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Risk factors, prevalence trend, and clustering of hypospadias cases in Puerto Rico

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Abstract *Objective:* The aim was to determine the distribution pattern of hypospadias cases across a well-defined geographic space.
Materials and methods: The dataset for this study was produced by the Birth Defects Prevention and Surveillance System of the Department of Health of Puerto Rico (BDSS-PR), which linked the information of male newborns of the Puerto Rico Birth Cohort dataset (PRBC; $n = 92{,}285$) from 2007 to 2010. A population-based case—control study was conducted to determine prevalence trend and to estimate the potential effects of maternal age, paternal age, birth-related variables, and health insurance status on hypospadias. Two types of geographic information systems (GIS) methods (Anselin Local Moran's I and Getis-Ord G) were used to determine the spatial distribution of hypospadias prevalence.
Results: Birthweight (<2500 g), age of mother (40 + years), and private health insurance were associated with hypospadias as confirmed with univariate and multivariate analyses at 95% CI. A cluster of hypospadias cases was detected in the north-central region of Puerto Rico with both GIS methods ($p \leq 0.05$).
Conclusions: The clustering of hypospadias prevalence provides an opportunity to assess the underlying causes of the condition and their relationships with geographical space.

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Introduction

Hypospadias is traditionally defined by the anatomical position of the urethral meatus on the ventral surface of the penis other than close to the tip of the glans. This anatomical variation results from incomplete fusion of the urethral folds of the urethral spongiosum during intrauterine development and can range in position from the glans corona up to the perineum. Aside from variations in the localization of the urethral opening, hypospadias can also present with atypical shape of the urethral opening, of the glans, and of penile skin, various degrees of penile curvature, unilateral or bilateral cryptorchidism, among other variations in genital appearance. Severe hypospadias cases can also present with penile–scrotal transposition and/or enlarged prostatic utricle. In severe cases, clinical protocols for the management of intersexuality are commonly deployed. Given that hypospadias is not a monolithic clinical entity, we hypothesized that hypospadias prevalence is not uniformly distributed across space. The study of prevalence across space can provide valuable information about plausible gene/environment interactions that may underlie distinct distributions of cases. Moreover, the identification of hypospadias spatial clusters, if any, can be used to optimize the delivery of health services to manage the condition.

An impressive body of work on the etiology of hypospadias suggests that genetic and environmental factors are the main contributors to the high incidence of this male congenital condition. In fact, it has been suggested that, in the majority of cases, the etiology of this condition can be explained by a "two-hit hypothesis," whereby genetic susceptibility plus environmental exposure increases the risk for having offspring with hypospadias [1,2]. Early epidemiologic studies on incidence rates reported an increase of hypospadias in certain regions of the world including the United States [3,4]. However, more recent studies do not support such a view; for a recent review see Fisch et al. [5]. One of these early studies showed a higher incidence of hypospadias cases in the eastern and central regions of the United States than the western region [4]. But this study, based on a nationwide surveillance program, the Birth Defects Monitoring Program, is limited by the fact that such a database was not built with a random sample of US births by representative geographic populations [5,6].

We used the Puerto Rican archipelago as a case study to assess prevalence trend and to estimate the potential effects of maternal age, paternal age, birth-related variables, health insurance status, and the spatial distribution pattern of hypospadias prevalence. We found that birthweight (<2500 g), age of the mother (40 + years), and private health insurance were associated with hypospadias. In addition, clustering of confirmed hypospadias cases in the mainland of Puerto Rico was detected.

Materials and methods

The dataset for this analysis was produced by the Birth Defects Prevention and Surveillance System of the Department of Health of Puerto Rico (BDSS-PR), which linked the information of male newborns of the Puerto Rico Birth Cohort dataset (PRBC; $n = 92{,}285$) with a dataset of confirmed cases of hypospadias from 2007 to 2010. Initial diagnosis of hypospadias was made by a US board-certified physician in the birthing hospital and the birthing hospital reported each case to BDSS-PR routinely, as required by local and US law. A group of five BDSS-PR trained nurses in congenital defects visited the birthing hospital and reviewed the medical charts to confirm cases. Whenever necessary, BDSS-PR nurses interviewed medical staff in the birthing hospital if medical information was missing in the charts. In addition, BDSS-PR staff contacted the parents by phone to provide health information, genetic counseling, and/or referral to medical services when appropriate. Case follow-up by phone provided another opportunity to confirm diagnosis. Given the geographical area of Puerto Rico (9104 km^2), it was possible for BDSS-PR nurses to monitor birthing hospitals across the entire Island. Out of hospital births and home deliveries, which represented less than 1% of total births for the years 2009 and 2010 (Department of Health of Puerto Rico, Division of Statistical Analysis, personal communication), are required by law to provide birth information to the Puerto Rico Health Department before a birth certificate can be issued to the parents. There is a system in place where BDSS-PR is notified of births with congenital defects even when born outside the traditional health-care system. Therefore, case ascertainment following the established protocol identified 279 cases of hypospadias for the years 2007–10.

Case–control study

We conducted a population-based case–control study to estimate the potential effects of maternal age, paternal age, birth-related variables, and health insurance status on hypospadias. Cases were defined as confirmed cases of hypospadias for the years 2007–10 by BDSS-PR ($n = 279$), with or without another congenital condition. Control subjects were defined as those male newborns with no hypospadias and no other congenital condition according to the PRBC dataset for the years 2007–10 ($n = 91{,}615$).

We performed univariate analyses to estimate the prevalence odds ratio for hypospadias for the following variables: weeks of gestation (25–37 or 38+), birthweight (<2500 g or ≥ 2500 g), previous births (0 or 1+), father's age (<20, 20–24, 25–29, 30–34, 35–39, 40 + years), mother's age (<20, 20–24, 25–29, 30–34, 35–39, 40+), and health insurance status (private, including pay out-of-pocket cases, vs. government) with 95% confidence interval (CI). Age of the father and age of the mother category of 40 years or older was aggregated due to small sample size. Eligibility for the government health insurance plan in Puerto Rico is based on the relation of family income to family size, which is similar to US poverty guidelines [7]. Therefore, health insurance status was used as the criterion to provide an insight about socioeconomic status at the household level [8], which according to the American Community Survey Briefs, United States Census Bureau, 45% of the population in Puerto Rico in 2010 lived under the poverty line. A multivariate analysis to estimate the joint prevalence odds ratio for hypospadias was performed with those variables which their 95% CI for odds ratio did not