

MATERNAL AGE AS A RISK FACTOR FOR HYPOSPADIAS

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ABSTRACT

Purpose: Hypospadias incidence rates have been widely reported to be increasing. During the last 20 years there has been a significant increase in the number of women who delay childbearing until their mid 30s. Therefore, it was of interest to determine if increasing maternal age is an independent risk factor for hypospadias.

Materials and Methods: Data from the New York State Department of Health and California Birth Defects Monitoring Program were analyzed from 1983 to 1996 by maternal age groups of less than 20, 20 to 24, 25 to 29, 30 to 34, and 35 or greater years. A Poisson model was fitted to the data from each state using maternal age and year of birth from which relative rates were calculated.

Results: Our analysis revealed that advancing maternal age is significantly associated with hypospadias and is most evident for severe cases. For example, in California a 50% increase in severe cases was demonstrated for children of mothers older than 35 years compared to mothers younger than 20 years ($p < 0.05$).

Conclusions: Hypospadias is significantly associated with increasing maternal age. Women who elect to delay childbearing until their mid 30s or later should be aware that their offspring are at increased risk of hypospadias.

KEY WORDS: hypospadias, maternal age, endocrine system

There is an ongoing debate regarding whether there might be a decline in parameters of male reproductive health in the United States manifested as decreasing sperm counts, increased incidence of testicular cancer and, most recently, male reproductive tract birth defects such as cryptorchidism and hypospadias.^{1–6} Hypospadias is one of the most common male congenital anomalies and is caused by incomplete fusion of the urethral folds during embryological formation of the penile urethra, resulting in an abnormally positioned urethral opening on the ventral surface of the penis or on the scrotum.⁷ According to the Birth Defects Monitoring Program (BDMP), a nationwide surveillance program established by the Centers for Disease Control, the incidence of hypospadias in the United States has doubled during the last 30 years.⁴ Similar reports have appeared for England and Wales,⁸ and Hungary.⁹ Some have speculated that in utero exposure to endocrine active compounds from the environment (endocrine disrupters) might be responsible for any or all of these end points.^{10–12} To date, although a growing number of man-made endocrine active compounds have been identified in the environment, none has been implicated as being associated with hypospadias or having any adverse effects on male reproductive health. However, a recent study evaluating maternal vegetarian diet demonstrated an increased risk in developing hypospadias, possibly reflecting a deleterious effect of phytoestrogens and vegetarianism during development.¹³

An increasing number of couples who use some form of fertility treatment achieve and maintain a pregnancy. Several recent studies have reported as much as a 5-fold increase in the incidence of hypospadias in male infants conceived via in vitro fertilization.^{14–16} Since the age of women undergoing in vitro fertilization and fertility treatment is older than the general population having children, the question

arose as to whether maternal age has an independent effect on hypospadias incidence rates. We determine whether maternal age is a risk factor for hypospadias and, therefore, a contributory factor in the reported increase in hypospadias incidence.

MATERIALS AND METHODS

Data on hypospadias rates were available from New York State and California. The New York State Department of Health Congenital Malformations Registry began in 1982 and includes data from the entire state. A case is defined as a child born or living in the state of New York diagnosed with a major malformation before the age of 2 years. More than 90% of cases reported have been diagnosed before age 1 year. Cases are reported to the Congenital Malformations Registry by hospitals and physicians, and are generally ascertained through medical records departments. If a diagnosis is ambiguous, clarification is requested from the child's physician. Although New York State law mandates reporting, monitoring of data and hospital audits are performed to ensure more complete and accurate reporting. The California Birth Defects Monitoring Program conducts active surveillance of congenital malformations diagnosed at year of birth. Cases are ascertained through review of medical records at all hospitals and genetic centers. Information on maternal age is obtained through linkage with birth certificate data.

Hypospadias data were available for 1983 through 1996 for New York State and 1983 through 1995 for California. The California data set provided for this study encompasses 2 different coding schemes. From 1983 through 1989 the database includes all cases of hypospadias while from 1990 through 1995 the database includes only severe cases. Severe hypospadias is defined when the urethral opening is proximal to the glans. In addition, in this data set severe cases also include mild cases of hypospadias (glanular) associated with

other penile abnormalities including but not limited to chordee. All mild cases not associated with other penile anomalies are excluded from the 1990 to 1995 data set. For each state the data were grouped by year and maternal age. The maternal age groups were less than 20, 20 to 24, 25 to 29, 30 to 34 and 35 or greater. A Poisson model was fitted to the data from each state using maternal age and year of birth from which relative rates were calculated by comparing hypospadias rates for mothers 35 years old or older to each of the younger age groups. The yearly average number of births from 1983 to 1996 for the New York and California systems combined was 457,000.

RESULTS

The figure shows that the incidence of hypospadias had not increased in New York State from 1983 to 1996. During this period there was no change in categorization. In California the mean incidence of hypospadias between 1983 and 1989 was 2.8/1,000 total births (table 1) with a peak incidence in 1983 of 3/1,000 births. From 1990 to 1995, when only data regarding severe cases were available, the mean incidence of hypospadias in California was 1.5/1,000 cases (table 1) with a peak incidence of 1.6/1,000 cases in 1990. Table 2 compares hypospadias rates by maternal age and shows that the rates of hypospadias for infants born to older mothers were higher than for infants born to younger mothers. From the Poisson model, relative rates were calculated by maternal age comparing the rates for mothers 35 years old or older to each of the younger groups (table 2). For each state the rates of hypospadias for infants born to older mothers were statistically significantly different from the rates associated with infants born to younger mothers. For example, in California a 50% increase in severe cases was demonstrated for children of mothers older than 35 years compared to mothers younger than 20 years ($p < 0.05$). For all cases of hypospadias, including less severe cases, in New York State and California a 20% increase was seen in mothers 35 years old or older compared to mothers younger than 20 years.

DISCUSSION

The data analyzed in this study indicate that the incidence for hypospadias has not increased from 1983 to 1996, which is in sharp contrast to data from the Centers for Disease Control BDMP that reported a steady 2-fold increase in hypospadias rates in the United States from 1970 to 1993.⁴

An explanation for this disparity may be due to differences between state surveillance systems and the nationwide method of data collection by the BDMP. The BDMP, which no longer exists, collected data that were neither a random sample of United States births nor representative of a geographically well-defined population.¹⁷ Approximately 1,200 hospitals na-

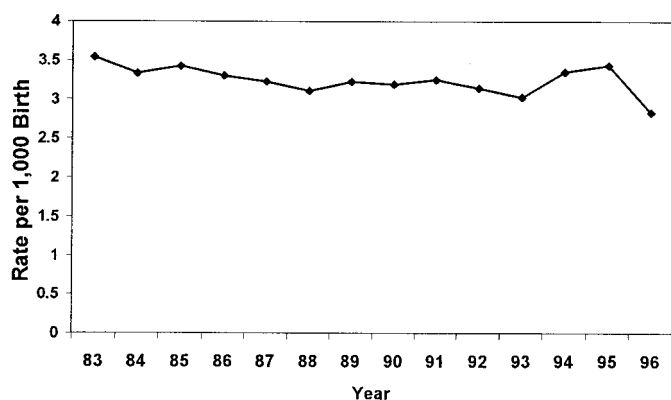
tionwide voluntarily participated in the BDMP from 1970 to 1993, representing 29% of live births in the United States.¹⁷ Since the data analyzed by the BDMP did not represent a random sampling of births, extrapolation to the rest of the country may not be valid. In this regard, the Birth Defects Prevention Act of 1998 authorized the collection and analysis of birth defects information on a national basis. Implemented as part of this Act were increased appropriations to improve state surveillance systems throughout the United States, with the intent of obtaining a more accurate assessment of the incidence of congenital malformations.¹⁸ Currently, the New York State Congenital Malformations Registry and the California Birth Defects Monitoring Program combined provide data on approximately 500,000 births annually, or approximately 16% of all United States births.

Our analysis of the data from New York State and California revealed that maternal age is a significant risk factor for development of hypospadias in offspring. A direct correlation is seen between advanced maternal age and increasing incidence of hypospadias, and was more marked with severe forms of this birth defect. In particular, the data demonstrate as much as a 50% increase in the incidence of severe cases in children born to mothers 35 years old or older compared to mothers younger than 20 years. The rate for all forms of hypospadias in New York State and California for mothers 35 years old or older was 20% higher than rates in mothers younger than 20 years and mothers age 20 to 24 years old.

The association between maternal age and the incidence of congenital defects has been recognized for many years. Down's syndrome and other chromosomal abnormalities are well known to increase in incidence with increasing maternal age, with an exponential increase starting at age 35 years.¹⁹⁻²¹ Some studies have reported a positive association between advancing maternal age and structural birth defects, including esophageal defects, cardiac malformations and hypospadias.²²⁻²⁴ For example, the Joint International Study on the Epidemiology of Hypospadias was a descriptive epidemiological study of hypospadias that used data from 7 worldwide malformation surveillance systems, including Denmark, Hungary, Italy, Mexico, South America, Spain and Sweden. Data from these surveillance systems revealed that Hungary, Spain and Mexico had increased incidences of hypospadias with increasing maternal age.²⁴

Between 1980 and today the number of live births to women 35 years old or older in the United States more than doubled from 5.7% to 12.2%.²⁵ For example, data from New York State and California for 1983 to 1996 revealed a dramatic increase in the number of women older than 35 years having children. In New York in 1983 women 35 years old or older having children represented only 7% of all births, while by 1996 women of this age were responsible for 17% of all births.²⁶ In California births for women 35 years old or older has increased approximately 50% from 1983 to 1995.²⁷ In 1996 approximately 1 in 6 births in California and New York State were from women 35 years old or older, representing a major demographic shift in the age of mothers.

When evaluating hypospadias incidence data, it is critical that maternal age be considered, especially in regions where hypospadias is increasing and maternal age is advancing. The phenomenon of delayed childbearing, as a result of more women pursuing career paths before starting a family, has made inroads into the public consciousness. The potential consequences to offspring born to women who delay childbearing have not received much publicity. The reasons for this are uncertain but it appears that there may be significant health issues that should be part of any decision to delay childbearing until age 35 years or older. It is clear that women who elect to delay childbearing until their mid 30s or later should be aware that their offspring are at increased risk of several age related outcomes, including hypospadias.



Hypospadias incidence for New York State

TABLE 1. *Hypospadias rates by maternal age per 1,000 total births*

Maternal Age	Mean (Range)					
	California 1990–1995		California 1983–1989		New York 1983–1996	
Less than 20	1.2	(0.9–1.5)	2.6	(2.1–3.2)	3.1	(2.4–3.8)
20–24	1.3	(1.0–1.6)	2.8	(2.2–3.5)	3.1	(2.6–3.4)
25–29	1.5	(1.3–1.9)	2.8	(2.1–3.1)	3.3	(3.0–3.6)
30–34	1.6	(1.4–1.8)	2.8	(2.4–3.2)	3.4	(3.0–3.8)
35 or Greater	1.8	(1.4–2.3)	2.9	(1.4–3.7)	3.7	(3.0–4.5)

TABLE 2. *Relative risk of hypospadias for mothers 35 years old or older compared to younger age groups*

Maternal Age	Odds* 95% Confidence Limit					
	California 1990–1995		California 1983–1989		New York 1983–1996	
35 or Greater vs. less than 20	1.5†	(1.2, 1.7)	1.2†	(1.1, 1.4)	1.2†	(1.1, 1.3)
35 or Greater vs. 20–24	1.4†	(1.2, 1.6)	1.2†	(1.0, 1.3)	1.2†	(1.1, 1.2)
35 or Greater vs. 25–29	1.3†	(1.1, 1.4)	1.1	(1.0, 1.2)	1.1†	(1.1, 1.2)
35 or Greater vs. 30–34	1.1	(1.0, 1.3)	1.1	(1.0, 1.2)	1.1†	(1.0, 1.1)

* Increased odds of hypospadias for maternal age 35 or greater.

† Statistically significant at $\alpha = 0.05$.

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