Acta Paediatrica Hungarica 27 (4), pp. 329—337 (1986)

Increased birth prevalence of isolated hypospadias in Hungary

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The birth prevalence of simple (isolated) hypospadias increased significantly in Hungary up to 1978. Since then, although fluctuating, it has remained at this higher level.

The Hungarian Congenital Malformation Registry (HCMR) indicated that the birth prevalence of hypospadias was increasing up to 1978, since then, although fluctuating it has remained at this high level (Table I). The increasing birth prevalence of hypospadias has been observed in other countries, too, e.g. in Norway [1], Sweden [11] and the United Kingdom [16, 13].

Evaluation of an increase in the birth prevalence of congenital anomalies is a difficult task. First, it is important to consider whether an unusual rise in birth prevalence might not be a random phenomenon only because in epidemiology "unexpected events are expected". Second, the possibility of technical biases, e.g. changes in definition and classification, diagnosis, ascertainment and notification, confounding variables including demographic traits of the study population, etc., have to be excluded. Third, it is necessary to attempt to establish adequate hypotheses explaining time trends and to test them.

The purpose of this paper is to evaluate critically the increased birth prevalence of hypospadias observed in Hungary.

Materials and Methods

First, the data recorded in the HCMR, 1970—1983 for hypospadias were evaluated.

Second, within the frame work of "A Joint International Study on the Epidemiology of Hypospadias" [12] one cohort of the HCMR material, index patients born in 1975, was selected for a follow-up study in 1983 to determine the rate of misdiagnosis and completeness of notification. This cohort was selected because index patients born in 1975 were after the usual term of surgery by the time of the study, and they had not been included in our previous study [4]. The HCMR involves 334 index patients born in 1975 with the four digit code of 752.6 entitled "Hypospadias and epispadias" (Fig. 1). This item includes only simple (isolated) abnormalities in the HCMR, multiple congenital abnormalities including hypospadias are recorded in different codes beginning with 759. As it ap-

TABLE I

Data-base of hypospadias in Hungary, 1970—1983

Year	Total birth	Total male livebirth	Total congenital		Simple (isolated) hypospadias				Complex hypospadias	Together		Multiple hypospadias	Total		
			No.	‰	No.	‰	ML‰	‰		No.	‰		No.	‰	%
1970	153.339	78.366	3711	24.20	85	0.55	1.08	2.29	5	90	0.59	11	101	0.66	2.72
1971	152.159	77.611	4843	31.83	172	1.13	2.22	3.55	3	175	1.15	17	192	1.26	3.96
1972	154.688	79.309	5349	34.58	173	1.12	2.18	3.23	3	176	1.14	20	196	1.27	3.66
1973	157.623	80.657	5288	33.55	217	1.38	2.69	4.10	3	220	1.40	25	245	1.55	4.63
1974	187.957	95.887	6750	35.91	252	1.34	2.63	3.73	15	267	1.42	19	286	1.52	4.23
1975	195.847	99.907	7441	37.99	334	1.71	3.34	4.49	12	346	1.77	29	375	1.91	5.04
1976	186.916	95.350	7572	40.51	365	1.95	3.83	4.82	16	381	2.03	29	410	2.19	5.41
1977	179.152	91.063	6585	36.76	377	2.10	4.14	5.73	14	391	2.18	25	416	2.32	6.32
1978	169.524	86.455	7277	42.93	402	2.37	4.65	5.52	14	416	2.45	34	450	2.65	6.18
1979	161.677	82.172	6905	42.75	329	2.03	4.00	4.76	6	335	2.07	28	363	2.25	5.26
1980	149.829	76.115	6912	46.13	331	2.21	4.35	4.79	8	339	2.26	20	359	2.40	5.19
1981	144.062	72.920	6223	43.20	310	2.15	4.25	4.98	10	320	2.22	16	336	2.33	5.40
1982	134.579	68.778	6161	45.78	322	2.39	4.68	5.23	8	330	2.45	14	344	2.56	5.58
1983*	128.160	65.082	5440	42.45	279	2.18	4.28	5.13	7	286	2.23	12	298	2.33	5.48

‰ per 1000 total births
ML male livebirth
* preliminary figures

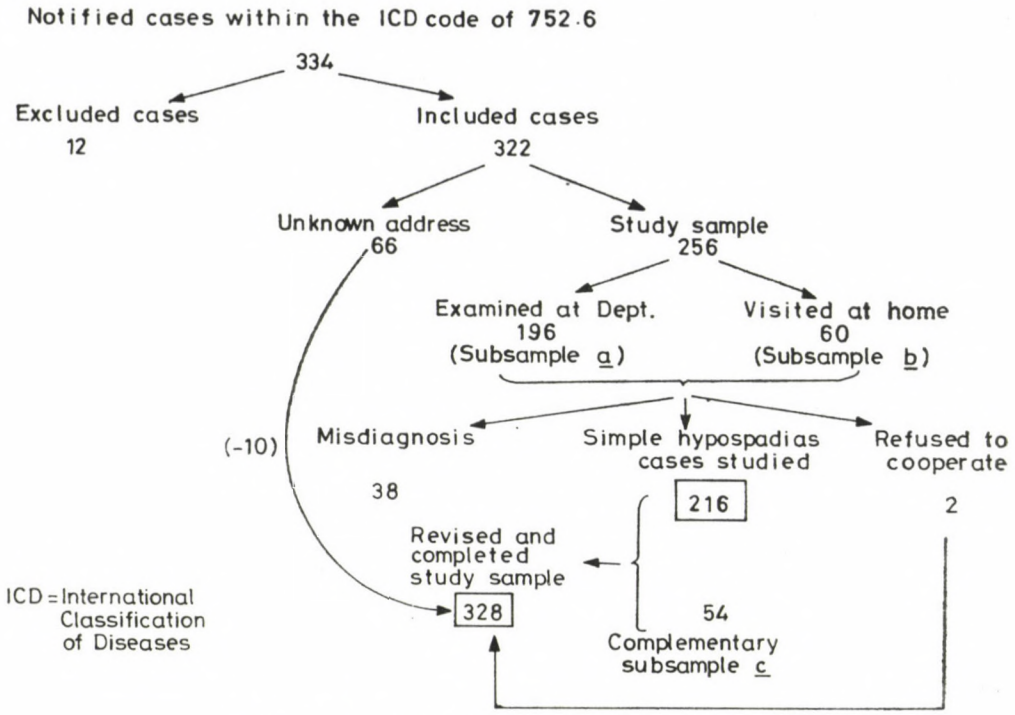

FIG. 1. Data base of study cohort born in 1975

peared at the check-up, six index patients (1.7%) were recorded twice. (They were notified with somewhat different personal data and first the computer could not identify them.) Two index patients with notified hypospadias turned out to be girls. Four children had epispadias. These 12 cases were excluded. The remaining 322 index patients were evaluated in two steps. First, we invited by letter the index patients with their parents for a personal examination into the Department of Paediatric Urology, Heim Pál Hospital for Sick Children, Budapest. Due to changed address, the letters to 66 index patients (20.5%) were returned to us. We assumed that there was no relationship between unknown addresses and the variables of hypospadias (i.e. there was no selection bias), and these cases were neglected. Out of the remaining 256 cases of the study sample, 196 index patients (76.6%) visited J. T. together with their first degree relatives. This is subsample *a*.

As a second step, the 60 index patients (subsample *b*) who did not appear at examination, were visited by E. C. that their hypospadias should be checked-up. We took advantage of the opportunity of meeting the parents of hypospadiacs, and epidemiological data were obtained by the help of the printed questionnaire by personal interview. The epidemiological data of subsamples *a* and *b* did not significantly differ, thus they were evaluated together. The parents of two index patients refused to cooperate, both boys had glandular hypospadias.

In a third phase of the cohort study an alphabetic list of names of index patients examined personally was sent to the head of all (eight) Hungarian paediatric surgery departments asking them to complete this list with the non-notified index pa-

tients born with hypospadias in 1975. All departments replied. This is the complementary subsample *c*.

Results and Discussion

Statistical evaluation of the increase of hypospadias

Three groups of hypospadias were separated (Table I).

(i) *Simple* (single or isolated) hypospadias: this term excludes cases of hypospadias associated with any other genital and extragenital congenital anomalies, but includes the direct consequences of the malformation: meatal stenosis, congenital torsion, chordae, bifid scrotum.

(ii) *Complex* hypospadias was defined as hypospadias associated with the following genital anomalies of males: undescended testicle(s), hydrocele, congenital inguinal hernia(s) and malformations of the external male genitalia. In general, complex hypospadias is the manifestation of GAM, i.e., *g*enital *a*nomalies of *m*ale [7].

(iii) *Multiple* hypospadias, i.e., multiple congenital abnormalities comprising hypospadias and other types of extragenital congenital abnormalities.

Using the Cohran test, the increase in the birth prevalence of simple hypospadias was shown to be significant ($p < 0.01$) in Hungary during the year 1970—1983. Neither complex nor multiple hypospadias had, however, shown a significant increase, their annual changes could be explained by random fluctuation (except the maximum of multiple cases in 1978). As far as we know the recent Hungarian birth prevalence values of simple hypospadias, particularly in 1978 and 1982, were the highest among the published figures based on populations [10, 12]. The male-specific live-birth prevalence of simple hypospadias was as high as 4.65 and 4.68, respectively. Only relatively small or hospital based incidences were higher than the recent Hungarian figures, e.g. 5.4 in New York based on 2,793 male births [15], 7.6 in Minnesota based on 4,474 male births [9] and 8.2 in Rochester, Minnesota, based on 13,776 male births [17]. All these allowed to conclude that the increase of birth prevalence of simple hypospadias in Hungary, 1970—1983, was significant statistically.

Technical biases and confounding variables

The following task was to estimate the impact, more precisely the proportion of technical biases and confounding variables in the increase of simple hypospadias.

(i) *Definition* and *classification* of hypospadias have not been modified in the last 14 years.

(ii) A change in *diagnostic skills* and attention, e.g., the detection of slight hypospadias, mainly minor forms of glandular type, could not be excluded. We exam-

ined personally 254 index patients (Fig. 1). Three index patients were notified as simple hypospadias but they also had other congenital anomalies (omphalocele, congenital pyloric stenosis and congenital dislocation of the hip, respectively). Thirty-five boys had no hypospadias by personal examination. Oedema of the penis at birth may lead to incorrect diagnosis of simple hypospadias [14]; they were reported with one exception (glandular) as hypospadias without the type being mentioned. These 38 misdiagnosed cases were excluded from the study sample. One of the further seven index patients had a minor anomaly (haemangioma in the pectoral region), the other six had functional disorders (Friedreich ataxia with a positive family history; mental retardation and hypacusis; mental retardation, deafness and squint; myopia; renal tubular acidosis), these cases were not excluded. Thus, out of 254 examined index patients, the diagnosis of simple hypospadias was confirmed in 216 cases, i.e., the *validity of diagnosis* was 85.0% (Fig. 1).

The type distribution of hypospadias was different in cases born in 1970—1972 and 1975 (Table II), the difference being most pronounced between our previous study sample (based on notified and operated non-notified cases) and the present study sample (based on notified cases) ($\chi^2_2 = 14.4$; $p < 0.01$). Percentage figures of mild hypospadias were 51%, 56% and 65% in the previous sample, the present complementary subsample *c* and the present revised study sample, respectively. Proportions of mild, medium and severe simple hypospadiacs were 66%, 29% and 5% in the present completed and revised study sample, with a probably decreasing relative order of ascertainment bias.

(iii) *Ascertainment* and *notification* of simple hypospadias have increased considerably mirroring the increase of notification of total congenital anomalies (Table I). Still, the increase in notification of simple hypospadias exceeded the general trend. On the one hand the proportion of simple hypospadias increased from 3.6% to 5.2% of the total congenital anomalies between 1971 and 1982. On the other hand, the increase was 44% in the total congenital anomalies while 112% in simple hypospadias in the period studied. (Index patients born in 1970 were obviously under-ascertained; while figures of 1983 are preliminary, therefore they were not considered in evaluation of the data.)

Further 68 cases with simple hypospadias in complementary subsample *c* were ascertained

TABLE II

Distribution of types of simple hypospadiasis in previous and present study samples

Category	Type	Definition	Previous study sample No.	%		Present study sample revied No.	%		Complementary subsample c No.	%		Present completed and revised study sample No.	%	
Mild	Glandular	the opening is distal to the sulcus coronarius	69	23.5		77	35.3		8	11.8		85	29.7	
	Coronal	the opening is within the sulcus coronarius	80	27.2		73	33.5		30	44.1		103	36.0	
Medium	Penile	the opening is proximal to the sulcus coronarius	134	45.6		59	27.1		25	36.8		84	29.4	
Severe	Penoscrotal	the opening is in the immediate vicinity of the penoscrotal junction	0	0.0		4	1.8		4	5.9		8	2.8	
	Scrotal	the opening is in the scrotal region	0	0.0	3.7	1	0.5	4.1	1	1.4	6.9	2	0.7	4.8
	Perineoscrotal	the opening is between the two halves of, or behind the cleft scrotum	11	3.7		4	1.8		0	0.0		4	1.4	
	Total		294	100.0		218	100.0		68	1000		286	100.0	

within the cohort born in 1975 from the records of paediatric surgery departments, and 14 cases were notified to the Registry but owing to an incorrect address they were not examined. Thus, we had 54 "new" cases. Taking into consideration these cases, too, the total number of ascertained simple hypospadias patients would be 376. This approach showed a 85.6% completeness of notification in simple hypospadias. Still, on the one hand it was necessary to subtract the 38 misdiagnosed cases from the above total of 376. On the other hand, it seemed wise to exclude further ten cases from the 66 index patients with unknown address owing to the 15% probability of misdiagnosis. Thus, the total number of index patients with simple hypospadias born in 1975 could be supposed to be 328, which represented a 1.67 birth prevalence in Hungary in 1975. It was only 2% lower than the recorded rate in the HCMR, because the rate of misdiagnosis and incompleteness of notification nearly completely balanced out each other. If it were a general pattern, it would augment the relevance of recorded birth prevalences, but data of one single year did not allow this conclusion.

Simple hypospadias was evaluated only in males in this study and the majority of our cases (327/328 = 99.7%) occurred in livebirths, thus a male-specific livebirth prevalence of 3.27 per 1000 male livebirths in 1975 could be calculated.

There are significant differences in birth prevalence data of simple hypospadias among the twenty territorial units of Hungary. The maximum (5.3) and the minimum (2.2) indicated a wide range. An obvious territorial trend, the so-called cline, however, could not be detected and the fluctuation mainly indicated the territorial differences in notification.

The problem of underreporting of congenital anomalies is well-known and usually high percentage figures (e.g., 44.3%) were reported [8].

(iv) Changes in *confounding variables.* Maternal age and particularly parity have a slight effect on the birth prevalence of simple hypospadias [5, 12]. There was no considerable shift in maternal age and parity distribution comparing the figures of the seventies with the data of the eighties in Hungary.

The conclusion is that the changes in diagnosis, ascertainment and notification may explain a considerable proportion of the increased prevalence of simple hypospadias in Hungary but probably not the entire rise. This statement is based on two arguments. First, owing to the incomplete notification, true birth prevalence figures

have been higher than the recorded ones in the past years. Second, recorded figures of 1978 and 1982 exceeded the true birth prevalence of simple hypospadias determined in 1973. Simple hypospadias was screened by neonatologists prepared for the study in a representative sample involving 10,203 livebirths in Hungary in 1973, and a rate of 2.2 per 1000 total births was found [5]. The recorded birth prevalence was 1.4 in 1973 (Table I). Some recent recorded birth prevalence figures exceeded the level of true birth prevalence of simple hypospadias found in 1973.

Finally, the aetiological factors should be studied. It is known that there are racial, probably genetic, differences in the rate of simple hypospadias [3]. The Hungarian population is, however, racially fairly homogeneous being exclusively of European origin. [The effect of environmental factors will be summarised in another paper [1].) The main conclusion of the aetiological approach was that the increasing frequency of couples with a history of infertility among parents in general may explain the recent increased birth prevalence of simple hypospadias in Hungary.

The ratio of fertile and subfertile couples depends on the reproductive activity of the fertile ones. Therefore, the proportion of children born of subfertile couples was low in the developed countries some decades ago because of the relatively high reproduction rate of fertile couples. Intensive birth control of fertile couples on the one hand and the increasingly effective treatment of subfertility on the other hand, increased the proportion of children of subfertile couples within the newborn population. Owing to the progress in the treatment of subfertility, the previous proportion of childless couples (about 12%) has decreased significantly (below 6%) in Hungary. Thus, the increasing proportion of children of subfertile couples may explain the increased birth prevalence of simple hypospadias (Fig. 2).

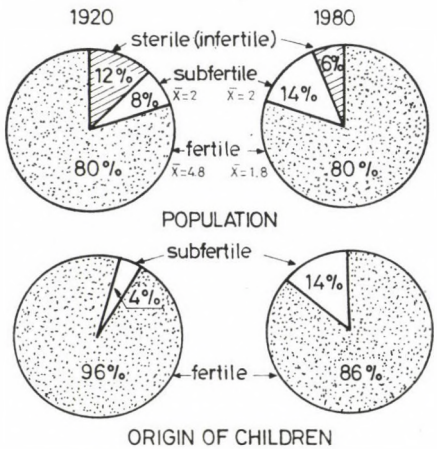

FIG. 2. Estimated proportion of fertility and origin of children

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Received 16 December 1986

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