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A population-based study of prevalence trends and geospatial analysis of hypospadias and cryptorchidism compared with non-endocrine mediated congenital anomalies

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Summary

Introduction
Several reports have suggested an increase in the prevalence of hypospadias and cryptorchidism over the last few decades. Endocrine disruption caused by exposure to environmental chemicals has been postulated as a possible cause.

Objectives
The objectives of our study were: 1) to determine whether the prevalence of hypospadias and cryptorchidism is increasing compared with other congenital anomalies not known to be mediated by endocrine factors; and 2) to perform a geospatial analysis of these congenital malformations looking for clustering that could offer insight into environmental risk factors.

Material and methods
Data were obtained from the Nova Scotia ATLEE Perinatal Database containing the perinatal records of all live births in Nova Scotia, Canada since 1988. Records from 1988 to 2013 defined the study cohort. Overall prevalence rates and prevalence trends by year were calculated for hypospadias, cryptorchidism, gastroschisis, and clubfoot. County of residence was collected and spatial autocorrelation testing for clustering was performed for each of the congenital anomalies.

Results
There were 258,147 live births during the study period. Overall prevalence rates for the four malformations over the study period were: hypospadias 78 per 10,000 male births, cryptorchidism 75 per 10,000 male births, clubfoot 24 per 10,000 total births, and gastroschisis 4 per 10,000 total births. Incidence rate ratios per year for hypospadias, cryptorchidism, clubfoot, and gastroschisis were 1.00 (0.99–1.01), 0.99 (0.98–1.00), 0.98 (0.97–0.99), and 1.04 (1.04–1.07), respectively. During the study period, the prevalence rates in the region were unchanged for hypospadias, slightly reduced for cryptorchidism and clubfoot, and rising for gastroschisis (Figure). Spatial autocorrelation testing revealed statistically significant clustering for hypospadias ($p = 0.03$) and cryptorchidism ($p = 0.03$), while no spatial autocorrelation was observed for the other malformations.

Discussion
Contrary to previous studies we show that hypospadias and cryptorchidism prevalence rates are not increasing over time in our region. Nonetheless, rates for these conditions in our area are high compared with other regions of the world. Local clustering of these congenital anomalies without clustering of the control, non-endocrine mediated congenital malformations supports a possible unique spatial distribution associated with environmental exposure. The hotspots identified for hypospadias and cryptorchidism are associated with intense agricultural activity.

Conclusions
Our study found no increase in hypospadias and cryptorchidism prevalence over a 26-year period compared with other congenital anomalies not known to be associated with endocrine factors. Geospatial analysis supports high clustering for hypospadias and cryptorchidism in areas of intense agricultural activity.

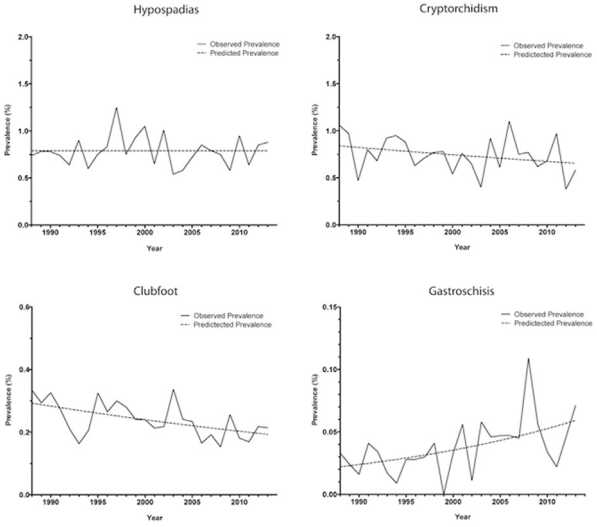

Figure Trends of prevalence rates (observed/predicted) of congenital anomalies by year in Nova Scotia, 1988–2013.

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Introduction

Hypospadias and cryptorchidism are the most common genitourinary congenital anomalies with reported prevalence rates ranging from 1 to 464 per 10,000 live births for hypospadias and 4 to 700 per 10,000 live births for cryptorchidism [1,2]. North American studies give an average prevalence of 40 per 10,000 for hypospadias and 300 per 10,000 for cryptorchidism. Both hypospadias and cryptorchidism are mediated by endocrine signaling during key stages of male development, and disruption of these mechanisms can lead to one or both of these disorders [1,3].

Recent reports have suggested an increase in the prevalence rates of both conditions [4]. Studies centered on population-based registries from different parts of the world have suggested that hypospadias may be increasing by as much as 3% per year [4,5]. A similar trend has been noted for cryptorchidism [6,7]. One common limitation of these studies is the lack of a control group comprising congenital anomalies not known to be endocrine-mediated.

Given the suggested increase in prevalence rates, many authors have hypothesized that environmental endocrine chemical disruptors (EECD) could play a role in the development of these genitourinary anomalies [8,9]. The observation that testicular cancer and male infertility rates also seem to be rising led to the development of the so-called testis dysgenesis syndrome (TDS) hypothesis, where a global exposure of males to these EECD would serve as a common causal pathway for the different entities [10]. Recent studies have examined pesticide exposure, proximity to landfill, exposure to petrochemical waste, phthalates and water supply as possible environmental exposures associated with these anomalies [8,11–16]. Taken together recent reviews have called for more rigorous study designs to make firm conclusions [17] about these associations.

The objectives of our study are:

1) To determine whether the prevalence rates of hypospadias and cryptorchidism are increasing compared with other congenital anomalies not mediated by endocrine factors in a Canadian province with stable population over a 26-year period.
2) To perform a geospatial analysis of these congenital malformations looking for distributions that could offer insight into environmental risk factors associated with their occurrence.

Methods/study design

Study design and data

Our study design is a population-based cohort study. We accessed data from all live births between 1988 and 2013 in the Canadian province of Nova Scotia (population 942,926) included in the Nova Scotia Atlee Perinatal Database (NSAPD), which is managed by the provincial Reproductive Care Program. Nova Scotia is an eastern peninsular province in Canada. All major and minor congenital anomalies diagnosed prenatally, soon after birth or at the time of death in neonates weighing >500 g or above 20 weeks gestational age are coded independently in the database. The study received approval from the IWK Health Centre Research Ethics Board and the Reproductive Care Program Data Access Committee.

Congenital anomalies

On the ATLEE database, several congenital malformations are coded individually as categorical variables (present vs. absent) based on ICD codes at the time of birth. Hence, hypospadias and cryptorchidism were identified as variables of interest. Clubfoot and gastroschisis were chosen as control congenital anomalies because of the lack of evidence for an endocrine-mediated pattern of occurrence [18,19]. Gastroschisis served as a positive control as the prevalence of gastroschisis is known to be rising in Canada and worldwide, and is currently estimated at 5/10,000 live births [20]. The prevalence of clubfoot has remained stable in the past two decades [21]. For each record we also obtained mother's county of residence (out of 18 possible counties) and year of birth.

Statistical analysis

We computed the prevalence of hypospadias and cryptorchidism for each calendar year as the number of male births with diagnosis of hypospadias or cryptorchidism divided by the total number of boys born alive. The yearly prevalences of clubfoot and gastroschisis were calculated as the number of persons born alive with clubfoot or gastroschisis divided by the total number of live births. These respective denominators were used throughout the study. The term prevalence was deliberately chosen over incidence in line with the existing literature on the topic; the rationale is that data on early abortions are not readily available both in terms of accurate numbers and documentation of congenital anomalies. In this setting, prevalence represents survival to late pregnancy or premature birth of a fetus usually above 20 weeks of gestational age.

Poisson regression was used to estimate the relative change in prevalence per calendar year. The logarithm of the number of births (as above) per year was used as the offset.

Poisson regression allows for calculation of incidence rate ratios (IRRs) and their respective 95% confidence intervals using count data; in other words, variation in the rates of congenital malformations per year can be compared. IRR $>$ 1 is interpreted as an increase in the rate of the malformations over the time period (i.e. incidence rate in current year/time period divided by rate in previous year/time period shows an increase), while IRR $<$ 1 means a reduction. Similar to other types of logistic regression, when the confidence interval of the IRR crosses 1, the ratio is not statistically significant, that is incidence rates have remained stable.

We calculated the expected births for each congenital malformation as the total number of births multiplied by the estimated prevalence and contrasted them with observed values by year graphically.