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Prevalence of Hypospadias in Danish Boys: A Longitudinal Study, 1977–2005

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Abstract

Background: Hypospadias is a relatively common congenital malformation. Data on temporal trends in prevalence of hypospadias are conflicting. It is unclear whether changes of maternal age distribution over time are associated with changes in hypospadias prevalence.
Objective: To study changes in prevalence of hypospadias in Denmark during a 29-yr period and to investigate whether maternal age was associated with the prevalence of hypospadias.
Design, setting, and participants: Through Denmark's National Patient Registry, covering all Danish hospitals, we identified all boys diagnosed with hypospadias in Denmark. From the Danish Medical Birth Registry, we obtained information on maternal age and on the annual total number of live-born boys from 1977 to 2005.
Measurements: Prevalence of hypospadias at birth.
Results and limitations: Among 921 745 boys born alive from 1977 to 2005, we identified 3490 boys with hypospadias. The prevalence increased from 0.24% in 1977 to 0.52% in 2005, corresponding with an annual increase in prevalence of 2.40% (95% confidence interval: 1.94–2.86). The prevalence of hypospadias did not differ according to maternal age. The mean annual prevalence was 0.38% in sons of mothers aged ≤25 yr, 0.37% in sons of mothers aged 26–30 yr, 0.39% in sons of mothers aged 31–35 yr, and 0.39% in sons of mothers >35 yr.
Conclusions: The hypospadias prevalence was increasing in Denmark from 1977 to 2005. Increased maternal age did not explain this trend.

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1. Introduction

Hypospadias is a relatively common congenital anomaly that occurs with a reported prevalence of 0.3–0.8% for live male births [1]. Since the 1970s, reports from several countries have shown an increase in the prevalence of hypospadias [2–10], but, overall, the data are conflicting [2,9].

The etiology of hypospadias remains largely unknown. In 1993, Sharpe and Skakkebaek suggested a link between an increasing level of environmental agents with estrogenic effect and the increased prevalence of hypospadias [11,12]. According to one proposed biologic mechanism, the elevated estrogen exposure causes changes in concentrations of sex hormones regulating the fetal genital development during pregnancy weeks 8–14 [12]. During the past decade, the proportion of women who give birth after age 35 has likewise increased [11,13]. An American study has shown that the prevalence of hypospadias is associated with increasing maternal age [14], but others did not find this [15,16]. Knowledge of differences in the prevalence of hypospadias in different populations (eg, those with exposure to different materials in certain regions or according to differences in lifestyle) may be useful in studying the etiology of hypospadias.

We aimed to examine the 29-yr trend in prevalence of hypospadias among children in Denmark, using routinely collected data from Danish population registries, and to examine the putative impact of maternal age on hypospadias occurrence.

2. Materials and methods

We included all boys born alive (according to the Danish Medical Birth Registry) in Denmark between 1977 and 2005 and who were hospitalized or seen in an outpatient clinic with a hypospadias diagnosis, regardless of the severity. We identified these cases in the National Patient Registry, which was established in 1977 and which has nearly complete coverage of hospital admissions countrywide [17]. In the National Patient Registry, diagnoses have been recorded according to the International Classification of Diseases (ICD) 8th revision (ICD-8) between 1977 and 1993 and according to the ICD 10th revision (ICD-10) thereafter. The codes for hypospadias are: 752.20, 752.21, 752.22, 752.28, and 752.29 (from ICD-8); and Q54.0–Q54.9 (from ICD-10).

Since 1968, a unique 10-digit civil registration number has been assigned to each Danish resident at birth by the Central Office of Civil Registration [18]. The date of birth and gender are encoded in this number. This number also allows unambiguous linkage between the different registries in Denmark. It is possible to compute the age of the mother at the birth of a child because a maternal civil registration number is recorded in the birth registry.

We computed the prevalence of hypospadias for each calendar year as the number of boys born that year with a hypospadias diagnosis registered within the first year of life divided by the total number of boys born alive that year. The relative change in prevalence per year was obtained by using Poisson regression, with the logarithm of the number of live-born boys used as the offset [19]. For each calendar year, we computed the expected number of hypospadias cases as the total number of male births multiplied by the estimated prevalence. We stratified the analyses according to maternal age (≤25 yr, 26–30 yr, 31–35 yr, >35 yr) and compared the prevalence of hypospadias in the different maternal-age groups by computing the prevalence rate ratios with adjustment for calendar time using Poisson regression. Analyses were performed by using SAS 9.1 (SAS Institute, Cary, NC, USA).

3. Results

Among a total of 921 745 live-born boys registered in the birth registry, we identified 3490 cases of hypospadias recorded in the National Patient Registry (Table 1). The annual prevalence increased during the study period from 0.24% in 1977 to 0.52%

Table 1 – Observed and expected number of boys with hypospadias by year of birth

Year of birth	Total live male births	Observed cases	Expected cases
1977	31 821	76	85.32
1978	31 875	74	87.41
1979	30 554	99	85.70
1980	29 351	81	84.21
1981	27 116	74	79.57
1982	27 061	92	81.22
1983	26 000	94	79.82
1984	26 572	112	83.44
1985	27 464	108	88.21
1986	28 435	87	93.41
1987	29 076	112	97.69
1988	30 324	100	104.21
1989	31 473	111	110.63
1990	32 618	103	117.27
1991	32 997	97	121.34
1992	34 810	130	130.93
1993	34 609	96	133.14
1994	35 639	132	140.24
1995	35 886	159	144.43
1996	34 818	126	143.33
1997	34 835	148	146.67
1998	34 108	129	146.89
1999	33 956	147	149.57
2000	34 490	167	155.39
2001	33 464	161	154.21
2002	32 980	145	155.45
2003	33 246	183	160.28
2004	33 227	174	163.84
2005	32 944	173	166.15

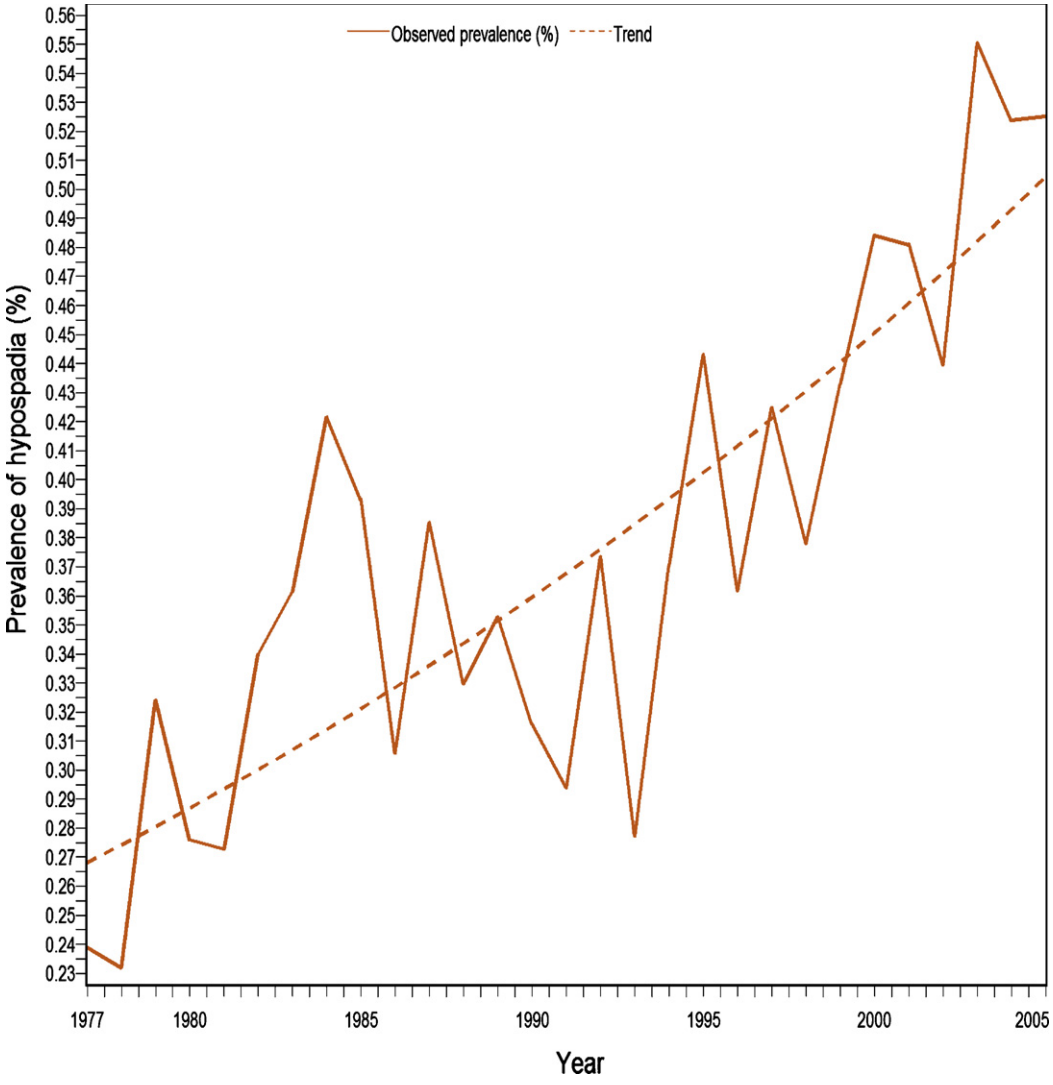

Fig. 1 – Observed prevalence and trend of hypospadias among newborn Danish boys, 1977–2005.

in 2005. This increase corresponds with a mean annual increase of 2.40% (95% confidence interval [CI]: 1.94–2.85) (Fig. 1). In the mid-1980s, there was a steep increase in the prevalence, followed by a leveling off from the mid-1990s.

Table 2 – Prevalence of hypospadias and maternal age among Danish boys born between 1977 and 2005, according to maternal age

Maternal age	No. of hypospadias cases	Mean annual prevalence of hypospadias	Prevalence rate ratio (95% CI)
≤25 yr	823	0.38%	1 (ref)
26–30 yr	1307	0.37%	0.92 (0.84–1.00)
31–35 yr	971	0.39%	0.91 (0.82–1.00)
>35 yr	389	0.39%	0.90 (0.79–1.03)

CI = confidence interval.

Table 2 shows prevalence of hypospadias according to maternal age. We found a similar mean annual prevalence of hypospadias in the four maternal age groups. The mean annual prevalence was 0.38% in sons of mothers aged ≤25 yr, 0.37% in sons of mothers aged 26–30 yr, 0.39% in sons of mothers aged 31–35 yr, and 0.39% in sons of mothers aged >35 yr. Using mothers who were ≤25 yr at their son's birth as the reference, the prevalence ratios for giving birth to a son with hypospadias were 0.92 (95% CI: 0.84–1.00) for mothers aged 26–30 yr, 0.91 (95% CI: 0.82–1.00) for mothers aged 31–35 yr, and 0.90 (95% CI: 0.79–1.03) for mothers >35 yr (Table 2).

4. Discussion

According to our study of more than 900 000 live-born boys, the prevalence of hypospadias in Den-

mark has increased in recent decades, especially in the mid-1980s and early 1990s. Changes in maternal age did not explain the increase.

We had virtually complete population coverage and long follow-up through access to data linked from different medical and population registries. In Denmark, the National Health Service universally enables free access to health care, thereby largely removing referral and diagnostic biases. At the same time, we based our information on hypospadias on diagnoses coded by physicians at discharge from hospitals or at outpatient visits in hospital clinics, and it is well known that these diagnoses may have coding errors. A previous Danish study from one county, however, found data on birth defects to be of high quality, with estimated 80–85% of diagnoses correctly coded, which is greater than estimates for birth defects data routinely collected in other countries [20].

More recent population-based data from diverse geographic regions tend not to agree with our finding of increasing hypospadias prevalence [2,9,16,21]. A study from the Metropolitan Atlanta Congenital Defects Program (MACDP) showed that the prevalence rate of severe cases increased from 1968 to 1993 while the ratio of mild to severe cases decreased [11]. This is evidence against the increased prevalence being explained by increased surveillance. Similarly, the US Centers for Disease Control and Prevention have reported an increase in prevalence predominantly among the severe cases of hypospadias in the United States while the prevalence of mild cases remained constant [4]. Based on recorded discharge diagnoses, we were unable to assess severity of hypospadias.

The average maternal age at first pregnancy has increased in recent years, and there is an association between the maternal age and the prevalence of congenital anomalies [14]. It is postulated that exogenous factors, such as estrogen level during the first months of pregnancy, may be a causal factor in the development of the anomalies, and older mothers may be more susceptible to hormonal disruption due to a weakening of maternal defense mechanisms with age [14]. In our study, however, with a relatively high number of births in different maternal age groups, we did not observe a difference of hypospadias prevalence according to maternal age, even for the oldest mothers. This finding is in accordance with other studies [6,15,16]. At the same time, in the period from 1996 to 2005, we found evidence for an increase in assisted reproductive techniques, based on data obtained from the Danish in vitro fertilization (IVF) registry. According to this registry, the number of live-born singletons (both males and females) born after IVF has increased by approximately 40%, from 1110 births in 1996 to 1537 births in 2005. We found that the annual number of children born after IVF treatment correlates with the annual prevalence of hypospadias (Spearman correlation coefficient: 0.72), suggesting that increased use of IVF may explain some of the increase in the hypospadias prevalence [22].

A recent Danish study found a high total rate of hypospadias (4.6%) in a large prospective cohort of 1072 newborn boys. The condition was associated with elevated serum follicle-stimulating hormone (FSH) levels at 3 mo of age [23]. The study also confirmed an association between fetal growth impairment and risk of hypospadias. We did not examine social and familial conditions, prematurity, birth weight, placental weight, reproductive hormone levels, or decreased fertility [6,16] with respect to their association with hypospadias. Those factors may be important subjects to investigate in future studies.

5. Conclusions

The increase in prevalence of hypospadias observed in our study is more likely to have occurred due to environmental causes rather than to genetic factors because these changes have occurred over a relatively short period.

Author contributions: Lars Lund had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lund, Sørensen, Nørgaard.
Acquisition of data: Lund, Pedersen.
Analysis and interpretation of data: Lund, Engebjerg, Ehrenstein, Pedersen.
Drafting of the manuscript: Lund, Ehrenstein.
Critical revision of the manuscript for important intellectual content: Lund, Sørensen, Nørgaard, Ehrenstein.
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