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Hormonal Changes in 3-Month-Old Cryptorchid Boys

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Context: Hormonal dysregulation has been suggested to be one of many etiological factors of cryptorchidism.

Objectives: The objective of this study was to assess the hypothalamic-pituitary-testicular axis in cryptorchid boys during the postnatal hormonal surge.

Design: This was a prospective, longitudinal, population-based study.

Setting: The study was performed at two primary obstetric centers.

Participants: Study participants included 388 Finnish and 433 Danish boys (88 and 34 with cryptorchidism, respectively).

Interventions: Clinical examinations were performed at 0 and 3 months. Blood samples were taken at 3 months.

Main Outcome Measures: The main outcome measures were testis position and reproductive hormone levels.

Results: Finnish cryptorchid boys had significantly higher FSH [1.59 (0.50–3.53) *vs.* 1.30 (0.49–2.92) IU/liter; $P < 0.0001$] and lower inhibin B [426 (254–770) *vs.* 459 (266–742) pg/ml; $P < 0.015$] levels than Finnish control boys [median (2.5th–97.5th percentiles)]. Danish cryptorchid boys had higher FSH levels than controls [1.47 (0.54–3.89) *vs.* 1.18 (0.41–3.04) IU/liter; $P = 0.018$]. Inhibin B levels in healthy Danish boys were lower than those in Finnish boys [380 (233–637) pg/ml; $P < 0.0001$] and were not reduced in Danish cryptorchid boys [392 (236–672) pg/ml; $P = 0.851$]. Changes in hormone levels were strongest in boys with severe, persistent cryptorchidism, but were also detectable in mild and transient cryptorchidism. Effects on Leydig cell function were subtle, with an increase in LH in Finnish (but not Danish) cryptorchid boys *vs.* controls [1.97 (0.77–5.91) *vs.* 1.75 (0.58–4.04) IU/liter; $P < 0.021$], but testosterone levels remained within the normal range.

Conclusions: Our results support the hypothesis that cryptorchidism is associated with a primary testicular disorder, which could be a cause or a consequence of cryptorchidism. This malfunction is reflected by low inhibin B production in the Finnish cohort and high gonadotropin drive in both the Finnish and Danish cohorts. **(*J Clin Endocrinol Metab* 91: 953–958, 2006)**

NORMAL FUNCTION OF the hypothalamic-pituitary-gonadal axis is necessary for optimal testicular development and maturation. Gonadotropins and androgens play an important role in fetal development and testicular descent (1, 2), although other factors, *e.g.* insulin-like hormone (INSL3), are also involved (3, 4). The function of undescended testes gradually deteriorates if the malposition continues after birth, and germ cell loss has been observed from as early as 18 months of age in undescended testes (5). Later in life, cryptorchidism is commonly followed by fertility problems (6) and an increased risk of testicular malignancies (7, 8). The risk of cancer seems to remain increased even after early treatment of cryptorchidism (8), which has prompted the hypothesis about a primary fetal defect in the differentiation of cryptorchid testes. Cryptorchidism could thus be the first symptom of an underlying disorder, whereas testicular cancer and infertility may be consecutive manifestations of the same prenatal defect (9).

The testicular maldevelopment is also reflected in serum hormone levels; testosterone and inhibin B decrease, whereas LH and FSH increase, as a consequence of reduced negative feedback (6, 10). This has been clearly documented from early puberty to adulthood. However, conflicting results have been reported on whether these hormonal changes can be found early in childhood (11–16). Insufficient classification of cryptorchidism, wide age ranges, small study and age groups, or poor sensitivity of assays have compromised many previous results.

The aim of this study was to evaluate reproductive hormone levels (testosterone, inhibin B, LH, FSH, and SHBG) in 3-month-old cryptorchid boys to assess the functional integrity of the hypothalamic-pituitary-gonadal axis. The study was performed as a prospective cohort study with careful standardized evaluation of testicular position in both a cryptorchid and a healthy control group and with blood sampling within a narrow time window during the physiological postnatal minipuberty at 3 months of age (17).

Subjects and Methods

The boys included in this study participated in a joint prospective cohort study performed from 1997–2001 at Turku University Hospital (Turku, Finland) and University Hospital (Copenhagen, Denmark). Recruitment and inclusion criteria were described in our previous report on the prevalence of cryptorchidism (18). Only full-term boys (gestational age, 37–42 wk) with available blood samples between 2.5 and 3.5

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Abbreviations: CV, Coefficient of variation; DK, Danish; FIN, Finnish; INSL3, insulin-like hormone.

months of age were included in the present study. Gestational age was based on routine ultrasonography at gestational wk 18–20, when available (n = 677), and otherwise on the last menstrual period (n = 144). To obtain genetically and environmentally well-defined Finnish/Danish populations, only families who met the following selection criteria were included in the study: both parents and grandparents were born and raised in Finland/Denmark with no more than 3 yr (mother) or 10 yr (father and grandparents) residence abroad. After exclusion of boys (n = 44) with other genital anomalies (*e.g.* hypospadias or testis torsion), performed orchipexy before 3 months, subsequent testicular ascent (acquired cryptorchidism), and those (n = 94) with blood samples taken outside the determined time frame, a total of 388 Finnish and 433 Danish boys were included in the final analysis.

All boys were examined at birth (≤5 d) and at 3 months (mean, 3.0 months; 2.5th–97.5th percentile, 2.6–3.4 months) of age. The examination technique was adapted from Scorer and was carefully standardized between researchers (18). The lowest testicular position after a firm, but not forced, manipulation was recorded. Five categories for testicular position, scrotal (*i.e.* normal), high scrotal, suprascrotal, inguinal, and nonpalpable, were used for clinical diagnosis (18). Retractile testes were considered normal. Boys with at least one high scrotal testis were classified as cryptorchid; in bilateral cases the classification was made according to the most pathological position. Three hundred Finnish (FIN) and 399 Danish (DK) had both testes descended at both examinations (control groups). At birth, 88 FIN and 34 DK boys were classified as cryptorchid. At the 3-month examination, 32 (FIN) and 23 (DK) of them had recovered (spontaneous descent), whereas 56 FIN and 11 DK boys were still unilaterally (n = 58) or bilaterally (n = 9) cryptorchid. Testicular position in these boys was high scrotal (n = 17 FIN and 5 DK), *i.e.* mildly cryptorchid, suprascrotal/inguinal or nondetectable (n = 39 FIN and 6 DK), *i.e.* severely cryptorchid. Inguinal hernia was found in one control and three cryptorchid boys.

Data concerning parity, maternal smoking, and diabetes mellitus were obtained from a prenatal questionnaire or hospital records. Birth weight was obtained from birth records, and at 3 months, the boys were weighed by us on a digital baby scale (Baby-Scale model, Solotop Oy, Helsinki, Finland) to the nearest 0.005 kg. Children were considered small for gestational age when age-adjusted birth weight was less than −2 SD (Finland) or less than −22% (Denmark; approximate to less than −2 SD) for a gender-differentiated reference group (19, 20). In Denmark, all recruited healthy boys were included in the control group. In Finland, due to restrictions in funding, the control group was formed by matching two controls per case on date of birth (±14 d), parity, gestational age (±7 d), maternal smoking, and diabetes and additionally selecting every 10th of the remaining healthy boys as random controls.

Blood samples were collected at 3 months of age. The samples were taken between 1200 and 1800 h in Finland and between 0800 and 1700 h in Denmark. EMLA cream (ASTRA Zeneca, Copenhagen, Denmark) or Lidocaine spray (SAD, Copenhagen, Denmark) was used as a local anesthetic, and up to 4 ml of peripheral venous blood was collected. After clotting, the blood samples were centrifuged, and the sera were separated and stored at −20 C until analyzed.

Assays

All blood samples were analyzed blinded for outcome in the same laboratory (Rigshospitalet, Copenhagen, Denmark) by a few skilled technicians. All samples were analyzed in duplicate. Each set of analyses contained blood samples from both cryptorchid and control boys from both Finland and Denmark.

Serum FSH, LH, and SHBG were analyzed by time-resolved immunofluorometric assays (Delfia, Wallac, Inc., Turku, Finland). Detection limits were 0.06 and 0.05 IU/liter for FSH and LH, respectively, and 0.23 nmol/liter for SHBG. The intra- and interassay coefficients of variation (CV) were less than 5% in both gonadotropin assays and less than 6% in the SHBG assay. Serum testosterone was measured by RIA (Coat-a-Count, Diagnostic Products Corp., Los Angeles, CA), with a detection limit of 0.23 nmol/liter and intra- and interassay CVs less than 10%. The free testosterone index was calculated from testosterone and SHBG [(testosterone × 100)/SHBG]. Ratios between LH/testosterone and LH/free testosterone were calculated by simple division, and the ratio between FSH and inhibin B was calculated as FSH × 1000/inhibin B.

Serum inhibin B was analyzed by a double antibody enzyme immunometric assay using a monoclonal antibody raised against the inhibin β_B-subunit in combination with labeled antibody raised against the α-subunit (Oxford Bio-Innovation, Oxford, UK). The detection limit was 20 pg/ml, and intra- and interassay CVs were less than 15% and 18%, respectively.

The study was conducted according to the Helsinki II Declaration and was approved by the local Finnish ethics committee (7/1996), the local Danish ethics committee [(KF) 01-030/97], and the Danish Data Protection Agency (1997-1200-074). Written informed consent was given by the parents.

Statistics

Population characteristics for control and cryptorchid boys were compared by nonparametric tests, $P < 0.05$ was defined as statistically significant (Table 1). Serum hormone levels of cases and controls were compared separately for each country by nonparametric tests (Table 2). Kruskal-Wallis test was applied to compare all four groups (controls, recovered, mildly cryptorchid, and severely cryptorchid), and the Mann-Whitney test was used for comparison of two group combinations, respectively. Final significance levels were estimated in all nonparametric tests by two-tailed Monte Carlo approximation.

TABLE 1. Characteristics of Finnish and Danish control and cryptorchid boys

	Control boys		Cryptorchid boys		
	n	%	n	%	*P*
Total no.	699		122		
Parity					0.172
1	385	55.1	61	50.0	
2	219	31.3	39	32.0	
3	70	10.0	15	12.3	
≥4	17	2.4	6	4.9	
Maternal diabetes	25	3.6	13	10.7	0.0001
Smoking during pregnancy	170	24.3	31	25.4	0.804

	Control boys		Cryptorchid boys		
	Median	Range	Median	Range	*P*
Gestational age (d)	282	(259–294)	280	(259–294)	0.625
Birth weight (kg)	3.66	(2.05–5.68)	3.65	(1.95–4.85)	0.147
Weight 3 month (kg)	6.48	(3.86–8.79)	6.54	(4.27–8.29)	0.826
Weight gain 0–3 months (kg)	2.84	(1.09–4.67)	2.88	(1.35–4.50)	0.149
Age at blood sampling (months)	3.01	(2.53–3.45)	3.01	(2.53–3.38)	0.487

P values for differences were obtained by nonparametric tests.

Results

The characteristics of the cryptorchid and control boys are described in Table 1. There was no difference between the groups with respect to parity, maternal smoking, gestational age or age at blood sampling, birth weight, weight for gestational age, weight at 3 months, and weight gain during the first 3 months. This was also true if data from each country were analyzed separately (data not shown). Mothers of cryptorchid boys more often had diabetes during pregnancy than those of control boys (10.7% *vs.* 3.6%, respectively; $P < 0.001$), but no association between maternal diabetes and hormone levels was found (data not shown). Thus, these confounding factors were no longer included in the comparisons of healthy and cryptorchid boys.

In the Finnish boys, a clear pattern of hormonal changes was seen for boys with cryptorchidism (Table 2). Inhibin B values were lower ($P < 0.015$) and FSH values were significantly higher ($P < 0.0001$) in cryptorchid than in control boys, resulting in a significantly higher ratio of FSH/inhibin B ($P < 0.0001$) in cryptorchidism. The effect of cryptorchidism on these hormone levels increased with the severity of the disease, being greatest for the group of boys with persistent severe cryptorchidism at 3 months compared with controls (inhibin B, $P < 0.005$; FSH, $P < 0.005$; FSH/inhibin B ratio, $P < 0.0001$). Changes in Leydig cell hormones were subtle, with an increase in LH ($P < 0.021$) for the total group of cryptorchid boys. In boys with persistent severe cryptorchidism at 3 months, serum LH was clearly elevated ($P < 0.028$), and the LH/testosterone ratio ($P < 0.008$) and the LH/free testosterone ratio ($P < 0.031$) were higher than those in controls.

Finnish cryptorchid boys with spontaneous testicular descent between birth and 3 months of age had higher FSH ($P < 0.044$) and higher FSH/inhibin B ratios ($P < 0.018$) than controls. Due to significantly higher levels of testosterone ($P < 0.026$) and free testosterone ($P < 0.0001$), they also showed lower LH/free testosterone ratios ($P < 0.016$). The only parameter that differed significantly between boys with spontaneous descent and boys with high scrotal testes at 3 months was SHBG ($P < 0.023$). Boys with mild *vs.* severe persistent cryptorchidism at 3 months differed significantly in testosterone ($P < 0.003$), SHBG ($P < 0.049$), and LH/testosterone ratio ($P < 0.003$), but not in FSH ($P = 0.575$) or inhibin B ($P = 0.422$).

In the Danish control boys, inhibin B ($P < 0.0001$), SHBG ($P < 0.003$), and FSH ($P < 0.047$) values were significantly lower than those in the Finnish control boys. There was no significant effect of mild or severe cryptorchidism on inhibin B concentrations ($P = 0.851$; Table 2), but FSH was significantly higher in cryptorchid boys ($P < 0.018$), with the increase in the FSH/inhibin B ratio not reaching statistical significance ($P = 0.090$). In the subgroups, both boys with spontaneous descent at 3 months and boys with persistent severe cryptorchidism showed significantly higher FSH levels than controls ($P < 0.044$ and 0.037, respectively). LH showed a tendency for higher values in severely cryptorchid boys at 3 months ($P = 0.083$), but did not reach statistical significance in any subgroup comparison, nor did hormonal ratios. Boys with mild *vs.* severe cryptorchidism at 3 months did not differ significantly in any hormonal parameter.

Discussion

We performed a large prospective clinical study in which cryptorchid and healthy boys with well-documented clinical testicular position at birth and 3 months were evaluated for reproductive hormone levels during the physiological postnatal hormonal surge.

The most pertinent findings were changes in hormonal parameters reflecting Sertoli cell function. Inhibin B was lower and FSH was higher in Finnish cryptorchid boys, with

TABLE 2. Serum reproductive hormone levels (medians, 2.5th −97.5th percentiles) and their ratios in control and cryptorchid boys grouped together (all cases at any time) or by severity at 3 months: recovered (spontaneous descent between 0 and 3 months), mild (high scrotal), and severe (suprascrotal, inguinal or nonpalpable) in Finnish and Danish boys

	Controls	All cases	*P*	3 months' examination		
Finnish boys						
n	300	88		32 (recovered)	17 (mild)	39 (severe)
Inhibin B (pg/ml)	459 (266–742)	426 (254–770)	0.015	438 (259–818)	428 (275–626)	407 (209–594)
Testosterone (nmol/liter)	3.26 (0.64–7.90)	3.72 (0.73–8.55)	0.180	4.15 (1.24–7.39)	4.62 (0.96–12.7)	2.91 (0.35–6.82)
Free testosterone index	2.33 (0.44–4.99)	2.66 (0.57–4.93)	0.036	3.19 (1.01–5.72)	2.65 (0.69–4.55)	2.29 (0.19–4.35)
SHBG (nmol/liter)	144 (74–268)	139 (84–299)	0.491	127 (69–270)	157 (110–340)	134 (87–240)
LH (IU/liter)	1.75 (0.58–4.04)	1.97 (0.77–5.91)	0.021	1.99 (0.75–6.73)	1.80 (0.42–4.16)	2.05 (0.95–6.14)
FSH (IU/liter)	1.30 (0.49–2.92)	1.59 (0.50–3.53)	0.0001	1.53 (0.49–5.21)	1.56 (0.31–2.81)	1.73 (0.56–3.58)
LH/testosterone	0.54 (0.18–2.16)	0.54 (0.23–2.90)	0.776	0.47 (0.25–2.35)	0.38 (0.20–1.90)	0.73 (0.23–5.31)
LH/ free testosterone index	0.78 (0.27–3.12)	0.68 (0.35–3.92)	0.941	0.58 (0.40–2.90)	0.68 (0.33–2.64)	1.12 (0.34–9.78)
FSH/inhibin B	2.9 (0.7–8.8)	3.7 (0.8–12.8)	0.0001	3.5 (0.7–14.7)	3.3 (0.6–10.2)	3.9 (1.3–13.0)
Danish boys						
n	399	34		23 (recovered)	5 (mild)	6 (severe)
Inhibin B (pg/ml)	380 (233–637)	392 (236–672)	0.851	412 (236–577)	389 (309–672)	375 (240–546)
Testosterone (nmol/liter)	3.30 (0.58–7.69)	3.33 (0.92–7.21)	0.835	3.64 (0.92–6.84)	2.50 (1.55–3.36)	4.29 (1.84–7.21)
Free testosterone index	2.42 (0.46–5.29)	2.34 (0.66–6.63)	0.630	2.58 (0.66–4.22)	1.80 (1.15–2.87)	2.00 (1.23–6.63)
SHBG (nmol/liter)	136 (66–272)	133 (86–300)	0.999	129 (95–280)	135 (86–158)	164 (99–300)
LH (IU/liter)	1.77 (0.55–4.11)	2.00 (0.51–3.99)	0.100	1.88 (0.51–3.99)	2.13 (1.37–3.40)	2.72 (1.43–3.23)
FSH (IU/liter)	1.18 (0.41–3.04)	1.47 (0.54–3.89)	0.018	1.47 (0.54–2.61)	1.02 (0.75–1.75)	1.69 (1.10–3.89)
LH/testosterone	0.54 (0.16–2.52)	0.60 (0.10–2.23)	0.409	0.55 (0.10–2.23)	0.68 (0.55–2.19)	0.61 (0.29–1.09)
LH/ free testosterone index	0.74 (0.21–2.77)	0.83 (0.15–3.21)	0.249	0.76 (0.15–3.12)	0.95 (0.76–2.96)	1.25 (0.40–1.44)
FSH/inhibin B	3.0 (0.8–10.2)	3.8 (1.1–16.2)	0.090	3.8 (1.1–10.4)	2.9 (1.1–5.5)	4.6 (2.0–16.2)

The *P* value is given for statistical comparison of all controls *vs.* all cases (Mann-Whitney test).

a relationship to the severity and persistence of cryptorchidism from birth to 3 months of age. The effect on Leydig cell function was overall subtle, with a slightly increased LH drive leading to testosterone values within the normal range. Lower testosterone levels were only seen in severely and persistently cryptorchid boys. These findings are in agreement with the clinical experience of adult consequences of cryptorchidism, which include not only an impact on Sertoli cell function and fertility, but also an impairment of Leydig cell function with a higher LH drive and a shift of serum testosterone toward lower levels (21).

The effects of cryptorchidism on hormonal parameters were clearly seen within the Finnish study population, but were not as obvious within the Danish population. In part, this may be caused by the much lower number of Danish cases with persistent and severe cryptorchidism, considering the large individual variation in normal hormonal levels at 3 months of age. It may, however, also be related to the fact that the apparently healthy Danish control group showed lower levels of inhibin B than Finnish boys, which then were not further reduced in cryptorchidism. We currently have no causal explanation for the lower levels of inhibin B and FSH in healthy Danish children compared with Finnish boys. These serum parameters indicate that Danish boys may have a smaller population of Sertoli cells, which would be in agreement with our unpublished observations that Danish boys have a significantly lower testicular volume than Finnish boys between 0 and 18 months of age (Main, K. M., J. Toppari, A.-M. Suomi, M. Kaleva, M. Chellakooty, I. M. Schmidt, H. E. Virtanen, K. A. Boisen, C. M. Kai, I. N. Damgaard, and N. E. Skakkebaek, submitted for publication). The prevalence of both cryptorchidism and hypospadias is higher in Danish than in Finnish boys (18, 22). All these observations point to impaired perinatal testicular development in Danish boys, the etiology of which is currently unknown.

Previously, conflicting results of hormonal changes in cryptorchidism have been published. Lower basal serum T and LH have been observed in 1- to 3-month-old cryptorchid boys compared with those in boys with spontaneously descended testes (12, 13). Similarly, blunted LH and T responses after GnRH and human chorionic gonadotropin stimulation, respectively, have been found in cryptorchid boys during the first 11 months of life (14) as well as during adolescence until midpuberty (23). In contrast, De Muinck Keizer-Schrama *et al.* (11) found no differences in basal or stimulated LH, FSH, and testosterone levels or stimulated dihydrotestosterone or testosterone precursor levels among 29 persistently cryptorchid boys, 18 with spontaneous descent until 6 months, and 144 controls followed longitudinally from 3–12 months. In some of the previous studies, poor sensitivity of the assays could give misleading results when the measured hormone values were low. Moreover, definition of the exact testicular position is missing in many previous reports, and exclusion of retractile testis has been documented in only some studies.

The postnatal surge of reproductive hormones is characterized by a fast increase after the first month, followed by a decrease shortly after the age of 3 months (17, 24, 25). If the timing of blood samples is too broad, one would expect greater variability in hormone levels, thus complicating the interpretation. In our study the timing of blood sampling was therefore carefully controlled. Preterm boys were also excluded due to their possible different timing of the hormonal surge and a potentially different hormonal regulation. This importance of precise timing of blood samples within the postnatal hormonal activation is underlined by two recent studies of boys with Klinefelter syndrome (26, 27), showing that testosterone production, but not inhibin B, was lower than normal around 3 months of age. Blood samples in older infants would not detect this phenomenon.

In a recent American case-control study of 20 cryptorchid and 27 control boys, no difference in hormone levels around 2 months of age was found (16). The main difference in the design compared with our study was the selection of controls from the patients who were treated for nonendocrine-related causes, whereas the control group in the present study consisted of healthy boys. In addition, the size of the control group was much smaller than that in our study. Interestingly, using the same hormone analysis method, their control inhibin B values (mean, 392 pg/ml) were in the same range as those of Danish control boys (mean, 396 pg/ml; median, 380 pg/ml) in our study. Inhibin B values in Finnish control boys were higher (mean, 471 pg/ml; median, 459 pg/ml).

The biphasic process of testicular descent includes a transabdominal and an inguinoscrotal phase; in the latter, androgens are known to play an important role directly and/or indirectly (28, 29). INSL3 is suggested to be the main regulator of gubernacular development, whereas androgens play a role in degeneration of the cranial suspensory ligament, at least in the mouse. In our data, immunologically measured total testosterone and free testosterone index showed an increasing trend in boys with spontaneous descent and mild cryptorchidism, whereas in severely cryptorchid boys, both parameters were in the low normal range together with significantly increased LH. Thus, our results suggest that there may be a subtle degree of Leydig cell dysfunction in severe cryptorchidism. Recently, Raivio *et al.* (30) reported normal androgen bioactivity in 3-month-old boys with spontaneous postnatal testicular descent, but unmeasurable androgen bioactivities in all cases of severe cryptorchidism. Thus, the increased LH levels in severely cryptorchid boys could be promoted by compromised androgen bioactivity despite sufficient amounts of immunologically measurable testosterone. To date, no studies of INSL3 levels in children with cryptorchidism have been published.

Our findings of increased gonadotropin and decreased inhibin B levels among severely cryptorchid boys indicate a mild primary testicular dysfunction. The inhibin B decrease together with a clear FSH increment are in agreement with previous findings in 12 cryptorchid boys, aged 1–4 yr, in whom low total inhibin was associated with increased FSH (15). Our finding is the first documentation of decreased inhibin B levels in cryptorchid boys by 3 months of age. Thus, it appears possible that this testicular dysfunction already exists during the fetal period. However, whether it is a cause or a consequence of cryptorchidism is unknown. The longitudinal design of our study also revealed another noteworthy observation. Finnish boys with late spontaneous testicular descent and boys with mild cryptorchidism (high scrotal

testis) had similar hormonal profiles, which differed not only from those of severely cryptorchid boys, but also from those of healthy controls. This suggests that spontaneous postnatal descent in congenital cryptorchidism does not ameliorate hormonal parameters, and that high scrotal testicular position may be a clinical sign of subtle primary testicular dysfunction. There are as yet no systematic follow-up studies of these two very mild forms of cryptorchidism to be able to speculate whether they would be of consequence for adult testicular function.

Our study design permitted us to take several potential confounding factors into account. Partly due to the matching procedure in the Finnish cohort, the cryptorchid and control groups were identical with respect to main known confounders. The only identified difference between the case and control groups was an increased rate of maternal diabetes (10.7% *vs.* 3.6%) among cryptorchid boys. However, maternal diabetes did not affect hormonal levels. Mothers of cryptorchid boys have been observed to more often have diabetes than mothers of healthy boys (Ref. 31; and Virtanen, H. E., A. E. Tapanainen, M. M. Kaleva, A.-M. Suomi, K. M. Main, N. E. Skakkebaek, and J. Toppari, submitted for publication), but conflicting results have also been published (32, 33). Altered SHBG levels in diabetic mothers (34, 35) might contribute to their steroid levels and thus influence the risk of cryptorchidism.

In conclusion, 3-month-old cryptorchid boys had significantly elevated FSH and LH levels associated with reduced inhibin B levels compared with controls, and there was an association with the severity and persistence of cryptorchidism from birth to 3 months of age. The findings in the Finnish population were much stronger than those in the Danish population. Because male reproductive health differs significantly between these two Nordic countries, with Finland having a much lower prevalence than Denmark in congenital cryptorchidism, hypospadias, testicular cancer, and reduced sperm quality, our findings indicate that the degree of impact of cryptorchidism on testicular function may differ between populations. Our observations support the hypothesis that cryptorchidism is associated with a primary testicular disorder; however, it may also be the first sign of impaired testicular function caused by cryptorchidism.

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