

# Trends in the incidence of cryptorchidism and hypospadias, and methodological limitations of registry-based data

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**Cryptorchidism and hypospadias share possible risk factors, such as intrauterine growth retardation. According to the data collected by the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS), apparently increasing trends in the incidence of hypospadias were found in Sweden during the 1960s, and in Norway, Denmark, England and Hungary during the 1970s. In Norway and Denmark, the increase continued in the 1980s, while in the USA it has continued from the 1970s to the 1990s. Finland has shown a lower reported rate of hypospadias than other Nordic countries. However, it is difficult to make comparisons between countries because of variable inclusion criteria. Furthermore, the reliability of the data depends on correct ascertainment and reporting of the cases. The ICBDMS has also collected data on cryptorchidism, but these appear to be unreliable because of a discrepancy with the data from cohort studies. According to two comparable English studies, the incidence of cryptorchidism in full-term boys approximately doubled between the 1950s and the 1980s. Regionally there are large differences: e.g. in Finland the incidence of cryptorchidism is clearly lower than in Denmark. Regional and temporal trends may help to identify environmental factors that might be associated with these disorders.**

*Key words:* cryptorchidism/hypospadias/testicular cancer/testis

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### Introduction

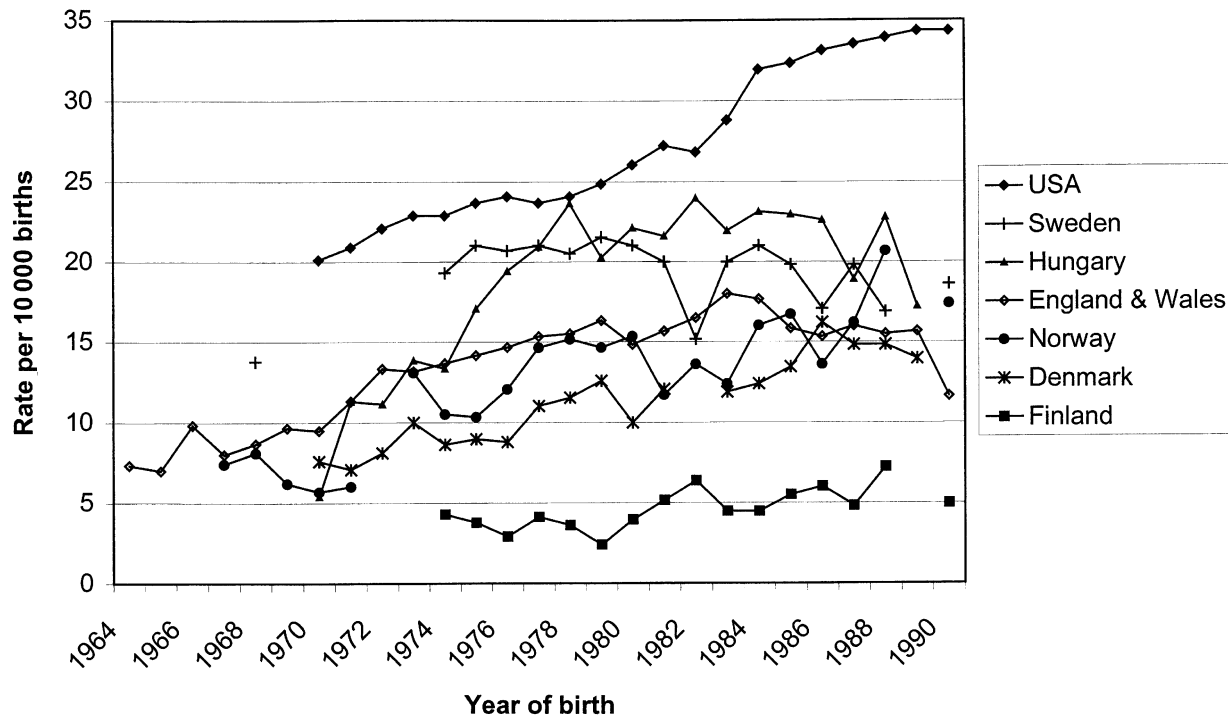
Although cryptorchidism and hypospadias are the most common developmental abnormalities of the male urogenital organs, they have often been considered mild malformations and have been reported poorly to malformation registers. Many countries, including Finland, have therefore stopped registering undescended testes (cryptorchidism). For hypospadias, the registers are more reliable, but comparisons between areas are discouraged because each register has different definitions for the conditions and the diagnoses, ascertainment and notification vary greatly. The International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) collects data from countries that have actively functioning registries, i.e. countries where systematic

collection and analysis of data is requested for comprehensive monitoring of congenital malformations. The ICBDMS does not accept data from registries that do not actively collect their data, but rather only relates health statistics from administrative sources. Despite this requirement, the registries differ from each other: in many programmes (e.g. Australia, Japan) only severe hypospadias (i.e. penile shaft, scrotum, perineum) are registered, and distal, coronal and glandular hypospadias are not registered at all. However, the majority of hypospadias are distal. Furthermore, defects among stillbirths are usually included in the registers, but definitions for stillbirths vary (Paulozzi, 1999). Variability in reporting therefore remains a major problem in malformation registers (Hemminki *et al.*, 1993).

### Hypospadias

An increase in the incidence of hypospadias has been reported in Scandinavian countries Denmark, Norway and Sweden (Källén and Winberg, 1982; Källén *et al.*, 1986; ICBDMS, 1991), Hungary (Czeizel, 1985), as well as in England and Wales (Matlai and Beral, 1985), the USA (Paulozzi *et al.*, 1997) and Italy (ICBDMS, 1991) (Figure 1). Interestingly, the increase occurred during different time periods in different areas, and in

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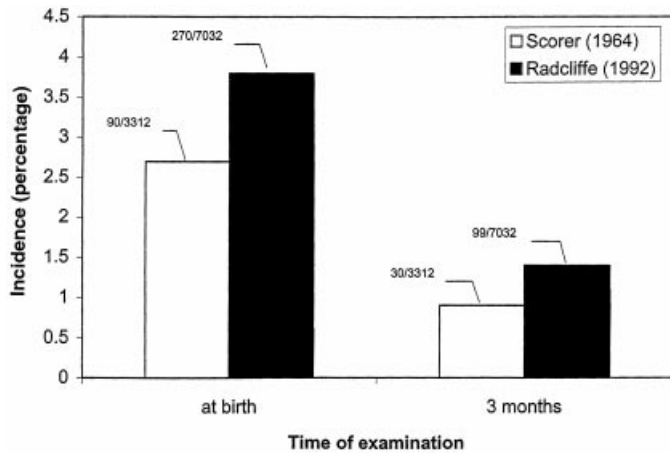
**Figure 1.** Incidence of hypospadias in Nordic countries, England and Wales, Hungary, and the USA (ICBDMS, 1991; Paulozzi *et al.*, 1997).

most European countries it seemed to level off during the 1980s. In Sweden, the incidence of hypospadias increased as early as the 1960s, whereas in Norway and Denmark it increased during the 1970s and early 1980s. At the end of the 1980s, the incidence was between 15–20 per 10 000 births in these countries. In the fourth Nordic country, Finland, the reported incidence during the 1980s was only one-third that of the neighbouring countries, and only mild forms of hypospadias were reported to have increased in number (Paulozzi, 1999). In Hungary, the incidence increased from 5.5 to 23.9 per 10 000 births during the 1960s and 1970s, while in England and Wales the corresponding increase was from 7.3 to 16 per 10 000 births between the 1960s and 1980s. In the USA, no levelling off could be seen in two population-based surveillance systems, the Birth Defects Monitoring Programme (BMDP) and the Metropolitan Atlanta Congenital Defects Programme (Paulozzi *et al.*, 1997). Between 1968 and 1993, the incidence of hypospadias doubled in the Metropolitan Atlanta area, and the ratio of severe to mild forms of hypospadias increased from three- to five-fold. In the national programme (BMDP) an increase from 20.2 to 39.7 per 10 000 births was reported for the period 1970–1993. All regions showed parallel increasing trends. The increase in the ratio of severe to mild forms of hypospadias in the Atlanta region suggests that the trend is not caused by an increase in the notification of mild cases. However, this remains a possible explanation for the increased rates in other countries.

As discussed earlier, registry data on cryptorchidism and hypospadias are very problematic as a basis for epidemiological studies. Unfortunately, registries are almost the only source for data thus far. National and international birth cohort studies may help to evaluate the accuracy of registry systems. We have performed a cohort study in Turku University Central Hospital

between 1997 and 1999 (Virtanen *et al.*, 2001), during which period a total of 11 162 children was born in the hospital. Only one case of severe hypospadias was found during the period, and the incidence of 17 per 10 000 births was much higher than previously reported (ICBDMS, 1991). However, the figures were close to the current data from the Finnish Birth Malformation Register (14.2 per 10 000 in 1996; ICBDM, 1998) that is now surveying the cases more actively than previously. The first impression of the findings was that there was an abrupt increase, but discussions with registry authorities made us cautious regarding previously published data, because the registration system was changed in 1993; the latest figures have resulted from an active surveillance of hospital registers by the agency. This change in registration system revealed that the hospitals were clearly under-reporting hypospadias. Furthermore, a recently published study based on Finnish hospital discharge registers indicated a similar rate of hypospadias in boys born between 1970 and 1986 as the rate in the cohort study (Aho *et al.*, 2000). No time trend was observed, indicating that in Finland only one-third of hypospadias cases were reported in the 1970s and 1980s (Aho *et al.*, 2000). Others (Källén *et al.*, 1986) estimated that during the 1970s one-third of the boys with hypospadias requiring surgery were primarily not registered in Sweden, and almost two-thirds remained unreported in Denmark. This suggests that there was a difference in the incidence between Finland and other Nordic countries, even though the figures for Finland in the ICBDM were too low.

A collaborative study with common methods and definitions has been performed in Denmark at the same time as the cohort study in Turku. In Denmark, the incidence seems to be considerably higher than in Finland (J. Toppari and colleagues, unpublished data), even though the current Finnish figures are



**Figure 2.** Incidence of cryptorchidism in full-term boys at birth and at the age of 3 months in England during the 1950s (Scorer, 1964) and the 1980s (John Radcliffe Hospital Cryptorchidism Study Group, 1992).

close to the register figures for Denmark published in 1991. Thus, the Danish registry data and the findings from the cohort study may differ markedly, and the numbers in the ICBDMS may present low estimates of true values, particularly in programmes that include the mild forms of hypospadias.

### Cryptorchidism

Cryptorchidism is registered more unreliably than hypospadias in the ICBDMS, and it is difficult to evaluate the data in a meaningful way. The reported values vary from 4 to 42 per 10 000 births (ICBDMS, 1991; Paulozzi, 1999; Toppari and Kaleva, 1999), these figures being much lower than those from cohort studies. For example, in the USA the incidence was less than 40 per 10 000 during the 1980s according to ICBDMS, but at the same time 19.8% of the boys with birth weight <2.5 kg and 2.2% of those with birth weight >2.5 kg were reported to be cryptorchid in the New York area (Berkowitz *et al.*, 1993). This cohort consisted of 6935 male infants. In the US-Atlanta system, the rate quadrupled during the 1980s but then fell sharply, reflecting changes in the register rather than true trends (Paulozzi, 1999). Thus, we cannot rely on registry data on the incidence of cryptorchidism. Highly variable figures are also reported from school and army surveys, in which the diagnostic criteria are often equivocal. The most reliable data originate from cohort studies in which the case definitions and examination techniques have been clearly described. The above-mentioned study from New York is such a study. It used similar criteria as two English studies (Scorer, 1964; John Radcliffe Hospital Cryptorchidism Study Group, 1992). In these three studies, previously described criteria (Scorer, 1964) were used to diagnose cryptorchidism. The two English studies also offer an opportunity to analyse temporal trends.

In England, the incidence of cryptorchidism increased more than 60% between the 1950s and 1980s (Figure 2). Scorer's study contained more than 3000 newborn boys in London during the late 1950s (the accurate time period was not specified). The incidences at birth were 21% and 2.7% for boys weighing less or

more than 2500 g respectively, while at the age of 3 months the corresponding figures were 1.7% and 0.9%. According to the John Radcliffe Hospital Study Group (1992), the incidence of cryptorchidism during 1984–1988 in Oxford was 4.1% at birth and 1.6% at 3 months for boys weighing >2499 g, the cohort consisting of 7441 consecutive newborn boys. The testes normally descend during late pregnancy, and therefore most testes that are undescended at birth in premature babies descend spontaneously before the age of 3 months. Hence, it is essential to specify the age at analysis and better to assess the data only from full-term babies.

Other data from Great Britain support the finding that the incidence of cryptorchidism has increased. In England and Wales, 1.4% of boys in a 1952 birth cohort underwent orchidopexy before the age of 15, whereas the corresponding figure in a 1977 cohort was 2.9% (Chilvers *et al.*, 1984). Of course, treatment strategies may have changed over that period, and the change is only suggestive of a true trend. According to hospital discharge data, the incidence of cryptorchidism increased also in Scotland between the 1960s and 1980s (Campbell *et al.*, 1987).

Several studies on the incidence of cryptorchidism in Denmark have been published. In the late 1950s, the incidence at birth in boys weighing >2500 g varied between 1 and 1.8% in different study groups (Buemann *et al.*, 1961). According to a cohort analysis of the data from the Danish National Register of Hospital In- and Outpatients, the incidence rate was ~2% during the period between 1982 and 1985 (Thorup and Cortes, 1990). Some school surveys suggested an incidence of 7% (Blom, 1984), though this figure may also include retractile testes, or ascending testis, and acquired cryptorchidism could thus partly explain the difference.

In our on-going cohort studies in Finland and Denmark, substantial differences in the incidence have emerged between countries. In Finland, the incidence is comparable with that in England during the late 1950s, whereas in Denmark it is double that at the age of 3 months (Kaleva *et al.*, 2000), suggesting an adverse temporal trend in Denmark. No previous data are available from Finland.

### Aetiology and risk factors of cryptorchidism and hypospadias

Development of the male external genitalia is dependent on normal androgen action. Defects in the production of dihydrotestosterone or androgen insensitivity result in hypospadias, and androgen insensitivity can be classified according to the severity of the disturbance. Transinguinal descent of the testes also depends on androgens (Hutson *et al.*, 1997). However, disrupted androgen action can explain only a minority of hypospadias cases, and an even smaller proportion of cases with cryptorchidism. In animals, several developmental genes have been implicated in normal testicular descent. Formation of the gubernaculum that is necessary for testicular descent depends on functional *insulin-like factor 3 (Insl3)* gene in the mouse (Nef and Parada, 1999; Zimmerman *et al.*, 1999), and its targeted deletion causes cryptorchidism. Several polymorphisms in this gene have been found in humans, but they were not associated with cryptorchidism (Koskimies *et al.*, 2000; Krausz *et al.*, 2000; Tomboc *et al.*, 2000). Two mutations were identified in the connecting peptide

region of the protein which could have caused cryptorchidism in the two patients (Tomboc *et al.*, 2000). Thus, among many hundreds of patients examined, only two have shown the *Insl3* gene defect to date. However, oestrogen treatment can disrupt the function of the gene and thereby delay testicular descent in mice (Emmen *et al.*, 2000; Nef *et al.*, 2000). Oestrogens can cause cryptorchidism in experimental animals, and this might be one mechanism underlying the effect. *Homeobox (HOX)* genes influence the development of genital organs, and may also play a role in maldevelopment. In mice, several *HOX* genes have been shown to be involved in the regulation of testicular descent (Rijli *et al.*, 1995; Satokata *et al.*, 1995). Others (Kolon *et al.*, 1999) reported a high number of mutations and polymorphisms in the *HOXA10* gene in cryptorchid boys, most evidently in familial cases. Functional analyses of the mutations have not been performed, and specific associations between mutations and non-descended testes require further study. Endocrine disruption of the function of the developmental genes, such as *Insl3* and the *HOX* family may be one reason for cryptorchidism, and possibly also for hypospadias.

Common aetiological factors have been suggested for cryptorchidism and hypospadias (Akre *et al.*, 1999; Weidner *et al.*, 1999). Both abnormalities are associated with an increased risk of testicular cancer (Møller *et al.*, 1995). The incidence of testicular cancer has increased rapidly over the past few decades (Adami *et al.*, 1994; Forman and Møller, 1994). Furthermore, poor semen quality may share risk factors with these conditions. According to one hypothesis, endocrine disruption causes the disturbances (Sharpe and Skakkebaek, 1993). This hypothesis is consistent with findings in animal models and studies on the effects of diethylstilboestrol in humans (for references, see Toppari *et al.*, 1996), but it is difficult to assess epidemiologically.

Several case-control studies on the risk factors of cryptorchidism and hypospadias have been published (Czeizel *et al.*, 1979, 1981; Swerdlow *et al.*, 1983; Hjertkvist *et al.*, 1989; Berkowitz *et al.*, 1995; Møller and Skakkebaek, 1996; Jones *et al.*, 1998; Akre *et al.*, 1999; Weidner *et al.*, 1999). These studies show a strong association between low birth weight and cryptorchidism and hypospadias. Since low birth weight is a natural consequence of prematurity, gestational age must also be taken into account. This analysis in recent studies has clearly shown that gestational age-adjusted low birth weight is a risk factor. Many of the studies have also linked low maternal parity to an increased risk of cryptorchidism and hypospadias, although this association may disappear once low birth weight is adjusted for. Interestingly, these are the same risk factors that have been identified as risk factors for testicular cancer (Møller and Skakkebaek, 1997).

Genetic reasons, such as androgen receptor mutations, may directly cause cryptorchidism and/or hypospadias, and genetic susceptibility to the conditions may also vary. According to a recent Danish study (Weidner *et al.*, 1999), the risk of cryptorchidism was four-fold in boys whose brother had been cryptorchid, and the risk for hypospadias was 10-fold if a brother had hypospadias. The risk for one of the malformations was three-fold if a brother had been cryptorchid or had hypospadias. Thus, the conditions may have distinct genetic predispositions and common environmental causes (Møller and Weidner, 1999).

## Conclusions

Epidemiological studies suggest that the incidence of both cryptorchidism and hypospadias has increased in many countries. Furthermore, there are large regional differences in incidence between countries. However, registry-based studies do not permit reliable comparisons to be made between countries, and the data contain many uncertainties. Further epidemiological studies using standardized diagnostic criteria and examination techniques are required in order to obtain a more precise estimation of the trends in the incidence of these malformations, and also of the possible environmental effects present in different countries. Advances in understanding the regulation of the descent of the testes and development of the sex organs combined with genetic and environmental epidemiology will provide the answers to questions concerning the aetiology of these malformations. The identification of possible environmental causes may provide us with opportunities to prevent these relatively common disorders.

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