

Hypospadias Rates in New York State are Not Increasing

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Purpose: The testicular dysgenesis syndrome describes urogenital abnormalities associated with exposure to environmental endocrine disruptors such as phthalates, specifically decreased semen quality, and increased rates of testis cancer and hypospadias. Recently there has been concern that these abnormalities described in animal studies may also be present in humans. To determine if hypospadias rates are increasing, we retrospectively reviewed the total prevalence of hypospadias in New York State from 1992 to 2005, categorized by maternal age younger than 35 years and 35 years or older.

Materials and Methods: Hypospadias rates were obtained from the New York State Congenital Malformations Registry from 1992 to 2005. An analysis was also performed on the rates of children with hypospadias who had mothers younger than 35 years and mothers 35 years or older. This investigation was approved by the Columbia University internal review board.

Results: There was no statistical change in hypospadias rates in New York State from 1992 to 2005 ($r = 0.127$, $p = 0.6$). Overall the mean \pm SE prevalence rate was 34.9 ± 0.36 per 10,000 live births. However, mean \pm SE hypospadias rates in children of mothers 35 years old or older (38.7 ± 0.7) were significantly greater than those in children of mothers younger than 35 years (34.1 ± 0.386 , t test $p < 0.01$).

Conclusions: Hypospadias rates have not changed in New York State from 1992 to 2005. Additionally advanced maternal age continues to be a risk factor for hypospadias. Combined with previous studies that demonstrate sperm counts are not declining, these data suggest that the testicular dysgenesis syndrome described in animal models may not be evident in humans.

Key Words: epidemiology, gonadal dysgenesis, hypospadias, pediatrics, phthalic acids

RECENTLY there has been considerable discussion regarding the potential deleterious effects of endocrine disruptors such as phthalates on male reproductive health. Phthalate esters are plasticizers currently used in vinyl floors, food wraps, cosmetics, medical products and toys. Much of the concern focuses on allegedly significant in utero exposure to these endocrine disruptors and the effects on the developing fetus. Some animal studies have shown increased risks of uro-

genital anomalies including hypospadias in the presence of relatively high levels of in utero exposure to certain compounds. Considerable controversy exists over claims that similar types of anomalies can be produced by levels of these compounds resulting from casual exposure to various plastics in the environment. As a result, some legislatures are now considering laws to ban phthalates and certain other endocrine disruptors. Thus, it is imperative that the scientific basis for

Abbreviations and Acronyms

NYS = New York State

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claims of damage from these compounds be firmly established.

Those who support the hypothesis that phthalates and other alleged endocrine disruptors are potentially harmful have indicated the presence of the testicular dysgenesis syndrome, a triad of urogenital abnormalities that includes increased hypospadias, decreased sperm counts and increased testicular cancer. However, the current evidence suggests that human sperm counts are not declining, and in isolated areas where a decline has been noted no association has been found between these declines and any type of endocrine disruptor.^{1,2}

Given the weaknesses in the evidence for declining sperm counts, it is particularly important to assess the strength of the evidence for the alleged increase in hypospadias rates. This report summarizes some of the evidence to date and adds an important inclusion of newer data. Together these data fail to support the alleged increase in hypospadias rates and, therefore, invalidate 1 of the 3 components comprising the testicular dysgenesis syndrome.

To determine if hypospadias rates are increasing, we retrospectively reviewed the New York State Congenital Malformations Registry from 1992 to 2005. In addition to evaluating the rates of hypospadias, we report the effect of advanced maternal age (35 years or older), since maternal age has been observed to be a risk factor for hypospadias.

MATERIALS AND METHODS

The prevalence of hypospadias per 10,000 live births was obtained from the New York State Congenital Malformations Registry from 1992 to 2005. Birth defects refer to congenital anomalies, as identified by codes 740 to 759 of the International Classification of Diseases, 9th revision. Hypospadias is identified by code 752.6. The registry includes only live births, and 12,764 births were reported.

Most of the reported data for incidence include children diagnosed after age 2 weeks and before age 2 months.

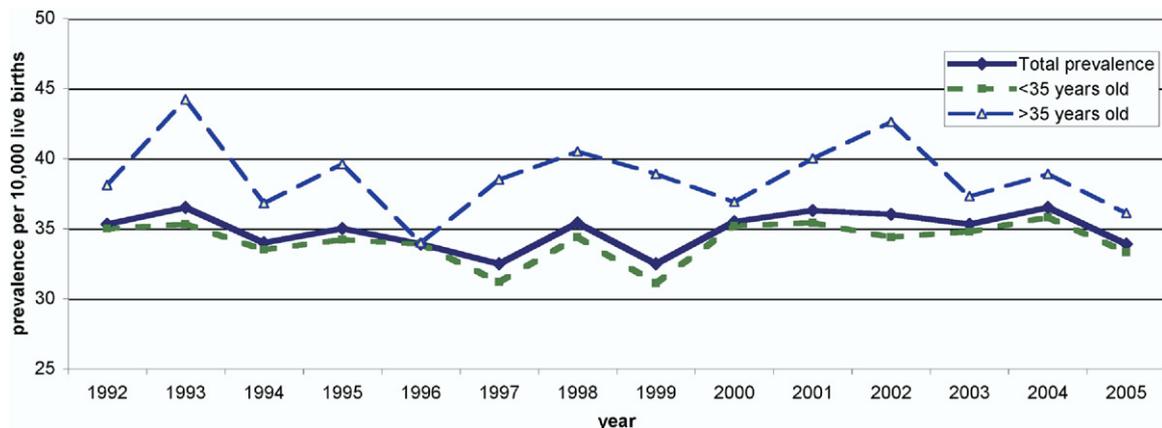
Pearson's correlation coefficient was used to determine the direction and magnitude of change. A Poisson model was fitted to the data using maternal age and year of birth, from which relative rates were calculated. A *t* test was used to compare mean hypospadias rates by maternal age. A *p* value of <0.05 was used to determine significance.

RESULTS

There was no statistical change in hypospadias rates in NYS from 1992 to 2005 ($r = 0.127$, $p = 0.6$). Overall the mean \pm SE prevalence rate was 34.9 ± 0.36 per 10,000 live births. However, mean \pm SE hypospadias rates among children of mothers 35 years old or older were significantly greater (38.7 ± 0.7) compared to those in children of mothers younger than 35 years (34.1 ± 0.386 , *t* test $p < 0.01$, see figure).

DISCUSSION

Prior data obtained from the NYS Congenital Malformations Registry from 1983 to 1995 revealed a standardized prevalence of hypospadias of 36.34 per 10,000 live births in 1983 and no significant change in prevalence throughout the study period. In combination with our current data demonstrating a stable mean \pm SE hypospadias prevalence of 34.9 ± 0.36 per 10,000 live births from 1992 to 2005 these new data now confirm a stable rate of hypospadias spanning a period of 22 years.³ Similarly data from Washington State evaluating the prevalence of hypospadias documented that the rate in 2002 (5.0 cases per 1,000 male births) was not significantly different from that in 1987.⁴ Furthermore, Carmichael et al, who studied the rates of hypospadias in California from 1984 to 1997, determined that rates did not increase during the 13-year period.⁵



Hypospadias prevalence in NYS from 1992 to 2005 by maternal age

This stable trend in hypospadias rates has also been documented in the United Kingdom. A linked register of congenital urogenital anomalies in Scotland documented that from 1988 to 1997 the rate remained unchanged.⁶ In this registry hypospadias constituted 73% of the genital anomalies evaluated. Although the prevalence of hypospadias did not change significantly, the authors noted an association between hypospadias and small size for gestational age (OR 1.43, $p < 0.001$), higher socioeconomic status (OR 0.73, $p < 0.01$ for low socioeconomic status) and increased maternal age (OR 1.2, $p < 0.05$). Finally Dolk et al studied the prevalence of hypospadias from 1980 to 1999 in 20 regions of Europe with European Surveillance of Congenital Anomalies population based registers, as well as from the England and Wales National Congenital Anomaly System.⁷ Their results did not suggest a continuation of trends of increasing hypospadias prevalence in Europe.

Advanced maternal age has consistently been recognized as a risk factor for hypospadias and other congenital anomalies. A review of the Metropolitan Atlanta Congenital Defects Program by the Centers for Disease Control and Prevention included 1,050,616 singleton infants born at 20 weeks of gestation or later in the 5 counties of metropolitan Atlanta from 1968 through 2000, who did not have a chromosomal abnormality and whose mother was 14 to 40 years old.⁸ This evaluation showed an increased risk of all heart defects, tricuspid atresia, right outflow tract defects, hypospadias second degree or higher, male genital defects excluding hypospadias and craniosynostosis in women 35 to 40 years old. Interestingly among the congenital anomalies evaluated male offspring born to women of advanced maternal age were at greatest risk for hypospadias.

This association between advanced maternal age and increased risk of hypospadias is also documented in data from New York State based on the current study and an investigation of the New York State Department of Health and California Birth Defects Monitoring Program (1983 to 1996).⁹ Evaluation during the earlier period correlates with current data revealing a significant association between advanced maternal age and hypospadias, especially in cases of severe hypospadias. While the association between advanced maternal age and congenital defects, especially hypospadias, is consistent through time and for a variety of geographic locations, the underlying causes for this association remain unclear.

The weight of available evidence strongly refutes claims for region wide increases in hypospadias rates. The hypothesis for a link between hypospadias and endocrine disruptors is based primarily on

animal studies, which have documented an increased risk of hypospadias in concert with exposure to high levels of endocrine disruptors. Gray et al demonstrated that in utero exposure to antiandrogens or phthalate esters in Sprague-Dawley rats resulted in reduced anogenital distance, retained nipples, hypospadias, undescended testes, a vaginal pouch, epididymal agenesis and small to absent sex accessory glands in male offspring in comparison to unexposed controls.¹⁰ Vilela et al examined hypospadias rates in pregnant mice exposed to genistein (a phytoestrogen) and vinclozolin (a fungicide) in comparison to controls.¹¹ They identified no hypospadias in the control group, although the rates of hypospadias in exposed mice were 25% with genistein alone, 42% with vinclozolin alone, and 41% with genistein and vinclozolin together.

These data have led some investigators to suggest that exposure to even low levels of phthalates and other alleged endocrine disruptors could have an adverse effect on male fetal development. An evaluation of women participating in the Avon Longitudinal Study of Pregnancy and Childhood identified 51 cases of hypospadias in a total of 7,928 boys born during the study period. Interestingly significant differences were detected in women who consumed a vegetarian diet or supplemented their diet with iron during the first half of pregnancy. Specifically women who consumed a vegetarian diet in pregnancy had an adjusted OR of 4.99 (95% CI, 2.10–11.88) of giving birth to a boy with hypospadias in comparison to omnivores who did not supplement their diet with iron.¹² These results raise the possibility that endocrine disruptors such as phytoestrogens or pesticides, which can be increased in quantity in the vegetarian diet, may adversely affect the developing male reproductive system.

CONCLUSIONS

Hypospadias rates have not changed in New York State from 1992 to 2005. When combined with hypospadias rates in NYS from 1983 to 1995 there is no evidence of any overall change in rates during the 22-year period. Additionally advanced maternal age continues to be a risk factor for hypospadias. Although effects of endocrine disruptors in the development of hypospadias in mouse models have been documented, these epidemiological data refute claims of an increasing prevalence of hypospadias in humans. The effects of endocrine disruptors such as phthalates on human development have yet to be elucidated fully and require further investigation. The stable prevalence of hypospadias suggests that alleged deleterious effects of endocrine disruptors on the rate of hypospadias described in animal models may not be evident in humans.

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