BIRTH DEFECT INVESTIGATION REPORT
Birth Defects Among Deliveries to Residents of Midlothian, Venus, & Cedar Hill, Texas, 1997-2001

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BACKGROUND

A community member expressed concern over birth defects in Midlothian (Ellis County), Venus (Johnson County), and Cedar Hill (Ellis and Dallas Counties), Texas. The community member also expressed concern about pollution from cement kilns in or near these 3 communities and a steel mill in or near Venus, Texas.

METHODS

Case Definition

The areas of interest are south of Dallas and Fort Worth. The Texas Birth Defects Registry began collecting information in this part of the state with deliveries in January 1997, and the most recent delivery year for which the registry has completed data collection is 2001.

Based on this information, a case was defined as an infant or fetus…

- with any of 48 specific birth defects, or with any birth defect monitored by the registry;
- born between January 1997 and December 2001;
- born to a mother who resided in Midlothian, Venus, or Cedar Hill at the time of delivery.

Each community was examined separately from the other 2 communities.

Case Finding

The Texas Birth Defects Registry was searched to find cases meeting the case definition. The mother's place of residence at the time of delivery was based on information reported on the child's birth or fetal death certificate, when available. If a birth or fetal death certificate could not be found, the mother's place of residence at the time of delivery was based on information in the Texas Birth Defects Registry that had been abstracted from hospital medical records.

Occurrence Evaluation

Unadjusted Prevalence: Cases in the registry were used to calculate prevalence rates per 10,000 live births for 48 specific birth defects and for infants and fetuses with any birth defect monitored by the registry. Calculations were done for the 3 communities separately. The 95% confidence interval for each prevalence was calculated based on the Poisson distribution. In order to determine if there was a statistically significant elevation in the occurrence of birth defects, the prevalence rates for the areas and time period of interest were compared to the prevalence rates for all of Texas during January 1999 through December 2001. Prevalence rates were considered statistically significantly different if their 95% confidence intervals did not overlap.

Adjusted Prevalence: The occurrence of many types of birth defects is known to vary between mothers of different age groups, mothers of different racial/ethnic groups, and between male and female infants. For each type of birth defect that was statistically significantly elevated based on the unadjusted prevalence, we calculated prevalence rates adjusted separately for age, race/ethnicity, and sex. Adjustment accounts for any differences in the age, racial/ethnic, or sex composition of populations being compared, in this case, differences between the communities of interest during 1997-2001 and all of Texas during 1999-2001.

Using the direct method of standardization, maternal age-specific rates for the area of interest were standardized (adjusted) to the maternal age distribution of all Texas resident live births during 1999-2001. The resulting adjusted rate is the hypothetical rate that would have been observed in the area of interest if that area had the same maternal age distribution as Texas overall in 1999-2001. Similarly, maternal racial/ethnic-specific rates for the area of interest were standardized to the maternal race/ethnic distribution of Texas resident live births during 1999-2001, yielding the hypothetical rate that would have been observed if the area of interest had the same maternal race/ethnic distribution as Texas. Finally, adjustment for infant sex was accomplished in the same manner.

The DIRST module of Computer Programs for Epidemiologists [1], version 4.0, was used to calculate directly standardized rates and their associated 95% confidence intervals.

Age-, Race-, and Sex-specific Prevalence: For the types of birth defects that were statistically significantly elevated based on the unadjusted prevalence and that remained statistically significant after adjustment, we have shown prevalence by maternal age group, maternal racial/ethnic group, and infant sex, plus 95% confidence intervals based on the Poisson distribution.

Estimated Date of Conception: The estimated date of conception was calculated and graphed for cases having the types of birth defects that remained statistically significantly elevated after adjustment. If the last menstrual period (LMP) date was available, the estimated date of conception was calculated as the LMP date plus 14 days. If LMP date was not available, the estimated date of conception was calculated as the expected date of delivery minus 266 days.

Spot Map: For the types of birth defects that remained statistically significant after adjustment, a spot map was made using the mother's residence address at the time of delivery, as reported on the child's birth or fetal death certificate. The map is not included in this report to protect the privacy of the families.

RESULTS

Unadjusted Prevalence: We examined the occurrence of 48 types of birth defects and any birth defect monitored by the registry among deliveries during January 1997 through December 2001 to residents of Midlothian, Venus, and Cedar Hill separately.

For Venus and for Cedar Hill during 1997-2001, none of the birth defects examined was statistically significantly higher than the statewide prevalence in 1999-2001. The prevalence of any monitored birth defect also was not statistically significantly elevated in Venus or Cedar Hill, compared to the entire state.

For Midlothian during 1997-2001, 2 categories of birth defects were statistically significantly higher than the statewide prevalence in 1999-2001.

The unadjusted prevalence of hypospadias or epispadias among Midlothian resident deliveries during 1997-2001 was 102.39 cases per 10,000 live births (95% confidence interval 52.91-178.85) (Table 1), which was 3.5 times the prevalence for Texas in 1999-2001 (28.87 cases per 10,000 live births, 95% CI 27.86-29.88) and statistically significant.

The unadjusted prevalence of any monitored birth defect among Midlothian resident deliveries during 1997-2001 was 511.95 cases per 10,000 live births (95% CI 390.61-658.96) (Table 2). This was 1.5 times the prevalence for Texas in 1999-2001 (350.12 cases per 10,000 live births, 95% CI 346.59-353.65) and statistically significant.

Adjusted Prevalence: Adjusted prevalences were calculated for hypospadias or epispadias and for any monitored birth defect among Midlothian resident deliveries during 1997-2001.

For hypospadias or epispadias (Table 1), adjusting for infant sex had no impact on the prevalence, yielding a sex-adjusted prevalence of 102.75 cases per 10,000 live births, which was essentially

unchanged from the unadjusted prevalence of 102.39 cases per 10,000 live births. Adjusting for maternal age group caused the prevalence of hypospadias or epispadias to increase very slightly, from 102.39 unadjusted to 106.02 after adjustment. Adjusting for maternal race/ethnicity caused the prevalence of hypospadias/epispadias to increase from 102.39 unadjusted to 119.86 after adjustment.

This means that the elevation observed in Midlothian during 1997-2001 for hypospadias or epispadias cannot be attributed to differences between Midlothian and Texas overall in the proportion of boys and girls being born, or in the race/ethnic or age distribution of women having children. The prevalence of hypospadias or epispadias remained statistically significantly elevated in Midlothian after adjustment for sex, maternal age, and maternal race/ethnicity.

Table 1. Unadjusted and adjusted prevalence of hypospadias or epispadias among Midlothian resident deliveries, 1997-2001, compared to Texas, 1999-2001.

Mother's residence at delivery	Time Period	Adjusted* for	Prevalence per 10,000 live births	95% Confidence Interval for Prevalence
Midlothian	1997-2001	Unadjusted	102.39	52.90 - 178.84
		Infant sex	102.75	45.20 - 160.29
		Maternal age group	106.02	45.38 - 166.66
		Maternal race/ethnicity	119.86	27.86 - 211.86
Texas	1999-2001	Unadjusted	28.87	27.86 - 29.88

* Adjusted to the distribution of Texas resident live births during 1999-2001.

For any monitored birth defect (Table 2), adjusting for sex had no impact on the prevalence. The sex-adjusted prevalence, 512.58 cases per 10,000 live births, was nearly the same as the unadjusted prevalence, 511.95. Likewise, adjusting for maternal age group had no impact on the prevalence of any monitored defect (511.95 unadjusted compared to 513.71 after adjustment).

Adjusting for maternal race/ethnicity caused the prevalence of any monitored birth defect to decrease from 511.95 per 10,000 unadjusted to 402.69 adjusted (95% CI 256.37-549.01) (Table 2). Further, the adjusted prevalence was no longer statistically significantly elevated compared to Texas in 1999-2001 (350.12; 95% CI 346.59-353.65).

This means that the elevation observed in Midlothian during 1997-2001 for any monitored birth defect can be explained by differences between Midlothian and Texas overall in the race/ethnic distribution of women having children. In Midlothian, 83.2% of mothers who gave birth in 1997-2001 were non-Hispanic White women, while in Texas during 1999-2001, only 39.2% of births were to non-Hispanic White mothers. Further, in Texas overall during 1999-2001, the prevalence of any monitored birth defect was statistically significantly higher among non-Hispanic White mothers (374.16 per 10,000 live births; 95% CI 368.33-380.00) than among African American mothers (339.69; 95% CI 329.34-350.04) or Hispanic mothers (340.34; 95% CI 335.21-345.48). Because most Midlothian mothers are non-Hispanic White women, and because the prevalence of any monitored birth defect is higher among mothers of this race/ethnic group, the unadjusted prevalence of any monitored birth defect in Midlothian was higher than the Texas prevalence, and it decreased after adjustment for race/ethnicity.

Table 2. Unadjusted and adjusted prevalence of any monitored birth defect among Midlothian resident deliveries, 1997-2001, compared to Texas, 1999-2001.

Mother's residence at delivery	Time Period	Adjusted* for	Prevalence per 10,000 live births	95% Confidence Interval for Prevalence
Midlothian	1997-2001	Unadjusted	511.95	390.61 - 658.96
		Infant sex	512.58	386.66 - 638.50
		Maternal age group	513.71	385.32 - 642.11
		Maternal race/ethnicity	402.69	256.37 - 549.01
Texas	1999-2001	Unadjusted	350.12	346.59 - 353.65

* Adjusted to the distribution of Texas resident live births during 1999-2001.

Age-, Race-, and Sex-specific Prevalence: Since hypospadias or epispadias was the only type of birth defect that was statistically significantly elevated after adjustment, we took a closer look at it. Table 3 shows the prevalence of hypospadias or epispadias by maternal age group, maternal race/ethnicity, and infant sex among Midlothian resident deliveries during 1997-2001. Data for Texas in 1999-2001 are also presented for comparison.

The mothers of Midlothian children with hypospadias or epispadias ranged in age from 17 to 37. The prevalence of hypospadias or epispadias among mothers less than 20 years old was statistically significantly higher in Midlothian than in Texas. For all other maternal age groups, the Midlothian prevalences did not attain statistical significance.

Midlothian mothers of 'Other' race/ethnicity were significantly more likely to have a child with hypospadias or epispadias than mothers of 'Other' race/ethnicity statewide. This was the only racial/ethnic group that was statistically significantly higher than the state.

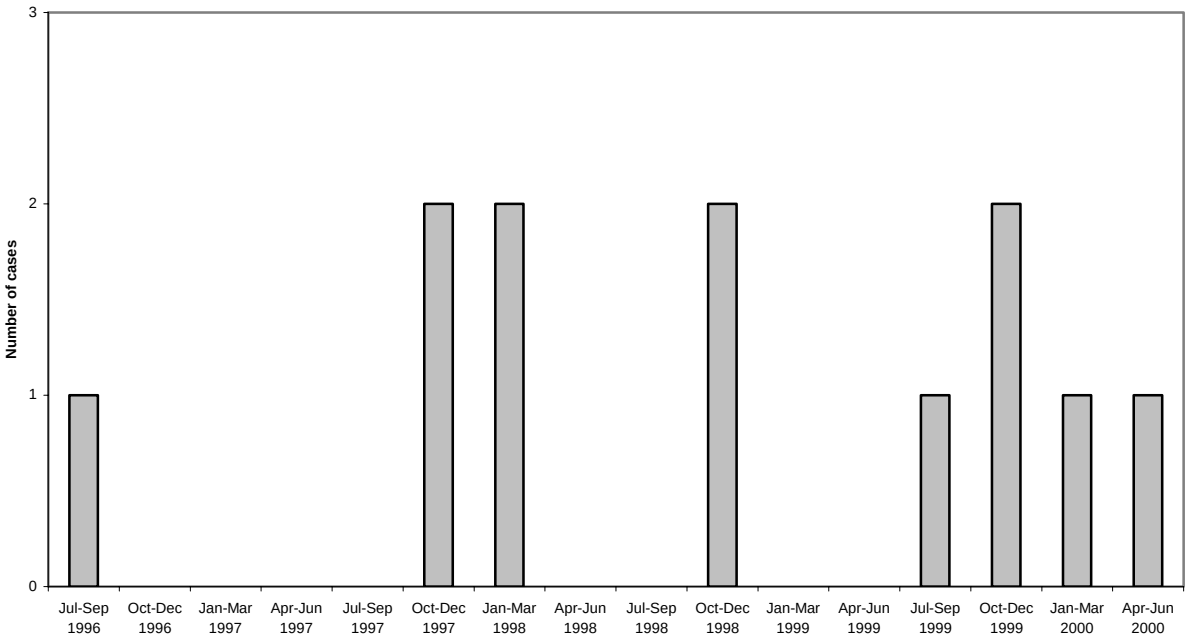
The prevalence of hypospadias or epispadias among male infants was also statistically significantly higher in Midlothian than Texas.

Table 3. Prevalence of hypospadias or epispadias by maternal age group, maternal race/ethnicity, and infant sex, Midlothian 1997-2001 and Texas 1999-2001.

Area and Time Period	Characteristic		Cases	Live Births	Prevalence per 10,000 live births	95% Confidence Interval for Prevalence
Midlothian, 1997-2001	Total		12	1172	102.39	52.90 - 178.84
	Maternal age group	<20	3	141	212.77	43.97 - 621.99
		20-24	3	278	107.91	22.30 - 315.47
		25-29	4	393	101.78	27.74 - 260.56
		30-34	0	234	0.00	0.00 - 157.69
		35-39	2	109	183.49	22.02 - 662.39
		40+	0	17	0.00	0.00 - 2170.59
	Maternal race/ ethnicity	non-Hispanic White	9	975	92.31	42.26 - 175.18
		African American	0	11	0.00	0.00 - 3354.55
		Hispanic	1	174	57.47	1.72 - 320.11
		Other	2	12	1666.67	200.00 - 6016.67
	Infant sex	Male	12	597	201.01	103.85 - 351.09
		Female	0	575	0.00	0.00 - 64.17
Texas, 1999-2001	Total		3111	1077574	28.87	27.86 - 29.88
	Maternal age group	<20	435	164724	26.41	23.93 - 28.89
		20-24	771	304357	25.33	23.54 - 27.12
		25-29	825	288532	28.59	26.64 - 30.54
		30-34	679	208993	32.49	30.05 - 34.93
		35-39	334	92476	36.12	32.24 - 39.99
		40+	67	18368	36.48	28.27 - 46.32
	Maternal race/ ethnicity	non-Hispanic White	1730	422278	40.97	39.04 - 42.90
		African American	422	121787	34.65	31.34 - 37.96
		Hispanic	883	495559	17.82	16.64 - 18.99
		Other	69	36946	18.68	14.53 - 23.64
	Infant sex	Male	3098	550818	56.24	54.26 - 58.22
		Female	1	526756	0.02	0.00 - 0.11

Estimated Dates of Conception: The 12 Midlothian children born during 1997-2001 with hypospadias or epispadias were estimated to have been conceived from September 1996 through April 2000. No more than 1 case was conceived in any given month during this time period, nor was there any other evidence of clustering in time (Figure 1).

Figure 1. Estimated dates of conception for Midlothian children born during 1997-2001 with hypospadias or epispadias.



Spot map: The spot map of maternal residence address at time of delivery for the 12 Midlothian children born during 1997-2001 with hypospadias or epispadias did not show any strong evidence of geographic clustering within Midlothian. Seven of the residences were distributed within the current Midlothian city limits and five were outside the city limits. The map is not included in this report to protect the privacy of the families.

DISCUSSION

Using data in the Texas Birth Defects Registry, we examined the occurrence of 48 specific birth defects and any defect monitored by the registry among deliveries during 1997-2001 to residents of Midlothian, Venus, and Cedar Hill, Texas. None of the birth defects examined were statistically significantly elevated in Venus or Cedar Hill. Any monitored birth defect and hypospadias or epispadias were elevated in Midlothian during 1997-2001.

The prevalence of any monitored defect in Midlothian decreased and was no longer statistically significantly elevated after adjusting for maternal race/ethnicity. This indicates that the elevation observed in Midlothian for any monitored birth defect can be attributed to differences between Midlothian and Texas in the race/ethnic distribution of women having children. If Midlothian had the same maternal race/ethnic distribution as Texas, the prevalence of any monitored birth defect in Midlothian would have been within the range of what is expected.

Hypospadias or epispadias remained statistically significantly elevated in Midlothian after adjustment for sex, race/ethnicity, and age, meaning that this elevation cannot be explained by differences between Midlothian and the state in the proportion of boys and girls being born, or in the race/ethnic or age distribution of women having children.

Hypospadias is a congenital defect in which the urinary meatus (urinary outlet) is on the underside of the penis or on the perineum (the area between the genitals and the anus). In epispadias, the urinary meatus opens above (dorsal to) the normal position. The corresponding defects in females are very rare.

All of the 12 Midlothian children had hypospadias, rather than epispadias. A summary of risk factors for hypospadias reported in the scientific literature can be found in the addendum to this report.

A spot map did not indicate geographic clustering within Midlothian of the residences of the mothers of children with hypospadias, and a graph of estimated conception dates did not indicate clustering in time of conception.

We made 147 comparisons of community level birth defects data to statewide data (48 birth defects plus any monitored defect, times 3 communities). At the 95% level of significance, we would expect 5% of the 147 comparisons, or 7 comparisons, to have been statistically significant due to chance. We found 2 that were statistically significant, and 1 that remained significant after adjustment for sex, maternal race/ethnicity, and maternal age.

Although hypospadias/epispadias was elevated in Midlothian, it does not meet criteria to continue this investigation and thus further study at this time is unlikely to yield useful results. To continue, our protocol requires at least 3 cases with a documented biologically plausible exposure that the cases have in common, or at least 5 cases with an observed rate of more than 10 times the expected rate. However, because of the elevation, the Texas Birth Defects Registry will continue to monitor hypospadias. As more years of data become available in the future, we will re-examine the prevalence of hypospadias in the area.

CONCLUSIONS

Hypospadias or epispadias was elevated among Midlothian resident deliveries during 1997-2001. We will re-examine the occurrence of hypospadias or epispadias after subsequent delivery years are completed in the Texas Birth Defects Registry.

REFERENCE

1. Abramson JH, Gahlinger PM. Computer Programs for Epidemiologists: PEPI, version 4.0. Salt Lake City, Utah: Sagebrush Press, 2001.

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ADDENDUM
Summary of Risk Factors for Hypospadias

Prepared by staff of the Birth Defects Epidemiology and Surveillance Branch
Texas Department of State Health Services
Last Updated October 3, 2002

Please Note: *The primary purpose of this report is to provide background necessary for conducting cluster investigations. It summarizes literature about risk factors associated with this defect. The strengths and limitations of each reference were not critically examined prior to inclusion in this report. Consumers and professionals using this information are advised to consult the references given for more in-depth information.*

This report is for information purposes only and is not intended to diagnose, cure, mitigate, treat, or prevent disease or other conditions and is not intended to provide a determination or assessment of the state of health. Individuals affected by this condition should consult their physician and when appropriate, seek genetic counseling.

DESCRIPTION

Hypospadias occurs when the urethral opening (meatus) is located ventral to the tip of the glans. Hypospadias is rare in females and may not truly occur in females (Harris, 1990). The condition is often recognized by physical examination shortly after birth, although milder form may be missed. Approximately 30-50% of cases are associated with chordee (downward curvature of the penis).

Hypospadias is classified by the location of the urethral meatus or the severity of the defect:

- 1st degree: glandular or coronal meatus (60-75% of cases)
- 2nd degree: penile meatus (15-25% of cases)
- 3rd degree: scrotal or perineal meatus (3-6% of cases)

Perineal hypospadias may also be classified as 4th degree hypospadias. Hypospadias is sometimes classified as distal or proximal. Severe hypospadias may be initially classified as ambiguous genitalia.

Hypospadias usually does not occur with chromosomal abnormalities but some cases have been associated with Down syndrome and with sex chromosome abnormalities (Torfs and Christianson, 1998; Stoll et al., 1990; Calzolari et al., 1986; Aarskog, 1979; Svennson et al., 1979; Avellan, 1977; Chen and Woolley, 1971). The mortality rate of infants with hypospadias is very low (Nazer et al., 1992; Kallen and Winberg, 1982).

EMBRYOLOGY

Hypospadias occurs due to failure of fusion of the genital folds after approximately eight weeks' gestation, with the resulting failure of formation of the preputial tissues on the ventral penis (Baskin et al., 2001).

DEMOGRAPHIC AND REPRODUCTIVE FACTORS

Race/ethnicity has been associated with hypospadias risk, with rates of the defect being highest in whites, followed by blacks, Native Americans, Asians, and Hispanics (Shaw et al., 2002; Leck and Lancashire, 1995; Chavez et al., 1988; Lowry et al., 1986; Chung and Myrianthopoulos, 1968).

Secular trends have been reported for hypospadias, with rates of hypospadias reported to have increased in Australia, Denmark, Great Britain, Hungary, Ireland, Norway, Sweden, and the United States (Paulozzi et al., 1997; Riley et al., 1998; Giwercman et al., 1993; Czeizel and Toth, 1990; Kallen et al., 1986; Simpkin et al., 1985; Kallen and Winberg, 1982; Bjerkedal and Bakketeig, 1975). Nevertheless, other studies failed to find an increase in the defect (Aho et al., 2000; Chambers and Malone, 1999; Kallen et al., 1986; Baird, 1985; Leung et al., 1985; Monteleone et al., 1981). One potential explanation

for the secular increases observed in some areas may involve the fact that the diagnosis of hypospadias is not well defined. Increased ascertainment of mild cases that may be considered normal variants may result in a perceived increase in overall rate. However, secular increases have been observed when observations are limited to the more severe forms of the defect (Paulozzi et al., 1997). One investigation where all consecutive males were examined for hypospadias reported a higher hypospadias rate than that reported by various birth defects registries (Pierik et al., 2002).

Various investigations have reported **seasonal differences** in hypospadias rates (Kallen et al., 1986; Angerpointner, 1984; Monteleone et al., 1981; Czeizel et al., 1979; Svensson, 1979; Avellan, 1977; Campbell et al., 1973; Roberts and Lloyd, 1973; Wehrung and Hay, 1970). However, there was no consistent pattern in seasonality, and other studies found no effect of seasonality on hypospadias rates (Nazer et al., 1992; Castilla et al., 1990; Stoll et al., 1990; Calzolari et al., 1986; Baird, 1985; Leung et al., 1985; Sweet et al., 1974; Record and Armstrong, 1973; Chen and Woolley, 1970).

Hypospadias rates have been found to vary by **residence**, both between countries and within countries (Kallen et al., 1986; Angerpointner, 1984; Kallen and Winberg, 1982). One investigation reported hypospadias risk to be increased with lower **altitude** (Castilla et al., 1999).

Neither **maternal age** nor **paternal age** appear to affect hypospadias risk (Kallen, 2002; Akre et al., 1999; Chambers and Malone, 1999; Weidner et al., 1999; Nazer et al., 1992; Stoll et al., 1991; Calzolari et al., 1986; Kallen and Winberg, 1982; Monteleone et al., 1981; Czeizel et al., 1979), although one investigation reported increased risk of hypospadias with older mothers (Fisch et al., 2001). A number of investigations have noted an association of hypospadias with **parity**, with increased risk of the defect among lower birth ranks, particularly firstborns (Kallen, 2002; Akre et al., 1999; Weidner et al., 1999; Angerpointner, 1984; Czeizel et al., 1979; Hay and Barbano, 1972; Chen and Woolley, 1970).

Hypospadias is more common among infants with lower **birth weight** (Fredell et al., 2002; Hughes et al., 2002; Akre et al., 1999; Weidner et al., 1999; Riley et al., 1998; Mili et al., 1991; Calzolari et al., 1986; Kallen et al., 1986; Angerpointner, 1984; Kallen and Winberg, 1982; Monteleone et al., 1981; Czeizel et al., 1979; Avellan, 1977; Sweet et al., 1974; Chen and Woolley, 1970), lower **placental weight** (Stoll et al., 1990), lower **gestational age** (Rasmussen et al., 2001; Weidner et al., 1999; Calzolari et al., 1986; Kallen et al., 1986; Angerpointner, 1984; Kallen and Winberg, 1982; Avellan, 1977; Sweet et al., 1974), and **intrauterine growth retardation** (Hassain et al., 2002; Khoury et al., 1988; Kallen et al., 1986). There is no association between hypospadias and epispadias and **macrosomia** (Lapunzina et al., 2002; Waller et al., 2001). Hypospadias risk is positively associated with **multiple gestation pregnancy** (Fredell et al., 2002; Akre et al., 1999; Mastroiacovo et al., 1999; Weidner et al., 1999; Ramos-Arroyo, 1991; Kallen et al., 1986; Leung et al., 1985; Monteleone et al., 1981; Czeizel et al., 1979; Roberts and Lloyd, 1973), although one study reported no such association (Kallen, 1986).

Several studies have found no association between **previous abortions** and hypospadias risk (Stoll et al., 1991; Calzolari et al., 1986), although another investigation reported an association between the birth defect and **previous stillbirths** (Weidner et al., 1999).

There is a **hereditary** component to hypospadias with a 4-10% risk of hypospadias among the siblings, children, and other relatives of an individual with the defect (Fredell et al., 2002; Weidner et al., 1999; Calzolari et al., 1986; Kallen et al., 1986; Leung et al., 1985; Angerpointner, 1984; Monteleone et al., 1981; Czeizel et al., 1979; Avellan, 1977; Sweet et al., 1974; Chen and Woolley, 1970). However, the clustering of hypospadias in families may also be considered as evidence of a shared environmental exposure (Baskin et al., 2001).

One investigation found no association between parental **consanguinity** and hypospadias (Rittler et al., 2001).

Abnormalities of the father's testes or scrotum have been associated with hypospadias (Sweet et al., 1974), as has **abnormalities in the sperm** (Fritz and Czeizel, 1996).

FACTORS IN LIFESTYLE OR ENVIRONMENT

There is no association between **parental education** and hypospadias risk (Stoll et al., 1990; Polednak and Janerich, 1983), although one analysis noted increased risk of hypospadias with maternal education of less than 10 years (Kallen, 2002). Several investigations have reported no association between hypospadias risk and **parental occupation** (Matte et al., 1993; Kallen, 1988; Czeizel et al., 1979). The literature on the relationship between hypospadias and **parental gardening and farming** is contradictory (Weidner et al., 1998; Angerpointner, 1984). An article that reviewed recent studies of **paternal occupation** and birth defects described increased risk of hypospadias with paternal occupation of forestry and logging worker, fireman, policeman and guard, and vehicle manufacturer (Chia and Shi, 2002).

Partly as a result of the secular increases in hypospadias rates observed in certain areas, a potential association between the defect and **chemicals with estrogenic or anti-androgenic effects (polychlorobiphenyls, dioxins, organochlorine pesticides, alkylphenol polyethoxylates, and phthalates)** has been suggested, but there has been no strong evidence of this (Dolk, 1998). One study reported no relationship between maternal serum levels of **DDE (1,1-Dichloro-2,2-bis(p-chlorophenyl)ethylene)**, a metabolite of the pesticide DDT that inhibits binding of androgen to the androgen receptor, and risk of hypospadias (Longnecker et al., 2002). Hypospadias rates do not seem to be influenced by residence in **proximity to a variety of industries** (Castilla et al., 2000) and **hazardous waste sites** (Dolk et al., 1998), and exposure to **pesticides and other contaminants in the water** (Chambers and Malone, 1999), although one investigation reported increased risk of hypospadias with **parental pesticide exposure** (Kristensen et al., 1997). Another study found a slightly increased risk of hypospadias and epispadias with proximity to **landfill sites** (Elliott et al., 2001). Hypospadias may be associated with **dioxin (TCDD)** exposure in a dose-response fashion (Mastroiacovo et al., 1988).

Another potential association has been proposed between **sex hormones** used as **oral contraceptives**, **pregnancy tests**, and to treat threatened abortions or because of previous miscarriages. A number of investigations have reported increased risk of hypospadias with sex hormones (Lopez-Camelo and Orioli, 1996; Calzolari et al., 1986; Angerpointner, 1984; Monteleone et al., 1981; Aarskog, 1979; Czeizel et al., 1979; Sweet et al., 1974). However, other investigations, including a meta-analysis, found no association between hypospadias and sex hormones or oral contraceptives (Chambers and Malone, 1999; Raman-Wilms et al., 1995; Kallen et al., 1991; Czeizel and Toth, 1990; Stoll et al., 1990; Czeizel and Huiskes, 1988; Kallen, 1988; Polednak and Janerich, 1983; Kallen and Winberg, 1982; Mau, 1981; Janerich et al., 1980). Since these sex hormones are often used to treat particular conditions, it might be that the underlying condition and not the treatment was associated with increased risk of hypospadias. **Threatened abortion** has been connected with increased risk of hypospadias by some studies (Calzolari et al., 1986; Kallen and Winberg, 1982; Czeizel et al., 1979), but not others (Stoll et al., 1990). No association of the defect was found with **subfertility** (Akre et al., 1999; Kallen, 1988).

Several investigations have reported increased risk of hypospadias with **assisted reproductive technologies** such as **in vitro fertilization**, **gamete intrafallopian transfer** (**GIFT**), and **intracytoplasmic sperm injection** (**ICSI**) (Wennerholm et al., 2000; Silver et al., 1999; Macnab and Zouves, 1991), although this association possibly may be due to the underlying fertility problems.

Neither **alcohol** nor **smoking** appear to influence hypospadias risk (North and Golding, 2000; Akre et al., 1999; Chambers and Malone, 1999; Stoll et al., 1990; Van Den Eeden et al., 1990; Kallen, 1988; Calzolari et al., 1986; Kallen and Winberg, 1982). However, one study noted decreased risk of hypospadias with maternal smoking (Kallen, 2002).

Hypospadias has been associated with the anticonvulsants **valproic acid** and **carbamazepine** (Arpino et al., 2000; Lindhout et al., 1992), **co-trimoxazole** (trimethoprim and sulfamethoxazole, an antibacterial agent and folic acid antagonist) (Czeizel, 1990), **antiemetics** (Monteleone et al., 1981), and **codeine** (North and Golding, 2000). Hypospadias risk does not appear to be associated with the **benzodiazepines** nitrazepam, medazepam, tofisopam, alprazolum, and clonazepam (Eros et al., 2002), the antibiotic **oxytetracycline** (Czeizel and Rockenbauer, 2000), **cephalosporin antibiotics** (Czeizel et

al., 2001a), **nalidixic acid** (Czeizel et al., 2001b), **ampicillin** (Czeizel et al., 2001c), **cotrimoxazole (trimethoprim-sulfamethoxazole)** (Czeizel et al., 2001d), **calcium channel blockers** (Sorensen et al., 2001), **antineurotic and antidepressant medications** (Kallen and Winberg, 1982), **thyroid medications** (Polednak and Janerich, 1983), and **immunizations** and **radiation** (Stoll et al., 1990; Monteleone et al., 1981). The relationship is unclear between **aspirin** and hypospadias (Correy et al., 1991; Slone et al., 1976) and **vaginal spermicides** and hypospadias (Louik et al., 1987; Jick et al., 1981). Investigations have reported increased risk of hypospadias with maternal use of **oral anti-tuberculosis medications** and **augmentin**; however, when the analyses were limited to exposure during the critical period of hypospadias formation, the results were not significant (Czeizel et al., 2001e; Czeizel et al., 2001f). Although case reports have suggested an association between hypospadias and **misoprostol**, a synthetic prostaglandin used for elective termination, a case-control study failed to find increased risk of hypospadias with the medication (Orioli and Castilla, 2000). It has been suggested that maternal prenatal **cocaine** use may increase risk of hypospadias (Battin et al., 1995), although other studies have reported no association between fetal cocaine exposure and birth defects (Behnke et al., 2001).

Hypospadias does not appear to be associated with maternal **diabetes** (Ramos-Arroyo et al., 1992; Becerra et al., 1990; Polednak and Janerich, 1983; Kallen, 1988), although one investigation reported increased rates of hypospadias with maternal preexisting diabetes but not gestational diabetes (Aberg et al., 2001). Hypospadias risk is not influenced by **epilepsy** (Polednak and Janerich, 1983), **hypothyroidism** or **hyperthyroidism** (Khoury et al., 1989), **cold** in the first trimester (Zhang and Cai, 1993), **early pregnancy bleeding** (Kallen, 1988), **vaginal bleeding** (Monteleone et al., 1981), **abruptio placentae** (Kallen, 1988; Kallen and Winberg, 1982), or **placenta previa** (Kallen, 1988). One investigation reported increased risk of hypospadias if the mother was exposed to **diethylstilbestrol (DES)** in utero (Klip et al., 2002), while another found no cases of hypospadias among DES offspring (Gill et al., 1979). One study observed increased risk of hypospadias with maternal **influenza** in the first trimester (North and Golding, 2000).

Maternal **folic acid** use during pregnancy does not reduce risk of hypospadias (Kallen and Olausson, 2002; Czeizel et al., 1996). However, mothers who are **vegatarian** or took **iron** supplements increases risk of hypospadias (North and Golding, 2000).

PREVALENCE

The reported prevalence for hypospadias has shown variation between studies, ranging between 7.6 and 44.4 per 10,000 births or 22.6 and 82.0 per 10,000 male births (Table 1). Differences in prevalence may be due to differences in case inclusion criteria.

Table 1. Prevalence per 10,000 births of hypospadias

Reference	Location	Time period	Rate
Pierik et al., 2002	Netherlands	1998-2000	72.7*
Sekhobo and Druschel, 2002	New York, USA	1996	34.1
Aho et al., 2000	Finland	1970-1986	28.1*
Chambers and Malone, 1999	Great Britian	1992-1994	24.6
Richards et al., 1999	Great Britain	1994-1995	12.6
Riley et al., 1998	Australia	1983-1995	24.4
Papp et al., 1995	Hungary	1988-1990	20.4
Finley et al., 1994	Sweden	1985-1986	11.6, 22.6*

Reference	Location	Time period	Rate
Finley et al., 1994	Alabama, USA	1986-1987	14.9
Ramos-Arroyo et al., 1992	Spain	1980-1985	19.5
Correy et al., 1991	Australia	1981-1989	18.7
Castilla and Lopez-Camelo, 1990	Central & South America	1982-1986	8.3
Czeizel and Toth, 1990	Hungary	1970-1983	39.8*
Stoll et al., 1990	France	1979-1987	14.8, 28.9*
Calzolari et al., 1987	Italy	1978-1984	19.4
Calzolari et al., 1986	Italy	1978-1983	40.9*
Czeizel et al., 1986	Hungary	1970-1983	19.4, 38.0*
Kallen et al., 1986	Europe, Central & South America	1967-1982	15.1
Lowry et al., 1986	Canada	1966-1981	24.1, 47.1*
Baird, 1985	Canada	1966-1981	44.4*
Leung et al., 1985	Canada	1966-1981	44.4*
Simpkin et al., 1985	Ireland	1960-1982	17.6
Czeizel and Vitez, 1981	Hungary	1970-1977	44.4
Monteleone Neto et al., 1981	South America	1967-1975	7.6
Avellan, 1975	Sweden	1965-1968	13.9
Sweet et al., 1974	Minnesota, USA	1940-1970	82.0*
Roberts and Lloyd, 1973	Great Birtain	1964-1966	11.8

*rate per male births only

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