Human Reproduction Vol.17, No.4 pp. 1112–1115, 2002

A high hypospadias rate in The Netherlands

Frank H.Pierik[1,2,6], Alex Burdorf[2], J.M.Rien Nijman[3], Sabine M.P.F.de Muinck Keizer-Schrama[4], R.E.Juttmann[2,5] and Robertus F.A.Weber[1]

Departments of [1]Andrology, [2]Public Health, [3]Paediatric Urology and [4]Paediatric Endocrinology, Erasmus Medical Centre, P.O.Box 1738, 3000 DR Rotterdam and [5]Department of Child Health Care, The Rotterdam Homecare Foundation, P.O.Box 21994, 3001 AZ Rotterdam, The Netherlands

[6]To whom correspondence should be addressed at: Department of Public Health, Erasmus MC, PO Box 1738, 3000 DR Rotterdam, The Netherlands. E-mail: pierik@mgz.fgg.eur.nl

BACKGROUND: Reports on increasing hypospadias trends are based on birth defect registries, which are prone to inaccuracy. We assessed the prevalence of hypospadias precisely, by prospective examination of all newborns in Rotterdam over a 2-year period. METHODS: A total of 7292 consecutive male births were examined for the presence of hypospadias, classified by severity. RESULTS: The frequency of hypospadias in newborn boys was 0.73% (53/7292). The rate among live births was 38 per 10 000, which is 6 times the previously reported rate for the Southwestern Netherlands (6.2) ($P < 0.0001$). This registry excludes glandular hypospadias. Without glandular cases, our rate is 26 per 10 000, which is still 4-fold higher ($P < 0.0001$). The ratio of minor to major hypospadias was 0.3. In 79% of cases, surgery was indicated. CONCLUSIONS: We found a 4-fold higher than expected hypospadias rate, which may be explained by case ascertainment differences. The proportion of major cases was higher than generally assumed. This study provides evidence for substantial geographical differences. Explanations for temporal and geographical differences need to be explored. To monitor hypospadias rates and trends accurately, complete case ascertainment, including standardized classification of severity, is warranted.

Key words: birth defect registries/congenital abnormality/epidemiology/hypospadias/prevalence

Introduction

Hypospadias is a developmental anomaly defined by a displacement of the urethral meatus from the tip of the glans penis to the ventral side of the phallus, scrotum, or perineum (Figure 1), and often requires surgical reconstruction. Some reports have suggested an increase in hypospadias rates during the period 1960–1990 in European and USA registries (Czeizel, 1985; Matlai and Beral, 1985; Källén *et al.*, 1986; Paulozzi *et al.*, 1997; Paulozzi, 1999). There are large geographical differences in reported hypospadias rates, ranging from 2.0 to 39.7/10 000 live births (EUROCAT Working Group, 1997; Paulozzi, 1999; Toppari *et al.*, 2001). Several explanations have been proposed for the increasing trends and geographical differences. As male sexual differentiation is critically dependent on normal androgen concentrations, increased exposure to environmental factors affecting androgen homeostasis during fetal life (e.g. endocrine disrupters with oestrogenic or anti-androgenic properties) may cause hypospadias (Sharpe and Skakkebæk, 1993; Sharpe, 2001; Skakkebaek *et al.*, 2001; Sultan *et al.*, 2001a). Genetic factors may also predispose for development of hypospadias (e.g. androgen receptor gene mutations; homebox gene polymorphisms) (Boehmer *et al.*, 2001; Sultan *et al.*, 2001b; Toppari *et al.*, 2001).

However, the temporal and geographical differences in hypospadias rates may also be explained by methodological problems. The published hypospadias trends are exclusively derived from birth defect registries. Since registries are not based on a structured assessment of all newborns, cases may not be diagnosed or reported, leading to underreporting. Differences in case ascertainment in these registers may account for some of the observed trends, but the extent of confounding by these differences is not known. Dolk recently discussed the possibility that the rise in hypospadias is due to an increasing tendency to report minor hypospadias. This hypothesis is difficult to prove, as the subtype is not specified in the majority of cases reported to registries (Dolk, 1998). We accurately assessed the rate of hypospadias, including subtypes, by prospective structured examination of newborns in Rotterdam in a 2-year period.

Materials and methods

The study protocol was approved by the local Ethics Committee.

Study design and protocol

In a cross-sectional design, 7292 consecutive newborn boys were examined for hypospadias at their first visit to Child Health Care

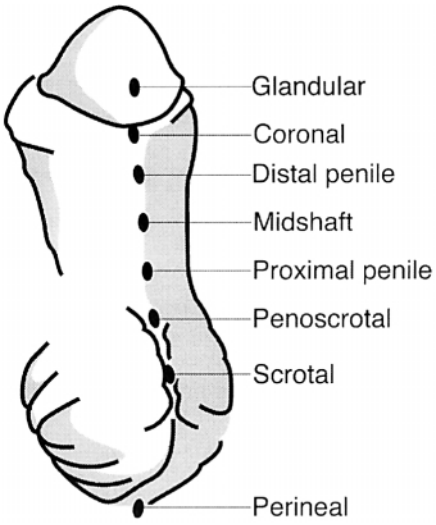

Figure 1. The classification of hypospadias

Centres (CHC) in Rotterdam, followed by verification and grading by a paediatric urologist and a paediatric endocrinologist. In the Netherlands, CHC receive notifications of all newborns within 2 days after registration in the municipal birth register. CHC invite all parents to participate in the national preventive child healthcare programme, including early detection of health risk factors, health education, and vaccination. After training in a standardized examination, CHC physicians (n = 30) examined the external genitalia of boys born in Rotterdam in the period October 1998 to October 2000, at their first visit to the CHC, before the age of 6 months. Hypospadias was defined as a displacement of the urethral meatus from the tip of the glans penis to the ventral side of the phallus, scrotum or perineum.

Of 7652 boys registered in the birth register, we report on 7292 boys (95%) who were examined by CHC physicians. To restrict potential failure to identify borderline cases, CHC physicians were instructed to refer cases if they were in doubt on the diagnosis. Moreover, cases with preputial abnormalities (e.g. cleft prepuce or inability to retract the prepuce) were also indexed in the CHC information system, as a hidden hypospadias may be present. Index cases were referred to a paediatric urologist and a paediatric endocrinologist at the Sophia Children's Hospital, Erasmus Medical Centre, Rotterdam, for verification and classification. As the classification requires ample experience, especially in cases with chordee (i.e. bending of the penis), grading was exclusively based on the examination by a paediatric urologist with extensive experience in diagnosis and surgical correction of hypospadias. The classification is based on the grading described by Duckett, following the anatomical position of the meatus (see Figure 1) (Duckett, 1998). Moreover, the need for surgical correction was assessed.

To allow comparison with the grading of hypospadias as minor and major in other reports, we chose to conform to their criteria. In EUROCAT (the European Registration of Congenital Anomalies), hypospadias is defined as minor 'when the opening of the urethra is before the coronary sulcus, glandular or first-degree' (EUROCAT Working Group, 1997), which corresponds to glandular in our grading system (Figure 1). In the MACDP grading used by Paulozzi, the glandular forms are categorized as first-degree, which is referred to as minor, whereas second and third degree together are classified as severe (major) (Paulozzi *et al.*, 1997).

Hypospadias rates are presented as the number of cases per 10 000 live births, thus including females, to allow comparison with other studies. These rates are calculated using the sex ratio of male to female live births in the study period.

Table I. Number of hypospadias by severity in a population of 7292 newborn boys in The Netherlands

Hypospadias type	Cases	Percentage of total
Glandular	12	22.6
Coronal	15	28.3
Distal penile	11	20.8
Midshaft	5	9.4
Proximal penile	3	5.7
Penoscrotal	1	1.9
Scrotal	1	1.9
Unknown	5	9.4
Total	53	

Hypospadias rate among boys: 53/7292 = 0.73%.

Statistics

Hypospadias rates are presented with 95% confidence intervals (CI). For comparison of hypospadias rates, χ^2-statistics are calculated, based on 2×2 cross-tabulations.

Results

CHC physicians examined 7292 newborn boys, and referred 60 boys with potential hypospadias or preputial abnormalities to the team of paediatricians (a paediatric urologist and a paediatric endocrinologist). The team diagnosed hypospadias in 53 of the 60 referred boys, whereas the other seven newborn boys had normal localization of the meatus despite a preputial abnormality. Thus, 88% of potential cases diagnosed by CHC physicians were verified.

The frequency of hypospadias in newborn boys was 0.73% [53/7292; 95% confidence interval (CI) 0.54–0.92%]. As 7652 boys and 7118 girls were born alive in the study period, the sex ratio of male to female was 1.075. Based on the sex ratio, the rate among live births (males and females) was 38 per 10 000 (CI 28–48). Table I shows the distribution of cases by severity. For five cases, the hypospadias grade was unknown because their parents were not willing to visit the Sophia Children's Hospital for verification, as their son had already been referred to another hospital. In these cases hypospadias was confirmed by a local paediatrician, but information on the classification was not used. The ratio of minor to major hypospadias was 0.3, on the basis of 12 minor (glandular) cases and 36 major cases (more proximal subtypes).

In 79% (38/48) of cases with known classification of severity, surgery was indicated. Surgery was required in three of 12 glandular, 14 of 15 coronal, and all penile, penoscrotal and scrotal cases, on the basis of micturition problems or chordee (i.e. bending of the penis).

Discussion

In a systematic inspection of 7292 consecutive male births in Rotterdam, we found a hypospadias rate of 38/10 000 (CI 28–48) live births in Rotterdam, which is significantly higher than expected on the basis of registry data. This rate is about 6 and 4 times higher than the rate for the Southwestern Netherlands (6.2/10 000) and 16 European regions (9.6/10 000) respectively

(EUROCAT Working Group, 1997) ($P < 0.0001$). Our study area constitutes ~25% of the births of the region Southwestern Netherlands. The EUROCAT registry excludes glandular hypospadias, unless occurring in combination with other anomalies. When applying the same definition (excluding hypospadias of glandular and unknown type), our observed rate is 26 per 10 000 (CI 17–33), which is still 4-fold higher than the EUROCAT rates for the Southwestern Netherlands ($P < 0.0001$). The registry-based hypospadias rates vary considerable, with a range of 6.3–25.0 for Europe (EUROCAT Working Group, 1997; Toppari *et al.*, 2001), and the highest rate (39.7) reported in the USA (Paulozzi *et al.*, 1997). It is difficult to compare our rate with registry-based rates, as registries may be flawed by methodological problems. For example, some ascertainment biases have been reported for the Southwestern Netherlands monitoring system (EUROCAT Working Group, 1997). As registries rely on the completeness of detection and reporting by health care providers, or on active searches in sources containing medical data (e.g. surgery records, birth certificates), cases may be missed. Moreover, assumptions are being made as to the number of reference subjects, which are not all examined for the anomaly. The denominator is approximated based on the number of births in participating hospitals or a geographical area, which can be biased, for example by a selection in the choice of hospitals, or delivery across the border of the registry area. We examined the complete reference population, so that both the numerator and denominator were exact. Further study would have to confirm whether the rate in Rotterdam is representative for the whole of the Netherlands. Although no differences were noticed between the two EUROCAT regions in the Netherlands (the urbanized area of Southwestern Netherlands and the predominantly rural area of Northeastern Netherlands) (EUROCAT, 1997), this comparison is based on registry data that may not be accurate.

Several authors have reported a rising trend in the occurrence of hypospadias. Dolk commented on this trend, and pinpointed the pitfalls in the interpretation of this data (Dolk, 1998). A major shortcoming of previous research is the lack of specification of the severity of hypospadias cases, whereas registries may exclude minor forms, for which criteria are not standardized. It has been suggested that the apparent increase may in fact be due to an increasing tendency to report minor cases to registries. This hypothesis could not be tested properly, as the severity was unknown in most cases reported to registries. A ratio minor/major of ~3 is generally assumed, on the basis of a large group of hypospadias cases (Paulozzi *et al.*, 1997). For this latter group, the hypospadias grade was specified in only ~40% of the cases. We verified the hypospadias severity among 91% of newborn boys with hypospadias and observed a minor/major rate of 0.3. As different cut-offs for minor and major are in use, we also provide the individual hypospadias subtypes. Clearly, the diagnostic criteria for hypospadias subtypes should be standardized. If our severity distribution is representative of the USA study population (Paulozzi *et al.*, 1997), increased reporting of glandular cases could not have explained the doubled hypospadias rate. Unfortunately, no accurate historical data are available to assess hypospadias trends over time in our study area. Our data do, however, provide a baseline for future trend studies.

The regional differences as indicated by registries (Paulozzi, 1999) should be confirmed by geographical comparisons based on systematic and standardized examination of complete birth cohorts. Recently, the results of a comparable prospective population-based study in Finland were published (Virtanen *et al.*, 2001). The rate of 38/10 000 in our cohort is 2.2 times higher than the rate of 17/10 000 in the Finnish birth cohort study ($P = 0.002$). The comparison of these two studies strongly indicates geographical differences in the prevalence of hypospadias. Moreover, the frequency distribution of subtypes appears different, with 95% (18/19) of the cases classified as glandular or coronal in contrast with 51% in our study. Interestingly, the prevalence of other related abnormalities of the male reproductive system (testicular cancer, cryptorchidism, reduced sperm count) is also different in Finland compared with other European countries (Toppari *et al.*, 1996), for which pathophysiological mechanisms have been suggested, but not yet confirmed.

Thus, research on causes and risk factors for hypospadias is needed. There clearly is a genetic component in the aetiology of some hypospadias cases, as illustrated by cases of familial predisposition (Bauer *et al.*, 1981; Chambers and Malone, 1999; Boehmer *et al.*, 2001). Hypospadias may be due to a defect in androgen synthesis or action due to, for example, mutations of the 5α-reductase type 2 or the androgen receptor gene (Boehmer *et al.*, 2001; Sultan *et al.*, 2001b). However, the proportion of hypospadias attributable to genetic defects in these reports was rather small. Assisted reproduction technologies may be associated with excess hypospadias. An increased hypospadias risk has been observed in male offspring after IVF and ICSI (Wennerholm *et al.*, 2000; Ericson and Kallen, 2001). Several environmental factors have been associated with hypospadias, such as exposure to endocrine disrupters (Sharpe, 2001), a maternal residence near hazardous-waste landfill sites (Dolk *et al.*, 1998; Elliott *et al.*, 2001), or a maternal vegetarian diet (North and Golding, 2000), which may coincide with a high intake of phyto-estrogens.

Little information is available on the indications for surgical hypospadias repair, especially in mild cases. In this study, 25 and 93% of glandular and coronal cases required surgery on the basis of voiding problems or chordee, whereas surgery was needed in all more severe cases. In the total series of cases with specified grade, 79% required surgical correction. These results may affect the interpretation of hypospadias rates based on surgical records.

We demonstrate that hypospadias is one of the most frequent congenital anomalies among newborn boys. After cryptorchidism (1–2% at the age of 3 months) (Toppari and Kaleva, 1999), hypospadias (0.7%) is more frequent than congenital heart disease (0.5%), which is the most frequent congenital abnormality in EUROCAT. Early detection and surgical correction can prevent cosmetic and mechanical problems, and concomitant psychological complications. Awareness of this anomaly is needed to avoid misdiagnosis and to initiate timely treatment. The present study demonstrates that the national preventive child healthcare programme provides an efficient

and accurate framework in the screening for hypospadias, as 88% of the potential cases identified by CHC physicians were confirmed by the expert specialists.

Summarizing, we report a 4-fold higher than expected hypospadias rate, which is not explained by a high inclusion of minor forms. This difference is probably due to under-reporting in registries. The present study is only the second report on accurate prevalence data where all male newborns in an open population were systematically screened for this congenital abnormality. Comparison of the first two studies implies a substantial geographical variation in hypospadias prevalence, which should be followed by comparable studies in other countries. The minor/major ratio is 0.3, in contrast with the previously reported ratio of 3.0 based on incomplete data. Based on the high prevalence and previously suggested trends, causes of hypospadias and the geographical and temporal differences need to be explored. For accurate monitoring of hypospadias rates, complete case ascertainment including standardized classification of severity is warranted.

Acknowledgements

We thank Marijke Vlasblom, Mayke Wala and the Child Health Care physicians for their co-operation. The Endocrine Modulators Study Group of the European Chemical Industry Council (EMSG–CEFIC) is acknowledged for financial support.

References

Bauer, S.B., Retik, A.B. and Colodny, A.H. (1981) Genetic aspects of hypospadias. *Urol. Clin. N. Am.*, **8**, 559–564.

Boehmer, A.L., Nijman, R.J., Lammers, B.A. *et al.* (2001) Etiological studies of severe or familial hypospadias. *J. Urol.*, **165**, 1246–1254.

Chambers, E.L. and Malone, P.S. (1999) The incidence of hypospadias in two English cities: a case-control comparison of possible causal factors. *BJU Int.*, **84**, 95–98.

Czeizel, A. (1985) Increasing trends in congenital malformations of male external genitalia. *Lancet*, **i**, 462–463.

Dolk, H. (1998) Rise in prevalence of hypospadias. *Lancet*, **351**, 770.

Dolk, H., Vrijheid, M., Armstrong, B. *et al.* (1998) Risk of congenital anomalies near hazardous-waste landfill sites in Europe: the EUROHAZCON study. *Lancet*, **352**, 423–427.

Duckett, J.W. (1998) Hypospadias. In Walsh, P.C., Retik, A.B., Vaughan, E.D.J. and Wein, A. (eds), *Campbell's Urology*, 7th edn. Saunders, Philadelphia, pp. 2093–2119.

Elliott, P., Briggs, D., Morris, S. *et al.* (2001) Risk of adverse birth outcomes in populations living near landfill sites. *Br. Med. J.*, **323**, 363–368.

Ericson, A. and Kallen, B. (2001) Congenital malformations in infants born after IVF: a population-based study. *Hum. Reprod.*, **16**, 504–509.

EUROCAT Working Group (1997) *Eurocat report 7. 15 years of surveillance of congenital anomalies in Europe 1980–1994*. Scientific Institute of Public Health-Louis Pasteur, Brussels.

Källén, B., Bertollini, R., Castilla, E. *et al.* (1986) A joint international study on the epidemiology of hypospadias. *Acta Paediatr. Scand. Suppl.*, **324**, 1–52.

Matlai, P. and Beral, V. (1985) Trends in congenital malformations of external genitalia. *Lancet*, **i**, 108.

North, K. and Golding, J. (2000) A maternal vegetarian diet in pregnancy is associated with hypospadias. *BJU Int.*, **85**, 107–113.

Paulozzi, L.J. (1999) International trends in rates of hypospadias and cryptorchidism. *Environ. Health Perspect.*, **107**, 297–302.

Paulozzi, L.J., Erickson, J.D. and Jackson, R.J. (1997) Hypospadias trends in two US surveillance systems. *Pediatrics*, **100**, 831–834.

Sharpe, R.M. (2001) Hormones and testis development and the possible adverse effects of environmental chemicals. *Toxicol. Lett.*, **120**, 221–232.

Sharpe, R.M. and Skakkebæk, N.E. (1993) Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet*, **341**, 1392–1395.

Skakkebaek, N.E., Rajpert-De Meyts, E. and Main, K.M. (2001) Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum. Reprod.*, **16**, 972–978.

Sultan, C., Balaguer, P., Terouanne, B. *et al.* (2001a) Environmental xenoestrogens, antiandrogens and disorders of male sexual differentiation. *Mol. Cell. Endocrinol.*, **178**, 99–105.

Sultan, C., Paris, F., Terouanne, B. *et al.* (2001b) Disorders linked to insufficient androgen action in male children. *Hum. Reprod. Update*, **7**, 314–322.

Toppari, J. and Kaleva, M. (1999) Maldescendus testis. *Horm Res*, **51**, 261–269.

Toppari, J., Larsen, J.C., Christiansen, P. *et al.* (1996) Male reproductive health and environmental xenoestrogens. *Environ. Health. Perspect.*, **104**, 741–803.

Toppari, J., Kaleva, M. and Virtanen, H.E. (2001) Trends in the incidence of cryptorchidism and hypospadias, and methodological limitations of registry-based data. *Hum. Reprod. Update*, **7**, 282–286.

Virtanen, H.E., Kaleva, M., Haavisto, A.M. *et al.* (2001) The birth rate of hypospadias in the Turku area in Finland. *Apmis*, **109**, 96–100.

Wennerholm, U.B., Bergh, C., Hamberger, L. *et al.* (2000) Incidence of congenital malformations in children born after ICSI. *Hum. Reprod.*, **15**, 944–948.

Submitted on September 21, 2001; accepted on November 28, 2001