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Rising hypospadias rates: Disproving a myth

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Abstract Hypospadias is one of the most common congenital abnormalities occurring in males. In recent years, the prevalence of hypospadias and whether that prevalence is rising or stable has become part of a larger debate over the potential effects of so-called 'endocrine disruptors', such as phthalates and bisphenol-A, on male reproductive health.

This commentary critically examines allegations suggesting a worldwide increase in hypospadias rates. Despite the lack of scientific support for this hypothesis and for related claims that the disorders of male reproductive health are related to endocrine disruptors, these constructs remain firmly entrenched in popular literature, and are being used in part to justify litigation banning suspected endocrine disruptors such as phthalates and bisphenol-A.

A review of the epidemiologic data on this issue amassed to date clearly demonstrates that the bulk of evidence refutes claims for an increase in hypospadias rates. This suggests that two of the three components of alleged testicular dysfunction syndrome, i.e. decline in sperm counts and rise in urogenital anomalies, lack clinical support. It further suggests that extrapolations from data derived in laboratory animal studies about alleged occult risks to humans of various candidate compounds are unwarranted at this time.

Introduction

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 [1].

In recent years the prevalence of hypospadias and whether it is rising or stable has become part of the larger debate over the potential effects of so-called 'endocrine disruptors', such as phthalates and bisphenol-A, on male reproductive health. These compounds, manufactured for over 50 years, are widely used in plastic bottles, vinyl floors, food wraps, cosmetics, medical products, and toys. Much of the concern focuses upon allegedly significant *in utero* exposure to these endocrine disruptors and subsequent effects on the developing fetus. Although there is no question that estrogenic compounds in high doses can be potent modulators of biochemical and physiologic functions, the implication that *in utero* or adult exposure to very low levels of environmental 'endocrine disruptors' produces clinically detectable effects in humans is highly uncertain.

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Some animal studies have demonstrated the increased risks of urogenital anomalies, including hypospadias, in the presence of relatively high levels of certain compounds delivered under laboratory conditions. Considerable controversy exists, however, over claims that similar types of anomalies can be produced by the far lower levels of these compounds that result from casual exposure to various plastics in the environment. Nonetheless, legislatures across the United States are now considering legislation to ban certain compounds because of their alleged 'endocrine disruptor' effects.

In support of the hypothesis that phthalates and other alleged endocrine disruptors are potentially harmful, advocates have pointed to the presence of 'testicular dysgenesis syndrome', which describes a triad of male reproductive abnormalities: declines in sperm counts, increase in testicular cancer and a rise in urogenital abnormalities, the most prominent of which is hypospadias. A recent review of the published epidemiologic data regarding human sperm counts found no evidence for a global decline, but did conclude a geographical variation [2]. This paper critically examines the evidence for the alleged rise in hypospadias rates.

Early studies

From 1975 to 1997, 11 papers reported some degree of rise in the rate of hypospadias from birth years ranging from 1964 to 1995 [3]. Analysis of these papers shows, however, that the increases that have been cited in support of the endocrine disruption hypothesis were primarily reported in the 1960s and 1970s and derive from a small number of countries in North America and Europe. The one early paper that showed the most dramatic rise in hypospadias rates used data that were collected in a manner now judged to be scientifically inadequate. In 1997, Paulozzi et al., used data from the Birth Defects Monitoring Program (BDMP), a nationwide surveillance program established by the Centers for Disease Control, and reported that the incidence of hypospadias in the United States had doubled from 1970 to 1993 [4]. But 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 [5], which makes extrapolation to the rest of the country invalid.

As will be explained in more detail below, data from roughly 1985 to the present show no rise, or an actual decline. More significant, however, there are a number of methodological and epidemiological factors that could plausibly explain the 'rises' observed in the early studies.

For example, it is possible that the definition of hypospadias has evolved to include more minor degrees of deviation from the normal position of the urethral opening on the tip of the penis. No anatomical marker defines when normal variation stops and first-degree hypospadias begins. Since minor deviations are much more common than more proximal meatal positions, a subtle change in the case definition could have produced a large change in overall rates. Supporting this possibility are studies from California and northeast Italy that show no increase in the rate of severe hypospadias, and a Finnish study that showed a decline in more serious degrees of hypospadias [3].

Another possible explanation for the observed rise in the prevalence of hypospadias in early studies is a gradual improvement over time in the detection and documentation of the disorder by physicians.

A more accurate system for collecting data on hypospadias was inaugurated with the Birth Defects Prevention Act of 1998, which 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.

New studies find no rise

In the wake of the Birth Defects Prevention Act of 1998, many states created registries of congenital malformations, and other states improved existing registry programs. At present, published data are available from New York, California, and Washington State.

A retrospective review of data from the New York State Congenital Malformations Registry from 1983 to 2005 showed a decrease in the rate of hypospadias, from a prevalence of 36.34 per 10,000 live births in 1983 to a rate of 34.9 ± 0.36 per 10,000 live births in the period 1992—2005 [6].

Similarly, an analysis of data from the California registry (March of Dimes Birth Defects Foundation/California Birth Defects Monitoring Program), from 1984 to 1997 determined that hypospadias prevalence had not increased during the 13-year study period [7]. Data from Washington State on the prevalence of hypospadias show that the birth prevalence in 2002 (5.0 cases per 1000 male births) was not significantly different from that in 1987 [8].

Data from other countries are consistent with the newer US data. For example, a linked register of congenital urogenital anomalies in Scotland documented that, from 1988 to 1997, the birth prevalence of urogenital anomalies remained unchanged [9]. And a review of data from 29 registries that monitor a total of 4 million births per year around the world revealed plausible increases in hypospadias rates in only two registries (Scandinavia and Japan); these data, like the early data from the US, only showed a rise during the 1970s and 80s, with a leveling of the trend since [3]. In Europe, 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 congenital anomaly registers, as well as data from the England and Wales National Congenital Anomaly System. Their results did not suggest a rising trend of hypospadias prevalence in Europe [10].

Conclusion

This article critically examines allegations of a worldwide increase in hypospadias rates. Despite the lack of scientific support for this hypothesis and for related claims that disorders in male reproductive health are related to 'endocrine disruptors', these constructs remain firmly entrenched in the popular literature and are being used, in

part, as a justification for legislation banning certain suspected 'endocrine disruptors' such as phthalates and bisphenol-A. A review of the epidemiological data amassed to date on this issue clearly demonstrates that the bulk of the evidence refutes claims for an increase in hypospadias rates. This suggests that two of the three components of an alleged 'testicular dysgenesis syndrome' — decline in sperm counts and a rise in urogenital abnormalities — lack clinical support. This casts significant doubt about the reality of such a 'syndrome'. It further suggests that extrapolations from laboratory animal studies about alleged health risks to humans of various candidate compounds are unwarranted at this time.

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