ORIGINAL ARTICLE

Risk of hypospadias in relation to maternal occupational exposure to potential endocrine disrupting chemicals

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Background: Reported rises in the prevalence of hypospadias and other abnormalities of the male reproductive system may be a result of exposure to endocrine disrupting chemicals.
Aims: To analyse the relation between risk of hypospadias and maternal occupation, particularly with regard to exposure to potential endocrine disrupting chemicals (EDCs).
Methods: Data (1980–96) from the National Congenital Anomaly System (NCAS) were used to analyse the proportion of all congenital anomaly cases (n = 35 962) which were notified with hypospadias (n = 3471) by occupational codes (348 individual job titles) and by categories of exposure to potential EDCs from a job exposure matrix.
Results: Five individual occupations (of 348) showed nominally statistically significant excesses, none of which had possible or probable exposure to potential EDCs. Odds ratios for "possible" or "probable" compared to "unlikely" exposure to potential EDCs did not show statistically significant increases in any of the EDC categories after adjustment for social class of the mother and father, nor was there evidence of an upward trend in risk with likelihood of exposure. In the 1992–96 time period odds ratios were increased for hairdressers (the largest group exposed to potential EDCs) and for probable exposure to phthalates (of which hairdressers form the largest group) before social class adjustment.
Conclusions: There was little evidence for a relation between risk of hypospadias and maternal occupation or occupational exposure to potential EDCs, but as the exposure classification was necessarily crude, these findings should be interpreted with caution.

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Hypospadias is a congenital abnormality of the male genitalia characterised by incomplete development of the urethra so that the external urethral opening is abnormal in position, ranging from positions near the tip of the glans to further down the shaft of the penis and in the perineum. Hypospadias has an estimated prevalence of 1–2 per 1000 births (or 2–4 per 1000 male births) in Europe.[1 2] There is some evidence that the prevalence of hypospadias has been increasing in the 1960s, 70s, and 80s in Europe[3–5] and in the USA,[6] although recent reports suggest that these trends might not be continuing.[7 8] At the same time, increases in related abnormalities such as cryptorchidism (undescended testes) and testicular cancer have been reported, as well as a fall in male fertility.[9] A hypothesis has been proposed that the underlying cause of the change in all these conditions may be exposure to endocrine disrupting chemicals (including xenoestrogens).[9–11] Potential endocrine disrupting chemicals include dioxins and furans, polychlorinated biphenyls, and organochlorine pesticides, and also dietary phytoestrogens (such as in soy products).[11–13] Exposure to these substances may occur particularly in the occupational setting but also through more general environmental exposure, exposure in the home, food packaging, and diet.[12]

Main messages

- There has been very little previous research into the hypothesised relation between exposure to potential endocrine disrupting chemicals (EDCs) and risk of hypospadias.
- This study classified 8% of cases with congenital anomalies as having probable exposure to potential EDCs through the occupation of the mother.
- Hairdressers, cleaners, and painters were the largest occupational groups with probable exposure to potential EDCs.
- The study finds little evidence for a relation between risk of hypospadias and maternal occupation or occupational exposure to potential EDCs, but our exposure classification was crude.
- There was some indication for an increased risk of hypospadias in the offspring of hairdressers and occupations exposed to phthalates (one group of potential EDCs).

Policy implications

- The results of this study largely indicate no areas of concern.
- Further studies are warranted to clarify the relation between work in hairdressing occupations and risk of hypospadias.

There has been very little previous research into the hypothesised relation between exposure to endocrine disrupting chemicals in the environment and risk of hypospadias. However, since the development of the male genital tract is under hormonal influence, indicators for both endogenous and exogenous endocrine factors have been suggested to play a role in the aetiology of hypospadias.[14] Possibly the most consistent findings have been associations with low birth weight,[15] and subfertility in father and/or mother and threatened abortion.[14 16]

Studies of occupational exposures in relation to hypospadias are few. Farmers and gardeners have been one occupational group of concern because of their work with pesticides, many of which have potential endocrine disrupting properties. Studies have suggested either no relation between hypospadias risk and parental work in agriculture or gardening,[17–19] or a positive relation.[20] More general studies of occupation and birth defects have identified several occupations with increased risks of hypospadias (paternal work as vehicle mechanics[21] and paternal work in forestry and logging, carpentry and woodwork, and as

Abbreviations: EDC, endocrine disrupting chemical; JEM, job exposure matrix; NCAS, National Congenital Anomaly System; O/E, observed/expected

Table 1 Total numbers by employment status

Employment status	All congenital anomalies	Hypospadias cases n	Hypospadias cases %	OR	95% CI
1980–89					
Occupation recorded (1–348)	29250	2794	9.6	1.00	
Inadequately described	2488	243	9.8	1.02	0.89 to 1.18
Occupation not stated	9339	807	8.6	0.90	0.83 to 0.97
Housewife	36775	3101	8.4	0.87	0.83 to 0.92
Other non-worker*	629	44	7.0	0.71	0.52 to 0.97
Total	78481	6989			
1992–96					
Occupation recorded (1–348)	6712	677	10.1	1.00	
Inadequately described	1515	153	10.1	1.00	0.83 to 1.20
Occupation not stated	1740	136	7.8	0.76	0.62 to 0.92
Housewife	4959	495	10.0	0.99	0.87 to 1.12
Other non-worker*	219	18	8.2	0.80	0.49 to 1.30
Total	15145	1479			

*Includes: no previous job, permanently sick, full-time student.

service station attendants[22]), but these associations are detected in many combinations of occupation and birth defects tested.

This paper analyses the relation between risk of hypospadias and occupation of the mother as recorded on the congenital anomaly register of the Office for National Statistics (ONS), particularly with regard to exposure to potential endocrine disrupting chemicals.

METHODS

This study uses data recorded on the National Congenital Anomaly System (NCAS) supplied by ONS. This register has been collecting data on liveborn and stillborn babies with congenital anomalies in England and Wales since 1964.[23] Local community trusts or health authorities forward notifications collected from doctors and midwives using standardised reporting forms. All reporting is on a voluntary basis.

Hypospadias cases

Cases were all cases of hypospadias (ICD9 7526) registered between 1980 and 1996 on NCAS, for whom occupation of the mother was recorded, excluding cases with chromosomal abnormalities.

Denominator data

The primary analysis is a "proportional analysis" and uses as the denominator all cases with a congenital anomaly (ICD9 740–759) registered on NCAS. The advantage of using the congenital anomaly data for denominator as well as numerator data is that information on maternal occupation originates from the same source (hospital maternity notes), thereby reducing the chance of information bias. Maternal occupation is usually registered at the mother's first booking appointment, early in pregnancy.

As a subsidiary analysis and check on the proportional analysis we repeated our analyses using live births registered on the ONS birth registration database as denominators. Occupation of the mother is routinely coded for a 10% random sample of all live births. Information on occupation of the mother in this database originates from birth registrations where occupation is recorded at the time the birth is registered by the parents at the registry office. Because of the differences in source of occupational information between malformation and birth data these analyses may be subject to substantial bias.

Occupational coding and classification of exposure to potential endocrine disrupting chemicals

Occupation is coded in NCAS using the CO80 job classification system in the 1980s[24] and the more expansive OC90 system in the 1990s.[25] The OC90 codes were translated back to CO80 codes using a spreadsheet provided by the Office for National Statistics. The CO80 system codes 348 different job titles.

Maternal occupational codes were classified into categories of likelihood of exposure to potential endocrine disrupting chemicals (EDCs), using a job-exposure matrix developed for this study.[26] For the job-exposure matrix, three occupational hygienists classified the CO80 jobs titles into three categories of unlikely, possible, and probable exposure to seven groups of EDCs: pesticides, polychlorinated organic compounds, phthalates, alkylphenolic compounds, biphenolic compounds, heavy metals (cadmium, lead, mercury), and other hormone disrupting chemicals. The hygienists used the following exposure categories:

0. It is very unlikely the exposure occurred among workers with this job title.
1. There is a possibility that some of the workers with this job title had exposure (but the probability is fairly low).
2. The probability exists that at least a proportion of the workers with this job title had some exposure.

The job exposure matrices of the three hygienists were compared, and in each case where there was a maximum difference between two of the coders (that is, 0 and 2), a consensus between the coders was formed.[26] Differences between the coders of one category were allowed to remain. The code assigned by the majority of the three hygienists' codes (median) was taken for each job title to form unlikely, possible, and probable exposure categories. Exposure to the total group of "any endocrine disrupting chemical" was classified by taking the score of the highest scoring substance category.

There were some substantial differences between the expert coders in their independent assessments.[26] Disagreement across two categories, requiring consensus by discussion, occurred in 137 assessments (out of 7×348 = 2436), most often for phthalates (n = 35 job titles) and alkylphenolic compounds (n = 38 job titles). For pesticides there were only six job titles with this extent of disagreement.

Study period

In 1990 ONS accepted stricter criteria for exclusion of "minor" congenital anomalies (including glanular hypospadias) which affected both hypospadias rates and rates of total congenital anomalies.[23] A sharp decrease in hypospadias rates and rates of total congenital anomalies can be seen in 1990 and 1991, with rates stabilising thereafter. Analyses of hypospadias cases as a proportion of all congenital anomaly cases were therefore carried out for the periods of 1980–89 and 1992–96 separately and these two periods combined, excluding 1990 and 1991 when the proportion was highly affected by the introduction of the new exclusion criteria. Analyses using births as denominators were based on the 1992–96 period only, because the recording of maternal occupation in the births data did not

Table 2 Proportion hypospadias cases by year of birth

1980–89 period				1992–96 period			
		Hypospadias cases*				Hypospadias cases*	
Year of birth	All congenital anomalies*	n	%	Year of birth	All congenital anomalies*	n	%
1980	3034	236	7.8	1992	1499	134	8.9
1981	2839	231	8.1	1993	1473	151	10.3
1982	2668	251	9.4	1994	1194	136	11.4
1983	2880	272	9.4	1995	1193	111	9.3
1984	2924	312	10.7	1996	1353	145	10.7
1985	2859	275	9.6			p for trend = 0.27	
1986	2966	286	9.6	Total	6712	677	10.1
1987	3107	319	10.3				
1988	3011	302	10.0				
1989	2962	310	10.5				
		p for trend < 0.001					
Total	29250	2794	9.6				

*Cases with maternal occupation recorded.

Table 3 Proportion of hypospadias cases by region, maternal age, and socioeconomic status

	Hypospadias		All years		1980–89		1992–96	
	n	%	OR	95% CI	OR	95% CI	OR	95% CI
Region								
1: North	239	10.6	1.00		1.00		1.00	
2: York + Humberside	338	9.7	0.90	0.76 to 1.07	0.99	0.81 to 1.20	0.66	0.45 to 0.95
3: East Midlands	606	11.0	1.04	0.89 to 1.22	1.04	0.87 to 1.25	1.17	0.82 to 1.66
4: East Anglia	375	9.4	0.87	0.73 to 1.03	0.92	0.77 to 1.12	0.60	0.38 to 0.95
5: South East	429	8.7	0.80	0.68 to 0.95	0.81	0.66 to 0.98	0.74	0.54 to 1.03
6: South West	179	9.7	0.90	0.74 to 1.11	0.95	0.75 to 1.21	0.76	0.51 to 1.12
7: West Midlands	857	9.0	0.83	0.71 to 0.96	0.85	0.71 to 1.00	0.86	0.60 to 1.24
8: North West	356	10.6	0.99	0.83 to 1.18	1.01	0.82 to 1.24	0.89	0.64 to 1.24
9: Wales	92	8.9	0.82	0.64 to 1.06	0.95	0.72 to 1.24	0.36	0.17 to 0.77
			p for heterogen < 0.001		p for heterogen = 0.008		p for heterogen = 0.001	
Maternal age								
<20	371	10.2	1.00		1.00		1.00	
20–24	1134	10.2	1.00	0.88 to 1.13	0.98	0.86 to 1.11	1.21	0.82 to 1.80
25–29	1144	9.4	0.92	0.81 to 1.04	0.86	0.76 to 0.99	1.28	0.88 to 1.87
30–34	600	9.4	0.91	0.80 to 1.05	0.87	0.75 to 1.02	1.18	0.80 to 1.74
35–39	160	7.9	0.76	0.63 to 0.92	0.72	0.58 to 0.90	1.00	0.63 to 1.60
40+	35	10.7	1.06	0.73 to 1.52	1.13	0.74 to 1.72	1.03	0.48 to 2.23
				p for trend = 0.005		p for trend = 0.002		p for trend = 0.65
Social class of mother								
I	69	9.2	1.00		1.00		1.00	
II	843	9.1	0.99	0.76 to 1.28	1.04	0.76 to 1.43	0.91	0.58 to 1.42
IIINM	1454	9.7	1.06	0.82 to 1.36	1.15	0.84 to 1.57	0.88	0.57 to 1.37
IIIM	311	10.4	1.15	0.87 to 1.51	1.15	0.82 to 1.60	1.26	0.78 to 2.05
IV	637	10.1	1.12	0.86 to 1.45	1.20	0.87 to 1.65	0.97	0.61 to 1.56
V	154	9.9	1.08	0.80 to 1.46	1.17	0.82 to 1.67	0.91	0.52 to 1.60
				p for trend = 0.02		p for trend = 0.03		p for trend = 0.40
Social class of father								
I	188	8.5	1.00		1.00		1.00	
II	637	9.4	1.12	0.94 to 1.33	1.08	0.90 to 1.31	1.29	0.87 to 1.91
IIINM	400	9.6	1.14	0.95 to 1.36	1.06	0.87 to 1.30	1.52	1.00 to 2.30
IIIM	992	10.0	1.19	1.01 to 1.40	1.15	0.96 to 1.37	1.39	0.95 to 2.04
IV	476	9.9	1.18	0.99 to 1.40	1.12	0.92 to 1.37	1.44	0.95 to 2.18
V	155	10.2	1.21	0.97 to 1.52	1.15	0.90 to 1.48	1.52	0.90 to 2.54
				p for trend = 0.04		p for trend = 0.13		p for trend = 0.10
Deprivation quintile								
1 – affluent	132	9.8	–		–		1.00	
2	147	10.4					1.07	0.83 to 1.37
3	152	10.0					1.02	0.80 to 1.31
4	148	10.9					1.14	0.89 to 1.45
5 – deprived	90	9.6					0.98	0.74 to 1.30
								p for trend = 0.83

start until 1986 and was relatively incomplete in the early years of recording.[27]

Exclusion of districts with poor occupational recording

The completeness of recording of occupation of the mother in the ONS congenital anomaly data is known to vary by district health authorities reporting the cases. Districts with poor occupational recording over the periods 1980–89 and 1992–96 combined (defined as less than 70% of congenital anomaly cases with occupation of the mother recorded) were excluded from the proportional analyses using congenital anomalies as denominator. Overall, the percentage of congenital anomaly

Table 4 Occupational codes with nominally statistically significantly raised observed/expected (O/E) ratios in at least one time period (out of a total of 348 occupations)

Occupations with statistically significant O/E ratios	All CA cases*	Hypospadias cases – observed	Hypospadias cases – expected†	O/E†	95% CI	Hypospadias cases – expected‡	O/E‡	95% CI
1980–89								
Management consultants	3	2	0.26	7.71	1.09 to 11.47	0.26	7.60	1.07 to 11.30
Physical and geological scientists and mathematicians	35	8	3.20	2.50	1.14 to 4.39	3.01	2.66	1.21 to 4.67
Tailors, tailoresses, dressmakers	41	10	3.93	2.54	1.29 to 4.21	3.96	2.53	1.28 to 4.18
Hairdressers, barbers	767	70	74.89	0.93	0.74 to 1.17	74.49	0.94	0.74 to 1.17
Vocational and industrial trainers	27	5	2.62	1.91	0.65 to 3.92	2.48	2.02	0.69 to 4.15
1992–96								
Management consultants	5	2	0.48	4.18	0.55 to 8.92	0.57	3.50	0.46 to 7.46
Physical and geological scientists and mathematicians	21	1	1.92	0.52	0.01 to 2.60	2.01	0.50	0.01 to 2.49
Tailors, tailoresses, dressmakers	4	1	0.34	2.95	0.07 to 9.50	0.42	2.40	0.06 to 7.73
Hairdressers, barbers	184	28	18.70	1.50	1.02 to 2.09	23.78	1.18	0.80 to 1.64
Vocational and industrial trainers	20	5	2.11	2.37	0.82 to 4.65	2.10	2.38	0.82 to 4.67
All years								
Management consultants	8	4	0.71	5.66	1.78 to 9.55	0.74	5.40	1.70 to 9.10
Physical and geological scientists and mathematicians	56	9	5.22	1.73	0.82 to 3.04	5.14	1.75	0.83 to 3.08
Tailors, tailoresses, dressmakers	45	11	4.30	2.56	1.35 to 4.14	4.60	2.39	1.26 to 3.87
Hairdressers, barbers	951	98	93.60	1.05	0.86 to 1.26	98.86	0.99	0.81 to 1.19
Vocational and industrial trainers	47	10	4.62	2.16	1.09 to 3.62	4.46	2.24	1.13 to 3.76

*CA, congenital anomaly.
†Adjusted for year of birth, region, maternal age.
‡Adjusted for year of birth, region, maternal age, social class mother, social class father.

cases for which maternal occupation was stated was 31% in districts with poor occupational recording and 88% in the other districts. Exclusion of districts with poor occupational recording resulted in exclusion of 36% of all cases of congenital anomaly (52 790/146 416) and 18% (7833/43 795) of cases with occupation of the mother stated. Because of different district boundaries used in the birth data in certain years it was not possible to exclude the same districts from analyses using births as denominators. Thus, the total number of hypospadias cases studied is higher in analyses using births as denominator than in those using congenital anomalies as denominator.

Statistical methods

The main analysis of this paper examines the proportion of all congenital anomaly cases which were notified with hypospadias by occupational codes (individual job titles) and by categories of exposure to potential endocrine disrupting chemicals. The ratio of the observed to the expected number of hypospadias cases was calculated for each job title. Expected numbers were calculated first by simply assuming the overall proportion of congenital anomalies that were hypospadias applied in each job, then by adjusting these expected proportions for potential confounders (year of birth, region, maternal age, social class of mother, social class of father, deprivation index of ward of residence) using logistic regression. Confidence intervals were calculated using the exact binomial distribution. Negative binomial regression was used to test for heterogeneity in the observed/expected (O/E) ratios. The Carstairs small area deprivation index (calculated from census variables for enumeration districts) was used as an area level measure of socioeconomic status for the 1992–96 data only.[28] We were not able to use the deprivation index in the 1980–89 data because full postcoding of the congenital anomaly data did not start until 1983, making linking of census variables in early years impossible.

Logistic regression was used to compare the proportion hypospadias cases in "possible" and "probable" exposure categories with the baseline "unlikely" exposure category and to investigate whether there is an upward trend with likelihood of exposure. Adjustments were made for the same potential confounders as above. Likelihood ratio tests were used to test for heterogeneity in odds ratios between the two time periods (1980–89 and 1992–96).

In analyses using the 10% of live births for which maternal occupation was coded as denominator (1992–96 period), expected numbers of hypospadias in occupations and in exposure categories (as above) were calculated by assuming the overall ratio of hypospadias cases to total live births applied to each relevant group of live births. Expected numbers were adjusted for confounding variables using logistic regression. Information available on potential confounding variables was limited to year of birth, social class of mother, social class of father, and deprivation quintile.

RESULTS

In the 1980–89 period there were 2794 cases of hypospadias out of a total of 29 250 cases of congenital anomaly (9.6%) for whom an occupation of the mother was recorded. In the 1992–96 period there were 677 hypospadias cases out of total of 6712 (10.1%) with maternal occupation recorded (table 1). Table 1 shows that the percentage of all congenital anomaly cases with hypospadias was higher for those with an occupation recorded than for those with occupation not stated (1980–89 and 1992–96), for housewives (1980–89), or for other non-workers (1980–89). Only cases for whom maternal occupation was recorded are used in further analyses.

The percentage of hypospadias cases showed an increasing trend with year of birth from 1980 to 1989 (table 2). There is little evidence of such a trend over the 1992 to 1996 period. Table 3 shows the percentage of hypospadias cases by potential confounding variables for the 1980–89 and 1992–96 periods separate and for both time periods combined. There was statistically significant heterogeneity in the proportion of hypospadias cases between regions in all time periods (p ranging from <0.001 to 0.008). The proportion of hypospadias cases shows a decreasing trend with maternal age in both periods combined ($p = 0.005$) and the 1980–89 period ($p = 0.002$). There is a statistically significant trend of an increasing proportion of hypospadias cases from the professional to the unskilled social classes for social class of the mother in both periods combined ($p = 0.02$) and in the

Table 5 Number of congenital anomaly cases and hypospadias cases in occupations classified as having "probable" expoure to potential endocrine disrupting chemicals

	CA* cases	Hypospadias cases (%)	
Pesticides			
Farm workers	69	7	10.1%
All other in farming and related	49	5	10.2%
Farmers, horticulturists, farm managers	33	2	6.1%
Horticultural workers	21	2	9.5%
Gardeners, groundsmen	16	0	0.0%
Forestry workers	1	0	0.0%
Polychlorinated organic compounds			
Electricians, electrical maintenance fitters	13	2	
Electrical engineers (so described)	3	0	0.0%
Paper, paperboard, and leatherboard workers	3	0	0.0%
Plant operators and attendants n.e.c. (electrical)	1	0	0.0%
Phthalates			
Hairdressers, barbers	951	98	10.3%
Painting, assembling, and related occupations	345	31	9.0%
Other making and repairing, paper goods	50	3	6.0%
Printers (so described)	46	3	6.5%
Assemblers (electrical, electronic)	43	3	7.0%
Printing machine minders and assistants	29	2	6.9%
Electricians, electrical maintenance fitters	13	2	15.4%
Painters and decorators n.e.c. French polishers	12	0	0.0%
Electronics wiremen	11	1	9.1%
Other making and repairing, plastics	11	1	9.1%
Screen and block printers	8	0	0.0%
Other spray painters	7	1	14.3%
Coach painters (so described)	3	2	66.7%
Electrical engineers (so described)	3	0	0.0%
Electrotypers, stereotypers, printing plate, cylinder preparers	3	0	0.0%
Other electronic maintenance engineers	3	0	0.0%
Radio and TV mechanics	3	0	0.0%
Telephone fitters	3	0	0.0%
Calendar and extruding machine operators	2	0	0.0%
Alkyl phenolic compounds			
Cleaners, window cleaners, chimney sweepers	561	47	8.4%
Laboratory technician	150	13	8.7%
Farm workers	69	7	10.1%
Laboratory assistants	53	6	11.3%
Other making and repairing, paper goods	50	3	6.0%
All other in farming and related	49	5	10.2%
Labourers and unskilled workers n.e.c. – textiles	34	5	14.7%
Farmers, horticulturists, farm managers	33	2	6.1%
Horticultural workers	21	2	9.5%
Gardeners, groundsmen	16	0	0.0%
Winders, reelers, textiles	15	2	13.3%
Bleachers, dyers, finishers, textiles	14	2	14.3%
Spinners, doublers, twisters, textiles	13	1	7.7%
Painters and decorators n.e.c. French polishers	12	0	0.0%
Other making and repairing, plastics	11	1	9.1%
Other spray painters	7	1	14.3%
Metal polishers	4	0	0.0%
Coach painters (so described)	3	2	66.7%
Preparatory fibre processors, textiles	3	0	0.0%
Metal making and treating workers	2	0	0.0%
Forestry workers	1	0	0.0%
Oilers, greasers, lubricators	1	0	0.0%
Biphenolic compounds			
Other making and repairing, plastics	11	1	9.1%
Dental technicians	11	0	0.0%
Dental practitioners	36	3	8.3%
Calendar and extruding machine operators	2	0	0.0%
Heavy metals			
Medical technicians, dental auxilliaries	89	6	6.7%
Dental practitioners	36	3	8.3%
UK armed forces	26	2	7.7%
Welders	24	0	0.0%
Petrol pump, forecourt attendants	23	0	0.0%
Traffic wardens	14	2	14.3%
Dental technicians	11	0	0.0%
Pottery decorators	10	1	10.0%
Foreign and Commonwealth armed forces	10	1	10.0%
Goldsmiths, silversmiths, precious stone	9	2	22.2%
Casters and other pottery makers	8	2	25.0%
Calendar and extruding machine operators	2	0	0.0%
Labourers and unskilled workers n.e.c. – glass and ceramics	2	0	0.0%
Other endocrine disrupting chemicals: no occupations clasified with probable exposure			

*CA, congenital anomaly.

Table 6 Odds ratios by categories of exposure to endocrine disrupting chemicals—1980–89 and 1992–96 combined

	All CA* cases	Hypospadias cases	% hypospadias	Adj. OR†	95% CI	Adj. OR‡	95% CI
Exposure to any substance							
Unlikely	31079	2993	9.6%	1.00		1.00	
Possible	2032	220	10.8%	1.10	0.95 to 1.28	1.06	0.89 to 1.25
Probable	2851	258	9.0%	0.92	0.81 to 1.06	0.87	0.74 to 1.01
					p for trend = 0.53		p for trend = 0.12
Exposure to pesticides							
Unlikely	35581	3434	9.7%	1.00		1.00	
Possible	192	21	10.9%	1.09	0.69 to 1.72	1.11	0.67 to 1.82
Probable	189	16	8.5%	0.85	0.51 to 1.43	0.84	0.50 to 1.41
					p for trend = 0.71		p for trend = 0.66
Exposure to polychlorinated organic compounds							
Unlikely	34912	3362	9.6%	1.00		1.00	
Possible	1030	107	10.4%	1.06	0.87 to 1.31	1.06	0.83 to 1.36
Probable	20	2	10.0%	0.96	0.22 to 0.41	0.90	0.21 to 3.91
					p for trend = 0.58		p for trend = 0.67
Exposure to phthalates							
Unlikely	32632	3130	9.6%	1.00		1.00	
Possible	1784	194	10.9%	1.12	0.96 to 1.30	1.12	0.94 to 1.33
Probable	1546	147	9.5%	0.97	0.82 to 1.16	0.90	0.74 to 1.10
					p for trend = 0.72		p for trend = 0.98
Exposure to alkylphenolic compounds							
Unlikely	32211	3111	9.7%	1.00		1.00	
Possible	2629	261	9.9%	1.01	0.88 to 1.16	0.93	0.79 to 1.10
Probable	1122	99	8.8%	0.90	0.73 to 1.11	0.84	0.66 to 1.07
					p for trend = 0.49		p for trend = 0.13
Exposure to biphenolic compounds							
Unlikely	34595	3325	9.6%	1.00		1.00	
Possible	1307	142	10.9%	1.13	0.94 to 1.35	1.14	0.93 to 1.41
Probable	60	4	6.7%	0.68	0.25 to 1.89	0.67	0.24 to 1.87
					p for trend = 0.37		p for trend = 0.43
Exposure to heavy metals							
Unlikely	35228	3409	9.7%	1.00		1.00	
Possible	470	43	9.1%	0.95	0.69 to 1.30	0.92	0.66 to 1.26
Probable	264	19	7.2%	0.72	0.45 to 1.15	0.69	0.42 to 1.16
					p for trend = 0.18		p for trend = 0.15
Expsure to other hormone disrupting chemicals							
Unlikely	34744	3345	9.6%	1.00		1.00	
Possible	1218	126	10.3%	1.06	0.88 to 1.28	1.00	0.81 to 1.24
Probable	0	0					
					p for trend = 0.55		p for trend = 0.97

*CA, congenital anomaly.
†Adjusted for year of birth, region, maternal age.
‡Adjusted for year of birth, region, maternal age, social class of mother, social class of father.

1980–89 period ($p = 0.03$), but in the 1992–96 period there is no evidence of such a trend ($p = 0.40$). Social class of the father shows some evidence of an increasing trend in all periods, which reaches statistical significance only in both periods combined ($p = 0.04$). There is no evidence of a trend with deprivation quintile ($p = 0.83$).

Analysis of the proportion of hypospadias cases by the 348 individual occupational codes showed that a few O/E ratios had lower confidence limits above 1 (thus nominal $p < 0.025$ in a one sided test), but a global test of heterogeneity showed no more variation on ratios overall than could be explained by chance ($p > 0.20$). Occupations with nominally statistically significantly raised observed/expected ratios were "management consultants" (1980–89 and all years combined), "physical and geological scientists" (1980–89), "tailors and dressmakers" (1980–89 and all years combined), "hairdressers" (1992–96, before adjustment for social class), and "vocational and industrial trainers" (all years) (table 4).

Overall, 5.6% of congenital anomaly cases were classified as having possible maternal occupational exposure to potential endocrine disrupting chemicals (EDCs) and 7.9% as having probable exposure. Table 5 shows occupational groups classified as having probable exposure to potential EDCs in seven substance groups, and the numbers of all congenital anomaly cases and hypospadias cases in these occupational groups. Hairdressers were the largest occupational group classified as having probable exposure to potential EDCs, with 951 congenital anomaly cases and 98 hypospadias cases, followed by cleaners (561 and 47 cases) and painting and assembling occupations (345 and 31 cases).

Table 6 shows the odds ratios by categories of maternal occupational exposure to potential EDCs for the periods 1980–89 and 1992–96 combined. There is no evidence for an increased proportion of hypospadias cases in the "possible" or "probable" exposure category compared to the "unlikely" exposure category for any of the seven substance groups separately or for exposure to the seven substance groups combined (exposure to *any* substance). There was no evidence for an upward trend with the likelihood for exposure in any of the substance groups. Adjustment for confounding factors did not substantially change results. Tests for heterogeneity in odds ratios between the two time periods (1980–89 and 1992–96) showed the strongest evidence for heterogeneity in substance groups of phthalates ($p = 0.05$), biphenolic compounds ($p = 0.13$), and "other" EDCs ($p = 0.10$). In other substance groups or in the combined substance group there was little evidence for heterogeneity (p values ranging between 0.2 and 0.6).

Results for the 1980–89 and 1992–96 periods separately showed essentially negative results as expected from the combined results and heterogeneity tests above. The only exception, consistent with the heterogeneity noted above for phthalates, was a statistically significant trend with likelihood of exposure to phthalates before social class adjustment ($p = 0.02$) but not after ($p = 0.26$) in the period 1992–96. The odds ratio for "probable" versus "unlikely" exposure to phthalates is 1.52 (95% CI 1.05 to 2.20) before adjustment and 1.26

(95% CI 0.81 to 1.97) after adjustment for social class. It was mainly social class of the mother that contributed to this shift in odds ratios; adjustment for social class of the father or deprivation only had very little effect on the odds ratio estimate. Hairdressers make up the majority of cases in the "probable" exposure category (28/35 hypospadias cases, 184/245 all congenital abnormality cases) and results are driven largely by results for this job code. In the 1992–96 data we also find an OR of borderline significance for "possible" versus "unlikely" exposure to other EDCs, again before social class adjustment (OR 1.45, 95% CI 0.99 to 2.12) but not after (OR 1.18, 95% CI 0.76 to 1.83). No occupations were classified as having "probable" exposure in this last substance group. Again, hairdressers made up the majority of the cases in the "possible" exposure category (28/32 hypospadias cases, 184/232 all congenital abnormality cases).

Results using births as denominator

Analyses using births as denominator were based on a total of 889 hypospadias cases and 181 964 births for which occupation of the mother was recorded in the 1992–96 period. Analysis of hypospadias risk by individual occupation showed three occupations ("managers", "shelf fillers", "barmen") with statistically significantly raised O/E ratios. Hairdressers did not show a raised O/E ratio (0.95, 95% CI 0.66 to 1.32). In most substance groups of potential endocrine disrupting chemicals there was no evidence for higher risk of hypospadias with increasing likelihood of exposure. A statistically significant trend ($p = 0.02$) is found for exposure to alkylphenolic compounds (OR for possible versus unlikely exposure 1.15, 95% CI 0.88 to 1.51; OR for probable versus unlikely exposure 1.56, 95% CI 1.06 to 2.29). Adjustment for social class results in lowering odds ratios in most substance groups. This is due mainly to adjustment for social class of the mother rather than social class of the father or area deprivation. After social class adjustment there is no longer evidence for a trend with exposure to alkylphenolic compounds (trend $p = 0.42$; adjusted OR for probable versus unlikely exposure 0.92, 95% CI 0.58 to 1.48).

DISCUSSION

We find little evidence for a relation between maternal occupational exposure to potential endocrine disrupting chemicals and a risk of hypospadias in the offspring. Few individual occupational groups showed raised risks of hypospadias, and these must be interpreted with extreme caution because of the large number of comparisons made, and the lack of evidence for heterogeneity overall. In fact, the number of occupations with lower confidence limit above one was less than expected on the basis of the implicit 0.025 significance level, a deficit probably reflecting the conservative nature of the exact confidence interval.[29]

Nevertheless, there was some indication in this study for an increased risk of hypospadias in the offspring of hairdressers and occupations exposed to phthalates (of which hairdressers form the largest occupational group), in the 1992–96 time period. Hairdressers were an occupational group of some a priori importance because they were the largest single occupational group that was assigned probable exposure to potential endocrine disrupters, more specifically phthalates. Hairdressers were also assigned "possible" exposure to alkylphenolic compounds and "other" EDCs. Hairdressers have in the literature been linked to high risks of other adverse reproductive outcomes,[30] but the few studies that have examined risk of birth defects in hairdressers have not found an association.[30–33] No previous studies have studied hypospadias risk in hairdressers. Our results for hairdressers as an individual group and for exposure to phthalates should be interpreted with caution since they are limited to only one time period (1992–96), do not occur in the analyses using births as denominators, and do not reach statistical significance after adjustment for social class of the mother. We have no information to suggest that exposure of hairdressers to potential EDCs may have increased in 1992–96 compared to 1980–89. The close relation between maternal social class and occupation makes it difficult to separate effects of occupation and social class. In the 1992–96 period, 180 of 184 hairdressers in the congenital anomaly database were classified under social class III–manual (the remaining four were hairdresser managers), and around a third (180/604) of mothers in social class III–manual were hairdressers. Since hairdressers are the largest exposed group, and the results of our study are ambiguous, further studies are warranted to clarify the relation between work in hairdressing occupations and risk of hypospadias.

Maternal occupational exposure to potential endocrine disrupting chemicals was assessed in this study by use of a job exposure matrix. Information on maternal occupation was taken from the congenital anomaly and birth registrations where only the job title is registered with no specification of timing, duration, and exact tasks. Furthermore, assessment of exposure to endocrine disrupters is complicated because of wide variation in endocrine disrupting potency of substances and mechanisms by which these substances produce their effect,[13] and because little is known about possible interactions that may occur in exposures to multiple endocrine disrupters or about levels of exposure to endocrine disrupters in many occupations.[26] In addition, the job exposure matrix (JEM) does not distinguish substances with different mechanisms or potency for endocrine disruption, nor does it incorporate any possible changes in exposure over time. There is currently no clear indication which mechanism may be related to hypospadias, although it has recently been suggested that an antiandrogenic mechanism may be responsible.[34] Further development of the JEM would be needed to take this into account. The strengths and limitations of the JEM used in this study are discussed in more detail elsewhere.[26] Validation of the JEM was beyond the scope of the present study. However, further studies could consider validating the JEM by determining oestrogenic activity in blood or urine, using the ER-Calux bioassay.[35]

With these limitations to the JEM, a high level of misclassification can be expected. We would not expect such misclassification to differentially affect hypospadias cases and other congenital anomaly cases, so it is likely to bias odds ratios towards one, and hence limit our ability to detect an effect of exposure to potential endocrine disrupters on hypospadias risk.[36]

It has long been known that the National Congenital Anomaly System is incomplete and that completeness of notification varies by type of anomaly, with those which are easily visible at birth being more completely notified.[37] We therefore expect a level of incompleteness in both the hypospadias data and congenital anomaly denominator data used for this study. The detection of hypospadias at birth, especially of milder forms, can be inconsistent. A small validation study of a sample of NCAS data for 1993–95 births found that only one quarter of eligible (non-glanular) cases had been notified to NCAS, and of those notified over one third were glanular hypospadias and therefore ineligible for notification.[38] Although we know of no evidence that notification of congenital anomalies varies by occupation, the fact that notification is incomplete makes this a possibility. Such differential notification could bias odds ratios either towards or away from one.

The use of malformed controls (that is, all malformations as denominator) is common in the study of teratogenic risk factors for congenital anomalies, mainly to limit the potential for information bias.[39–41] However, the congenital anomalies included in the denominator data may be associated with exposure to some of the groups of chemicals named as potential endocrine disrupters, even though no other congenital anomalies other than hypospadias and cryptorchidism have been linked to potential endocrine disrupting effects specifically. For example, there is some suggestive evidence that pesticides may be linked to neural tube defects, limb reduction defects, and oral clefts,[42 43] and organic solvents to neural tube defects, oral clefts, and some cardiac defects.[44] The inclusion of controls which are related to the exposure of interest would result in an underestimation of a possible effect.[40 41] We therefore analysed data using non-malformed live births as controls also. These results are hard to interpret since they are more likely to be subject to information bias as a result of the different sources of occupational data. However, they do not suggest a severe underestimation of the risks in the proportional analysis.

The introduction of stricter criteria for exclusion of "minor" congenital anomalies by ONS in 1990 meant that an essentially different case group is used in the 1992–96 period from the 1980–89 period. Since 1990, guidelines asked for reporting to be restricted to a group of more severe (that is, more proximal) forms of hypospadias. Annual hypospadias case numbers in the later period are around half those in the early period. In addition, the total congenital anomaly group used for denominator data will have excluded minor anomalies in the later period. The type of hypospadias that may result from exposure to potential endocrine disrupters is likely to depend on dose, timing, and type of exposure but very little is known about how these factors would influence the outcome. Heterogeneity in findings between time periods (such as for phthalate exposure, socioeconomic status, and maternal age) may in part reflect differences in the types of hypospadias being recorded between the time periods.

Several authors have recently argued that exposure to potential EDCs in the general population may be too low to be responsible for the general increase in male reproductive health outcomes reported.[13 45] Occupation, however, may represent a high exposure situation where effects are more likely to be found. Although the results of this study are largely reassuring, the exposure classification was necessarily crude and findings should be interpreted with caution.

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