Age at Cryptorchidism Diagnosis and Orchiopexy in Denmark: A Population Based Study of 508,964 Boys Born From 1995 to 2009

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Purpose: Early treatment for cryptorchidism may be necessary to preserve fertility. International guidelines now recommend that congenital cryptorchidism be treated with orchiopexy before age 1 year. Acquired cryptorchidism should be treated at presentation. To our knowledge the rate of adherence to these guidelines in recent years is unknown. Thus, we present data on age at cryptorchidism diagnosis and orchiopexy in recent Danish birth cohorts.

Materials and Methods: A population of 508,964 Danish boys born alive from January 1, 1995 to December 31, 2009 was identified using the Danish Civil Registration System. Five birth cohorts were defined, including 1995 to 1997, 1998 to 2000, 2001 to 2003, 2004 to 2006 and 2007 to 2009. The boys were followed in the Danish National Patient Registry for a diagnosis of cryptorchidism and for an orchiopexy procedure. Data were analyzed using the Kaplan-Meier estimator and Cox regression models.

Results: During followup 10,094 boys were diagnosed with cryptorchidism, of whom 5,473 underwent orchiopexy. Mean age at diagnosis in boys followed at least 6 years was 3.3 years (95% CI 3.3–3.4) in the 1995 to 1997 cohort, 3.1 (95% CI 3.1–3.2) in the 1998 to 2000 cohort and 2.9 (95% CI 2.8–2.9) in the 2001 to 2003 cohort while mean age at orchiopexy was 3.8 (3.7–3.9), 3.6 (3.5–3.7) and 3.3 years (3.2–3.4), respectively.

Conclusions: In the more recent birth cohorts of 1995 to 2009 we observed a shift toward younger age at cryptorchidism diagnosis and orchiopexy.

Key Words: testis, cryptorchidism, diagnosis, orchiopexy, age groups

Study received Danish National Board of Health and Danish Data Inspectorate approval.

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In recent years it has become evident that early cryptorchidism diagnosis and treatment in boys may improve future fertility. A randomized trial favored orchiopexy at age 9 months over orchiopexy at age 3 years when considering testicular volume at age 4 years.[1] A followup study indicated that young men operated on during year 1 of life had a higher sperm count than those operated on during year 2.[2] International guidelines now recommend that congenital cryptorchidism (prevalent at birth) be treated with orchiopexy before age 1 year.[3–6] Acquired cryptorchidism (incident cases during childhood) accounted for more than 50% of cases after age 18 months in a Danish cohort.[7] Some studies suggest that early treatment for cryptorchidism recognized during childhood may improve future fertility[8–10] while others do not.[11,12] The risk of testicular cancer may also be lower in

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those operated on before puberty,[13,14] although not all studies support this.[15–17]

International guidelines recommend that acquired cryptorchidism be treated at onset without delay.[3–6] A study of the registry based incidence of orchiopexy in Denmark during 1982 to 1985 showed the highest orchiopexy rate at ages 12 to 13 years,[18] ie at a much older age than what is considered optimal today.[3–6] A study of orchiopexy rates in Sweden, a Nordic neighbor country with comparable health services, during 1977 to 1991 showed the highest rates in 5 to 9-year-old boys but many were operated on when they were between ages 10 and 14 years.[19]

Knowledge of adherence to clinical guidelines in recent years has been inadequate. Thus, we describe age at cryptorchidism diagnosis and orchiopexy in Danish birth cohorts from 1995 to 2009, and present data on time from diagnosis to orchiopexy during that period.

MATERIALS AND METHODS

Study Design

A population of 508,964 Danish boys born alive from January 1, 1995 to December 31, 2009 was identified using the Danish Civil Registration System.[20] In the system each individual is assigned a unique 10-digit number at birth, which facilitates linkage to other population based registries and ensures almost complete followup. Cryptorchidism diagnoses and orchiopexy procedures were obtained by linkage to the Danish National Patient Registry, which contains information on all inpatient and outpatient clinic diagnoses and surgeries performed during followup.[21] The boys were followed for a cryptorchidism diagnosis, as coded in accordance with ICD-10 main discharge diagnosis codes Q53, Q531, Q531A, Q532, Q532A and Q539, or for this diagnosis plus an orchiopexy procedure using Nordic Classification of Surgical Procedures codes KKFH00, KKFH01 and KKFH10. Referral diagnoses from general practitioners were not included in this study. That is, hospital physicians, primarily pediatricians, general surgeons, urologists and pediatric urologists, made all diagnoses.

The study period started January 1, 1995 after ICD-10 was introduced in 1994.[21] During 1995 a new Nordic Classification of Surgical Procedures gradually replaced the existing classification with complete coverage by 1996. This new classification included documentation of the specific time and date of surgery. Before this the dates of admission to and discharge from the hospital where the surgery was performed served as proxies. In our data 98.5% of dates of surgery were documented with an accurate time and date.

The boys entered the risk set at birth on analyses of time to diagnosis and orchiopexy, and were followed until age at first diagnosis, first orchiopexy, death, emigration from Denmark or end of followup on December 31, 2009, whichever was first. At the end of followup 97% of the boys were alive and living in Denmark, 2.3% were lost due to emigration and 0.7% died during followup.

Statistical Analysis

We analyzed time to disease event, defined as cryptorchidism diagnosis or orchiopexy, using the Kaplan-Meier estimator and Cox regression models with age as the time variable. Competing risks were ignored when using the Kaplan-Meier estimator due to the low death and emigration rates in the study population. The period 1995 to 2009 was divided into 5 birth cohorts, each representing 3 years, including 1995 to 1997, 1998 to 2000, 2001 to 2003, 2004 to 2006 and 2007 to 2009. Kaplan-Meier failure estimates (1 − survivor) were calculated for each cohort using the available followup. These estimates are presented as age specific cumulative incidences and represent a good approximation, given the low censoring rate. As an overall test of equality of failure functions the Breslow-Gehan test was used to consecutively compare 2 cohorts adjacent in calendar time. This was done separately for the cryptorchidism diagnosis and for orchiopexy.

Theoretically differences in the age specific cumulative incidence between cohorts could be attributable to a change in age at disease event or to a change in final cumulative disease incidence. Part *A* of the figure shows an example in which the age specific cumulative orchiopexy incidence in the 1998 to 2000 cohort was shifted toward the left compared to that in the 1995 to 1997 cohort. This may have been due to a higher final cumulative orchiopexy incidence in the 1998 to 2000 cohort. However, this may also have been due to a downward shift in age at orchiopexy from the 1995 to 1997 cohort to the 1998 to 2000 cohort, ie boys with cryptorchidism were diagnosed and operated on at younger ages in the more recent cohort.

Evidence of a shift in age at disease event between 2 cohorts was formally tested by dividing followup (age) into intervals and calculating the ratios of disease hazards (HR) between cohorts for each interval. If the HR between cohorts changed as a function of age, this was evidence of a shift in age at disease event. Part *B* of the figure shows the HR of each 2-year age interval in the 2 cohorts (part *A* of figure). The HR of the younger cohort (1998 to 2000) compared to the older cohort (1995 to 1997) decreased as age increased, indicating that boys in the younger cohort were operated on at younger ages. We used 2-year age intervals for presentation purposes but the formal test for trend (trend HR, part *B* of figure) was done on a continuous variable with followup (age) divided into 1-year intervals. This test for trend, indicating diagnosis or orchiopexy at younger ages in the younger cohort when the trend HR was significantly less than 1, was done between cohorts adjacent in calendar time, ie we compared 2 adjacent cohorts at a time with the older cohort as the referent. This was also done separately for the cryptorchidism diagnosis and for orchiopexy. Parner et al discussed this analytical approach in detail.[22]

We estimated mean age at cryptorchidism diagnosis, mean age at orchiopexy and time from diagnosis to orchiopexy. Followup was truncated at 3, 6, 9, 12 and 15 years, and cohorts that were followed at least that time were compared at each truncation point. Mean age at