and that affected testes are not infrequently diagnosed as scrotal at an earlier age. We reviewed the available literature to define the epidemiology of congenital cryptorchidism and testicular ascent (acquired cryptorchidism), and their possible effects on rates and ages at orchiopexy as reported in large series.

## DEFINITIONS

The criteria used to define testicular position in childhood are not always clearly delineated.[4,5] The true position of the testis may be difficult to ascertain because of significant retractility of the testis in otherwise normal prepubertal boys. However, even the testis that can be maintained in a stable, but not dependent, scrotal position may be considered abnormal.[1,4] In early epidemiological studies Scorer defined normal descent as an upper pubis to mid testis measurement of at least 4 cm, although 5 to 8 cm is the distance measured in the "vast majority" of normal boys.[1] More recent definitions are qualitative, ie a normal testis is one that is visible and palpable at the base of the scrotum without need for manipulation.[4,5]

The John Radcliffe Hospital Cryptorchidism Study Group compared qualitative testicular position (scrotal vs nonscrotal) with Scorer's measurements in their studies, and found that the measurements increased the overall incidence of cryptorchidism by approximately 10%.[6] **Retractile testes** are those that move spontaneously out of the scrotum on a regular basis and/or on initial examination but will return, either spontaneously or with manipulation, to a *dependent* scrotal position and remain there for a finite but ill defined period. By this and most definitions retractile testes are considered a variant of normal, become nonretractile (fully descended) at puberty and are not associated with impairment of fertility. These testes are distinguished from **gliding testes**, which can also be manipulated into a satisfactory scrotal position but will retract quickly once released and are considered the most distal form of true undescended testis.[7,8] **Testicular ascent** and **acquired cryptorchidism** pertain

to testes that are documented to be in scrotal position at least once after birth but subsequently will not remain in satisfactory scrotal position.[9,10] This definition does not include testes identified as being undescended after inguinal surgery.

## INCIDENCE AND NATURAL HISTORY OF CONGENITAL CRYPTORCHIDISM

Documentation of testicular position is facilitated at birth in males without scrotal pathology such as hernia and hydrocele because the cremasteric reflex is rarely active during the first 6 months of life.[11] Once the cremasteric reflex is active, assessment of testicular position becomes more difficult. Several large series have addressed the incidence of congenital isolated (nonsyndromic) cryptorchidism. Including only those males born at 2,500 gm or greater, the incidence of cryptorchidism has been noted to be 2.2% to 3.8%, and unilateral cases occur twice as often (table 1).[1,6,9,12–16] Of full-term males noted to have cryptorchidism at birth spontaneous descent is reported to occur in 50% to 70%, usually by age 1 to 3 months, with descent at 6 to 9 months occurring rarely. Scorer noted that one-third of spontaneously descending testes failed to reach a fully dependent position, particularly if descent did not occur in the first month of life.[1] Higher testes and those associated with smaller relative scrotal size are less likely to descend spontaneously.[6] In contrast, smaller or premature neonates present differently, with higher rates of cryptorchidism (20% to 30%), bilateral presentation (50% to 75%) and complete spontaneous descent (80% to 90%), which may occur later in the first year of life. Suggestions that the incidence of congenital cryptorchidism has been increasing[3] are not confirmed by these prospective studies, which suggest no change or even a decrease in incidence with time.[14,16]

Job et al reported blunting of the normal testosterone and gonadotropin surge at age 2 to 3 months in males with persistent cryptorchidism as compared to those with spontaneously descending testes and controls.[17] Consequently, they hypothesized that postnatal descent occurs in response to this surge and that hypothalamic-pituitary-gonadal axis deficiency is associated with persistent cryptorchidism. However, such deficiency was not documented by others in studies of basal and stimulated cryptorchidism at age 3 months, and in some series many testes descended in the first month of life, before the hormonal surge.[1,15,18] Moreover, after initial spontaneous descent in early infancy testicular reascent was noted in as many as 38% of the boys followed to age 1.[6] This observation suggests that testes may appear to descend with increasing hormone levels but subsequently reascend as these levels return to baseline. A similar phenomenon occurs in some boys given hormone therapy for cryptorchidism, in whom complete response is noted but recurrent cryptorchidism is identified at some point after completion of therapy.[19]

## PREVALENCE OF RETRACTILE AND CRYPTORCHID TESTES IN CHILDHOOD

The prevalence of cryptorchidism at age 1 year (0.8% to 1%) is similar to that recorded in military recruits examined in the 1940s (table 1).[2] This finding has supported a widely held and long-standing view that spontaneous descent will not occur after the first year of life. Surprisingly, the prevalence of cryptorchidism in prepubertal boys is reportedly 1.7% to 4%.[3,20,21] The higher than expected rates are attributed to observer error due to the frequency of significantly retractile testes in young boys.[3] Indeed, Farrington noted a progressive increase in the proportion of testes not present in the scrotum on initial examination after the first 6 months of life, from 15% to a maximum incidence of 30% by age 4 years, a decrease by age 6 and absence by age 13.[11]

Although retractile testes are not intrinsically pathological, marked retractility hinders adequate determination of where the testes truly reside in the absence of cremasteric activation. As noted by Johnston, retractile testes may "reside for lengthy periods in the groin" but they can "readily be manipulated to the bottom of the scrotum where, after puberty, [they] will reside permanently and function normally. . .."[22] Other evidence suggests that the natural history of retractile testes is not always benign. In the first longitudinal study of its kind with 5-year followup Wyllie noted that unilaterally retractile testes in 100 boys attained a higher position and/or smaller size as compared to the normally descended partner in 64 cases.[23] Orchiopexy was performed in 45 patients, and others who did not undergo surgery were noted to have small (8 to 10 cc) upper scrotal testes after puberty. Wyllie noted that the "complexity of the retractile testis has been overlooked" and that signs of pathological retractility include rapid retraction, tightness of the cord or pain with manipulation of the testis into the scrotum and relative decrease in testicular size.[23] In addition to reiteration of these points, Goh and Hutson have suggested that retractility is pathological if testes spend "a substantial part of the time" out of the scrotum.[24] However, the frequency of cremaster muscle activation is difficult to document and as an isolated phenomenon has not been linked to subfertility based on limited available data.[25]

## SPONTANEOUS TESTICULAR DESCENT AFTER INFANCY

As noted previously, the likelihood of spontaneous testicular descent after the first year of life is considered low based on epidemiological data. Serial examination without treatment of cryptorchidism is rarely reported. Occasional descent noted in the placebo arm of double-blind studies of hormonal therapy may be due to misdiagnosis of retractile testes.[19] However, Johnson reported that spontaneous complete descent occurred between ages 7 and 17 years in 313 of 544 boys (57.5%) followed nonoperatively.[20] In contrast, Bremholm Rasmussen et al followed a large cohort of boys with bilateral cryptorchidism nonoperatively with annual examinations through puberty.[26] They reported the long-term fertility potential of 45 men from this group whose testes were at the external ring, superficial inguinal pouch and/or prescrotal positions but descended spontaneously between ages 10 and 16 years (mean 12). In these men the testes were reportedly dependent in the scrotum but were frequently borderline or

TABLE 1. *Incidence of congenital cryptorchidism in full-term and/or 2,500 gm or greater newborns*

| References | No. Pts | % Affected | | | % Unilat/Bilat |
|---|---|---|---|---|---|
| | | Birth | 3 Mos | 1 Yr | |
| Scorer[12] | 1,500 | 3.4 | — | — | — |
| Villumsen and Zachau-Christiansen[9], Beumann et al[13] | 4,500 | 1.8 | — | 0.7 | 71/29 |
| Scorer[1] | 3,222 | 2.8 | 0.9 | 0.7 | 89/11 |
| Radcliffe[6]* | 7,032 | 3.8 | 1.4 | — | 66/34 |
| Berkowitz et al[14] | 6,360 | 2.2 | 0.9 | 0.9 | 55/45† |
| Thong et al[15] | 882 | 2.4 | — | 0.8 | 71/29 |
| Ghirri et al[16] | 9,343 | 3.4 | — | 1.2–1.5 | 66/34† |

* John Radcliffe Hospital Cryptorchidism Study Group.
† All affected males (preterm and full term).

subnormal in size (75%) and associated with subnormal sperm concentration (53%). The subfertility in this group suggests that true cryptorchidism was present despite apparent complete descent at puberty. These patients may be similar to those whose testes descend partially after birth but remain significantly retractile or in a high scrotal position throughout childhood and are smaller, softer, higher and at higher risk for decreased spermatogenesis in adulthood.[1,6,22,23] However, in unilateral cases no clinical impact on paternity would be expected, as noted for males with treated unilateral cryptorchidism.[27]

TABLE 3. *Estimated cumulative incidence of orchiopexy in defined populations*

| References | Max Age (yrs) | Rate (%) |
|---|---|---|
| Chilvers et al:[3] | | |
| Before 1962 | 14 | 1.4 |
| 1962–1977 | 14 | 2.9 |
| Campbell et al[41] | 14 | 3.8 |
| Tamhne et al[42] | 16 | 2.6 |
| Jones et al[43] | 17 | 2.4 |
| MacKellar et al[40] | 15 | 2–4 |
| Fenton et al[44] | 16 | 2.6 |

## INCIDENCE OF TESTICULAR ASCENT

The observation that testes thought to be completely descended at birth may "ascend" to a suprascrotal position with time was noted by Villumsen and Zachau-Christiansen in 1966.[9] In that series 69 of 4,300 boys (2%) had unilateral (51) or bilateral (18) ascent of testes from a normal scrotal position at birth to a higher position by age 3 years. Others have noted this same phenomenon in case reports with well documented longitudinal data (table 2).[10,28–37] In the reports of patients followed long term with good documentation of previous testicular position boys with apparent testicular ascent constituted 2% to 20% of all those undergoing orchiopexy.[32,34,35,38] In retrospective series documentation of previous scrotal positioning of testes by other physicians is even more common. For example of 78 boys undergoing orchiopexy after age 3 years medical records indicated that the testis was previously in scrotal position, with or without retractility, in 34 (44%).[39] Unfortunately the accuracy of previous examinations cannot be confirmed in retrospective studies.

Nevertheless, orchiopexy rates and higher than expected mean age at orchiopexy suggest that testicular ascent is more common than indicated by the number of detailed case reports. Orchiopexy rates have been reported to be as high as 2% to 3% of all males up to age 14 to 17 years, despite an expected childhood prevalence of cryptorchidism of about 1% (table 3).[3,40–44] This discrepancy is attributed to inappropriate surgical management of retractile testes, yet differentiation of retractile and undescended testes is evident when patients are examined after induction of anesthesia. The recommended age for orchiopexy has been gradually decreased based on data suggesting that the first signs of spermatogenic injury occur in the undescended testis after the first year of life.[7] In the 1950s surgery was recommended after age 5 years, and often at 9 to 11 years, because of concerns about potential spermatic cord injury in young children.[9,45] In the late 1970s, after publication of studies showing early testicular injury in cryptorchidism, the recommendation for the timing of surgery was decreased to age 2 years.[7,39]

While the typical age at orchiopexy has gradually decreased, many patients older than 4 years still undergo the procedure (see figure).[39–42,45–52] Several studies demonstrate an increase in orchiopexy rates in younger age groups but no concomitant decrease in the rates in older boys.[53,54] While these types of data may be biased by variations in waiting time for elective surgery in different countries, 40% of boys who underwent orchiopexy at our institution in 2002 were 4 years or older (unpublished data). The continued high mean age at orchiopexy has been attributed to failure of primary physicians to screen, adequately diagnose and/or refer patients in a timely manner after identification of congenital cryptorchidism.[40,51] Alternatively a higher than appreciated incidence of acquired cryptorchidism may explain the significant subset of patients still undergoing late orchiopexy.

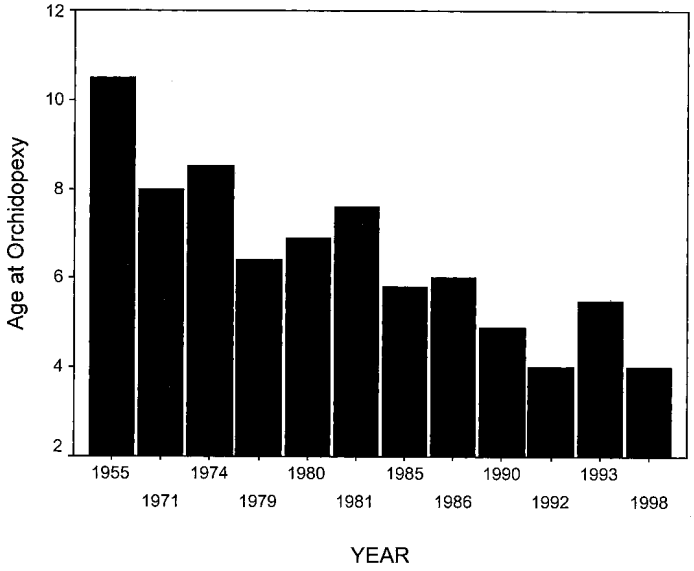
## CLINICAL FINDINGS IN TESTICULAR ASCENT

The data available from reviews of patients with good documentation of ascent indicate that boys with apparent acquired cryptorchidism are similar in many ways to comparable cases of presumed congenital cryptorchidism (table 2).[10,28–37] Mean age in most series was 7 years, higher than recent unselected orchiopexy series and the ascended testis most often is unilateral (see figure). The most common testicular location identified at orchiopexy was distal to the inguinal ring (prescrotal, superficial inguinal pouch or high scrotal). As with congenital cryptorchidism, the syndrome appears to be familial in some cases.[10] Patency of the processus vaginalis was observed in about half of cases with available data, which is lower than the 75% to 90% incidence reported in large unselected orchiopexy series.[45,47,49] However, a higher proportion of testes in these series was located above the external inguinal ring. In large series of boys undergoing orchiopexy more distal testicular location is associated with a lower (25% to 47%) incidence of patent processus vaginalis.[46,55]

The response to hormonal therapy in cases of testicular ascent is highly variable between series, which are small and not placebo controlled.[30,34,35,38,56] Retractile testes reportedly respond almost universally to hormone therapy, while the response rates are low in double-blind placebo controlled

TABLE 2. *Clinical data on cases of testicular ascent*

| References | No. Cases | Mean Age (yrs) | Position (at surgery) | | | | No. Hernias/ Testes | No. Side (unilat/bilat) |
|---|---|---|---|---|---|---|---|---|
| | | | Prescrotal/ High Scrotal | Superficial Inguinal Pouch | Inguinal | Abdominal | | |
| Myers and Officer[10] | 7 | 6.6 | — | — | — | — | — | 3/4 |
| Atwell[28] | 10 | 9.4 | 7 | 1 | 2 | — | 10/11 | 9/1 |
| Schiffer et al[29] | 3 | 6.7 | — | 2 | — | — | — | 3/0 |
| Belman[30] | 6 | — | 1 | 4 | 1 | — | 3/6 | — |
| Robertson et al[31] | 13 | 8.1 | — | — | — | — | 10/13 | 13/0 |
| Eardley et al[32] | 34 | 7.5 | 15 | 19 | 3 | — | 24/39 | 29/5 |
| Mayr et al[33] | 19 | 7.0 | 5 | 9 | 13 | — | 14/27 | 19/2 |
| Rabinowitz and Hulbert[34] | 21 | 7.2 | 2 | 19 | 2 | — | 12/23 | 19/2 |
| Gracia et al[35] | 36 | 7.0 | 8 | 5 | 32 | 1 | 18/46 | 11/8 |
| Clarnette et al[36] | 25 | 7.6 | — | — | — | — | 10/33 | 17/8 |
| Rusnack et al[37] | 91 | 7.4 | 79 | 11 | — | 1 | 39/91 | 91/0 |
| Total No. (%) | 265 | | 117 (48) | 70 (29) | 53 (22) | 2 | 140/289 (48) | 77 (23) |




Mean or median age at orchiopexy in large series (more than 200 cases) of cryptorchidism based on latest year reviewed.[39–42, 45–52]

trials conducted in unselected boys with true undescended testes.[19] In cases of testicular ascent less than half of patients responded and approximately one-third of testes remained descended with long-term followup after hormone therapy. The variable incidence of hernia in the small groups of patients studied may bias the results, since patency of the processus vaginalis seems to increase the likelihood of failure of human chorionic gonadotropin therapy.[57]

Preliminary studies of acquired undescended testes indicate that they exhibit similar germ cell maldevelopment to that observed in age matched patients with congenital cryptorchidism.[33, 35, 37] In contrast, 2 studies of secondary cryptorchidism first noted after hernia or hydrocele repair present differing findings of testicular pathology. Imthurn et al noted abnormalities in the affected testis that were less severe than those seen in primary cryptorchidism, progressive with time and unassociated with significant contralateral pathology.[58] Fenig et al found germ cell maldevelopment, suggesting that primary failure of descent may have been present but unrecognized before inguinal surgery.[59] Histological studies of retractile testes also indicate a subnormal tubule fertility index (number of spermatogonia per tubule) in 40% to 55% of prepubertal boys, although the abnormalities are less consistent and diffuse than in cryptorchid testes.[60–62] While "retractile" is often incompletely defined in these studies, they provide additional data supporting a link between pathological forms of testicular retractility and testicular ascent. In adults retractile and intermittently ascending testes are also associated with subfertility, and sperm counts may improve after orchiopexy.[63–65] High scrotal adult testes are more prone to intermittent ascent and associated impairment of spermatogenesis but scrotal position alone is not predictive of subfertility in men whose testes are not retractile or ascending.[65]

## THEORIES REGARDING THE ETIOLOGY OF TESTICULAR ASCENT

Use of the term testicular "ascent" is based on the assumption that affected testes were completely descended at some point after birth, as confirmed by an experienced observer, and were somehow pulled out of the scrotum by a pathological process. Suggested predisposing factors include a persisting processus vaginalis that allows the testis to ascend and become trapped in a higher position.[28, 31] Alternatively a closed but incompletely resorbed ligamentous processus vaginalis is theorized to create tethering of the testis in a high position with growth.[36] However, the data indicate that the processus vaginalis is as frequently patent as nonpatent in cases of documented testicular ascent, and this distribution follows that expected in unselected cryptorchid cases with testes situated distal to the inguinal canal.

Cremaster muscle spasticity is a possible cause of acquired cryptorchidism, for example in patients with cerebral palsy, but the proposed etiology of such spasticity in otherwise normal boys is unclear.[66] The cremaster muscle is androgen sensitive and exhibits decreased activity, resulting in decreased testicular retractility, during periods of high androgen production, specifically infancy and puberty. Interestingly, targeted disruption of the estrogen receptor in mice produces cremasteric hypertrophy and testicular retraction.[67] It is possible that environmental chemicals that influence sex steroid production or action could exaggerate the physiological hyperactivity of the cremaster muscle in young boys and increase the risk of true ascent.[68] However, reproductive hormone activity is normally low during mid childhood, and an association between such substances and ascent is theoretical.

The terms "testicular ascent" and "acquired cryptorchidism" may be erroneous if the testis was never truly descended. Indeed, the available data suggest that the most likely etiology of apparent testicular ascent is relative cranial migration, with linear growth of the patient, of a testis that is low but truly undescended, and whose retractility obscures the diagnosis in early childhood. This group would likely include the high scrotal testes noted by Scorer,[1] mobile superficial inguinal pouch testes that can be manipulated into a stable scrotal position in infancy[34] and testes whose ascent is facilitated by a hernia.

## CONCLUSIONS

It has been known for many years that testicular position after birth is not static, but that spontaneous descent and ascent may occur. Reascent of testes that descend spontaneously in the first year of life may occur in up to 40% of cases. Conversely, 2% to 45% of initially descended testes reportedly ascend, with the highest incidence seen in boys with significantly retractile testes. While 2% to 5% of newborns have cryptorchidism, the incidence in 1-year-olds is less than 1%, yet epidemiological studies reveal that 2% to 3% of boys undergo orchiopexy. Despite recommendations for intervention before age 2 years, many boys continue to present in mid childhood with undescended testes. Some individuals without overt cryptorchidism may retain abnormal testicular retractility into adulthood and consequent subfertility. Therefore, all boys should be examined routinely through childhood, and those with significantly retractile testes need especially close followup by an experienced observer through puberty. The response to hormonal therapy in cases of testicular ascent is variable and may not be durable. Therefore, surgical treatment is recommended. Prospective studies are needed to elucidate the incidence and significance of retractile and ascended testes, and to determine the fertility potential of boys with testicular ascent, particularly in view of the older age at treatment in this group.

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