Editorial

Early Orchiopexy to Prevent Germ Cell Loss during Infancy in Congenital Cryptorchidism

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Cryptorchidism is a problematic topic, beginning with its meaning. Although, by etymology, it refers to "hidden testes," the term cryptorchidism has been widely used to describe testes that are not in their normal position in the scrotum. The strictest terminology distinguishes between bilaterally absent testes ("anorchia"), the absence of one testis ("monorchia"), the existence of one or both testes in a position along ("undescended or maldescended testes") or outside ("ectopic testes") the normal pathway of descent from the abdominal cavity, and their spontaneously changing position back and forth from the scrotum to the inguinal canal ("retractile testes"). Although these rigorous definitions can only be applied after a definite diagnosis is made, most physicians use the terms cryptorchidism and ectopic or undescended testes to refer loosely to the absence of the testes in the scrotum, even before ascertaining their existence in the case of nonpalpable gonads. It is therefore not surprising that major controversies remain surrounding the epidemiology, the pathogenesis, the diagnosis, the long-term consequences, and the treatment of cryptorchidism. Moreover, conclusions based on inadequate study design have added to the confusion.

Testicular descent during fetal life can be schematically divided into two phases (1, 2). During the transabdominal phase, occurring during wk 8–15, insulin-like factor 3 secreted by Leydig cells provokes the thickening of the gubernaculum, thus inducing the anchoring of the testis to the inguinal region; androgens seem to have a minor role by driving the regression of the cranio-suspensory ligament, which releases the testis to descend. During the inguinoscrotal phase, occurring from wk 25 to term, androgens are the main driver of testicular descent, with the participation of subsidiary factors like the increase in the intraabdominal cavity pressure. The prevalence of cryptorchidism in newborns at term varies between studies from less than 1% to 9% and decreases owing to spontaneous descent in the first months after birth (3–5). In some cases, this wide prevalence range reflects true differences between populations likely explained by differences in genetics and/or the exposure to environmental factors, including endocrine disrupters and lifestyle (3), and in other cases, spurious differences resulting from the use of different sources of data and study designs and imprecise definitions for cryptorchidism.

The pathogenesis of congenital cryptorchidism is clear in newborns with impaired androgen secretion or action resulting also in disorders of sex development with ambiguous genitalia, in patients with isolated hypogonadotropic hypogonadism or multiple pituitary hormone deficiency resulting also in micropenis, in the rare cases with impaired insulin-like factor 3 secretion or action, and in those with abdominal wall defects. However, the etiology remains unknown in 80–90% of patients, who present with "isolated" cryptorchidism (5). It should therefore be kept in mind that cryptorchidism is only a sign, and patients with undescended gonads represent a heterogeneous group with underlying conditions of different etiologies and prognosis.

Infertility and testicular cancer risk are increased in patients with a history of cryptorchidism, which has driven the rationale for early treatment of boys with cryptorchidism. Actually, sperm production does not occur in gonads that remain undescended in adult life (1, 2), and the risk of testicular cancer development is increased more than

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5-fold in patients undergoing orchiopexy after the age of 13 yr (6).

However, these high-magnitude effects are observed only in very late treatment, and no clear evidence exists that the abnormal position of the gonads is solely responsible, or whether earlier treatment is effective prevention of the late outcomes in adult life. Moreover, in patients with unilateral cryptorchidism, an abnormal histology (7) and tumor development (8) have also been observed in the contralateral gonad normally positioned in the scrotum, which has led to the hypothesis that cryptorchidism, unilateral or bilateral, is the manifestation of a disease affecting both gonads (9).

The heterogeneity of the disorder is most likely responsible also for the controversies on the long-term consequences and the treatment of cryptorchidism. Much has been published— between 100 and 200 papers per year are retrieved in PubMed using search terms "cryptorchidism" and "human" for the period 1993–2012—yet robust evidence is still scarce about the advantages and disadvantages of hormonal *vs.* surgical treatment, or whether early treatment is beneficial regarding long-term outcomes, mainly fertility prognosis and risk of cancer development. In the 1970s, studies indicating that the cryptorchid testis has an almost normal histology during the first 2 yr of life, whereas the prepubertal cryptorchid testis is abnormal (10), prompted a change in the time of treatment from 6 to 2 yr of age. Many authors even advocated for surgery as early as 6 months after birth. For years, much was discussed about which were the best surrogate outcome measures to estimate the fertility prognosis in boys with cryptorchidism until the results of observational long-term follow-up studies became available. Unfortunately, the controversy was not resolved; some concluded that surgery before 1 yr of age resulted in better spermiogram quality (11), whereas others showed that the differences in the spermiograms of the patients were associated with the number of spermatogonia present in the biopsy at the time of surgery but not with the age (<6 months *vs.* 6–24 months) at orchiopexy (12). Uncontrolled confounders associated with the observational design of the studies may underlie the differences.

A Randomized Controlled Design to Avoid Confounders

The study by Kollin *et al.* (13), published in this issue of the *JCEM*, has addressed the potential advantage of early surgical treatment of cryptorchidism by comparing the histological and hormonal status between testes that remained cryptorchid for 9 months and those that remained cryptorchid for 3 yr. The key importance of this report lies in the study design. In fact, of the approximately 6000 articles on human cryptorchidism in PubMed, only 28 are randomized controlled trials, and none of those has addressed the potential role of early orchiopexy on testicular outcomes as this does. Kollin *et al.* (13) have used a randomized controlled design, which represents a major advantage. Other strengths of this study are the strict inclusion and exclusion criteria, avoiding heterogeneity due to prematurity, other congenital birth defects or recognized syndromes, and the clear definitions for undescended testes, which excluded retractile gonads. The studied sample of 225 patients included 147 with unilaterally undescended testes, 33 with bilaterally inguinal testes, and 33 with intraabdominal testes who were randomized at the age of 6 months to undergo orchiopexy at either 9 months or 3 yr. At orchiopexy, a biopsy was performed to analyze the histology of the gonads; hormonal activity of the gonadal axis was also assessed.

Interpretation of the Results, Based on a Developmental Physiology Approach

As surrogate outcomes to estimate testicular status at 6 months or 3 yr, the authors evaluated testicular volume by ultrasound, seminiferous tubule diameter, germ and Sertoli cell densities, and FSH and inhibin B serum levels. As opposed to relative stability in adulthood, the pediatric period of life is characterized by continuous developmental changes. Most variables analyzed as outcomes may change simply as an effect of time, even in the control group. Due to the design of Kollin's study, this point could not be properly controlled. For instance, whether the lower number of Sertoli cells per tubular cross-section at 3 yr is due to the effect of the abnormal position of the gonads or to a physiological decrease during infancy cannot be answered by comparing Sertoli cell counts in boys operated on at 6 months *vs.* those operated on at 3 yr. Although I am always tempted to blame the increase in my gray hair to the increasing load of administrative tasks I have faced for the last 3 yr, I must accept that I am 3 yr older….

Testicular volume

Testicular size was slightly smaller in boys that remained cryptorchid until the age of 3 yr. The clinical relevance is not easy to appraise. Until the age of 6 months, the testes are physiologically exposed to high gonadotropin levels, which sharply decline thereafter and remain low until the onset of puberty. Does gonadotropin stimulus withdrawal after the age of 6 months result in a decrease

in testicular volume? Clearly, no major decrease exists in testis volume between 1 and 3 yr of age (14, 15), yet no precise data exist between the ages of 0–6 and 6–12 months. Therefore, a possible pathological significance of the slightly lower volume observed in the 3-yr-old group *vs.* the 6-month-old group should be taken with caution.

Kollin *et al.* (13) found smaller seminiferous tubules and lower numbers of Sertoli cells per tubular cross-section, together with higher FSH in the group assigned to delayed orchiopexy. Although the differences are minor, the whole picture is consistent with a slightly greater damage of the seminiferous tubule in boys that remained cryptorchid until the age of 3 yr. Once again, this conclusion should be taken cautiously. The authors correctly chose to focus their assessment on Sertoli cells, the most active cell population in infancy and childhood (16). However, tubular diameter and Sertoli cell number per tubular cross-section physiologically show a slight decrease after the decline of gonadotropins occurring after the first 6 months of life (14). Although this seems contradictory with the increase in the total volume occupied by seminiferous tubules, it should be kept in mind that seminiferous tubules increase in length during this period, and Sertoli cell nuclei scatter along the tubules (17, 18), which is not accounted for by the methodology of this study. Also, the fact that it is not clear whether the observer analyzing the histological slides was blinded may be considered a weakness of the study.

Germ cell count

The decrease in germ cell count per tubular cross-section between 6 months and 3 yr in the cryptorchid boys of this study was dramatic. Although, as a consequence of the physiological increase in seminiferous tubule length, germ cell number per tubular cross-section normally decreases during infancy and childhood, the difference between the first and third years of life should not exceed 20% (19). The impressive decrease in the mean number of spermatogonia per cross-section from approximately 60–110 at 6 months to approximately 2–10 at 3 yr in undescended testes undoubtedly raises serious concerns. Germ cell counts showed large interindividual dispersion in both age groups, in concordance with previous work by other authors (12, 20). This observation likely reflects the heterogeneity of cryptorchid patients, as discussed at the beginning of this editorial, and may indicate that some patients might have damaged testes already at 6 months and others might keep relatively undamaged testes until the age of 3 yr. However, the randomized design represents a major strength in Kollin's study to support and add to the hypothesis that the persistence of the testes in an abnormal position has a deleterious effect on germ cells.

Added evidence and persistent uncertainties

The use of adequate study designs is pivotal to reach sound conclusions, and in this case to clarify some controversies surrounding cryptorchidism. The initiative of Kollin *et al.* (13) to use a randomized controlled design should be celebrated. The severe decrease in germ cell numbers occurring in the persistently cryptorchid testes during infancy provides robust evidence to support the recommendation of early orchidopexy; yet, the long-term consequences on fertility or cancer risk remain unclear. As the authors acknowledge, long-term follow-up of this cohort will confirm whether the germ cell loss observed at 3 yr will have been prevented by the early orchiopexy at 9 months or whether it is the natural history of undescended gonads independently of the timing of surgery. Again, we should not forget that cryptorchidism is a sign of heterogeneous disorders, and early orchiopexy may not be helpful in terms of reproductive outcomes when testicular dysgenesis or other congenital primary testicular disorders are the underlying cause. Continuous efforts will be needed with the aim of clarifying the as yet unknown etiologies of cryptorchidism so that adequately designed therapeutic studies can be conducted on populations representing more homogeneous conditions aiming to find personalized treatment.

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