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

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Risk factors;
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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 ≤ 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 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. Therefore, health insurance status was used as the criterion to estimate the joint prevalence odds ratio for hypospadias for the years 2007–10 (n = 91,615).

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 + years), 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
include 1. Statistical analyses were performed with SPSS v. 17 (IBM).

Spatial distribution of hypospadias’ prevalence

The annual prevalence at birth of hypospadias for the Puerto Rican archipelago (the islands of Puerto Rico, Vieques, and Culebra) was calculated by dividing the number of hypospadias cases by the corresponding number of male births for each year (2007–10). The overall 4-year prevalence at birth for hypospadias for the study period according to the mother’s municipality of residence was used to determine patterns in the spatial distribution of hypospadias prevalence. In order to statistically assess the existence of a series of neighboring municipalities with similar or dissimilar prevalence of hypospadias beyond what would be expected by chance, cluster analyses were conducted using two types of geographical information systems methods using the place of residence of the mother: (a) Cluster and Outlier Analysis (Anselin Local Moran’s I), to test for the plausible existence of clusters; and (b) Getis-Ord G, to test for the plausible clustering of hot spots (high prevalence) and cold spots (low prevalence) of hypospadias. The algorithms for cluster analyses were based on a comparison of each individual region (municipalities within the Puerto Rican archipelago) with its neighboring municipalities.

Moran’s I value, z-score, \( p \leq 0.05 \), and a code representing the cluster type for each prevalence per municipality were calculated, where z-scores and p-values represent the statistical significance of the computed index values. A positive value for Moran’s I indicates that a given municipality has neighboring municipalities with a similarly high (or similarly low) prevalence of hypospadias which defines a spatial cluster. A negative value for Moran’s I indicates that a given municipality has neighboring municipalities with dissimilar values, which defines a spatial outlier. The output field, cluster/outlier type (COType), distinguishes between statistically significant cluster of high values (HH) at \( p \leq 0.05 \), cluster of low values (LL), outliers in which a high value is surrounded primarily by low values (HL), and outliers in which a low value is surrounded primarily by high values (LH). Prevalence data were aggregated to detect hot and cold spots. Cluster analyses were performed with ARCGIS v10 (ESRI).

Results

As in other countries, hypospadias is the most common urogenital tract condition in Puerto Rico. For the time period 2007–10, we found that hypospadias prevalence remained relatively constant with an average prevalence of 30.2/10,000 male live births (Fig. 1A). Analysis by comorbidity showed that 251 out of 279 hypospadias cases did not have another congenital condition, whereas 14 cases had one additional condition and 14 cases had two or more additional congenital conditions (Fig. 1B). Those cases with one comorbidity were associated with cardiovascular \((n = 6)\), musculoskeletal \((n = 3)\), central nervous system \((n = 1)\), oral \((n = 1)\), eyes and ears \((n = 1)\), chromosomal—genetic \((n = 1)\), or genital ambiguity \((n = 1)\) conditions.

Case—control study

Table 1 shows that there is an increased odds ratio of having a newborn with hypospadias according to gestational age (25–37 weeks), birthweight (<2500 g), age of the mother of 40+ years, age of the father (30–34 years), and health insurance status (private insurance). A positive linear correlation for parental age was noted (Pearson correlation coefficient = 0.69; \( p < 0.01 \)). Therefore, the age of the father was not included in our multivariate logistic regression analysis as it showed the lowest OR value between these two variables and it did not meet the assumption of absence of multicollinearity. Similarly, a positive linear correlation between gestational age and birthweight was noted (Pearson correlation coefficient = 0.78; \( p < 0.001 \)). Therefore, gestational age was not included in our multivariate logistic regression analysis as it showed the lowest OR value between these two variables and it did not meet the assumption of absence of multicollinearity.

Multivariate analyses confirmed statistical significance as follows: birthweight less than 2500 g, OR = 3.84 (95% CI 2.99–4.95); age of the mother of 40+ years, OR = 2.63 (95% CI 1.19–5.81); and private health insurance, OR = 1.41 (95% CI 1.07–1.86).
Spatial distribution of hypospadias prevalence

The Puerto Rican Archipelago is divided into 78 municipalities, which include the mainland of Puerto Rico with a population of 3,725,778, the island municipality of Vieques with a population of 9,301, and the island municipality of Culebra with a population of 1,818. Therefore, the population of mainland Puerto Rico constitutes 99.7% of the total population of the archipelago [9]. Fig. 2A shows those municipalities below the average value of hypospadias prevalence and those above the average value of hypospadias prevalence for the years 2007–10. Cluster and outlier analysis (Anselin Local Moran’s I) detected six contiguous municipalities in the north-central region of the Island (from west to east: Vega Baja, Vega Alta, Dorado, Toa Baja, Cataño, and Bayamón) with a similar high prevalence of hypospadias (Fig. 2B, shown in black). Therefore, this cluster of municipalities is statistically different from the rest of the mainland with regard to hypospadias prevalence (\( p \leq 0.05 \)). Two municipalities (from north to south: San Sebastián and Maricao) were identified as spatial outliers for hypospadias prevalence where a high value is surrounded by low values (HL). Three municipalities (from north to south: Ceiba, San Lorenzo, and Naguabo) were identified as having low values (LL) for hypospadias prevalence. By using a second geographical information system, Getis-Ord G analysis, clustering of a hot spot (high hypospadias prevalence) in the north-central region was confirmed (Fig. 2C).

Discussion

The prevalence of hypospadias in Puerto Rico has remained relatively constant during the years 2007–10. The calculated prevalence was 30.2/10,000 male live births for this time period. This low prevalence allows us to interpret the odds ratio as a measure of risk. We found that 90% of these cases did not exhibit comorbid congenital conditions. Birthweight (<2500 g), age of the mother (40 + years), and private health insurance were found to be risk factors for having a newborn with hypospadias. A cluster of hypospadias cases was detected in the north-central region. Given the protocol for case ascertainment in the Island, the clustering of cases cannot be a statistical artifact related to a regional bias in the medical competency of the health professionals related to the surveillance system. Health-care provider density does not explain the clustering of cases either, as the highest densities for providers (San Juan, Mayaguez, and Ponce metropolitan municipalities) fell outside the hot spot for hypospadias prevalence.

Table 1 Risk factors for hypospadias in Puerto Rico.

<table>
<thead>
<tr>
<th></th>
<th>Hypospadias</th>
<th>Controls</th>
<th>Total</th>
<th>Prevalencea</th>
<th>OR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Total</td>
<td>279</td>
<td>91,615</td>
<td>91,894</td>
<td>30.36</td>
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<tr>
<td>Gestational age</td>
<td>275</td>
<td>90,948</td>
<td>91,239</td>
<td>30.14</td>
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<td></td>
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<td>25–37 weeks</td>
<td>140</td>
<td>34,074</td>
<td>34,214</td>
<td>40.92</td>
<td>1.73</td>
<td>1.36–2.19b</td>
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<td>38–44 weeks</td>
<td>135</td>
<td>56,874</td>
<td>56,384</td>
<td>23.77</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Birthweight</td>
<td>279</td>
<td>91,576</td>
<td>91,855</td>
<td>30.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2500 g</td>
<td>90</td>
<td>10,166</td>
<td>10,256</td>
<td>87.75</td>
<td>3.81</td>
<td>2.96–4.90b</td>
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<tr>
<td>&gt;2500 g</td>
<td>189</td>
<td>81,410</td>
<td>81,599</td>
<td>23.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior births</td>
<td>279</td>
<td>91,601</td>
<td>91,880</td>
<td>30.01</td>
<td>1</td>
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<tr>
<td>0</td>
<td>273</td>
<td>90,701</td>
<td>90,974</td>
<td>30.01</td>
<td></td>
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</tr>
<tr>
<td>1 +</td>
<td>6</td>
<td>900</td>
<td>906</td>
<td>66.23</td>
<td>2.22</td>
<td>0.98–4.99</td>
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<tr>
<td>Paternal age</td>
<td>268</td>
<td>88,479</td>
<td>88,747</td>
<td>30.36</td>
<td></td>
<td></td>
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<td>&lt;20</td>
<td>19</td>
<td>6481</td>
<td>6500</td>
<td>29.23</td>
<td>1.19</td>
<td>0.71–2.00</td>
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<tr>
<td>20–24</td>
<td>77</td>
<td>23,804</td>
<td>23,881</td>
<td>32.24</td>
<td>1.31</td>
<td>0.94–1.84</td>
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<tr>
<td>25–29</td>
<td>60</td>
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<td>24,394</td>
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<tr>
<td>30–34</td>
<td>64</td>
<td>17,858</td>
<td>17,922</td>
<td>35.71</td>
<td>1.45</td>
<td>1.02–2.07b</td>
</tr>
<tr>
<td>35–39</td>
<td>25</td>
<td>9566</td>
<td>9591</td>
<td>26.07</td>
<td>1.06</td>
<td>0.66–1.70</td>
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<tr>
<td>40–44</td>
<td>15</td>
<td>4005</td>
<td>4020</td>
<td>37.31</td>
<td>1.52</td>
<td>0.86–2.68</td>
</tr>
<tr>
<td>45 +</td>
<td>8</td>
<td>2431</td>
<td>2439</td>
<td>32.80</td>
<td>1.33</td>
<td>0.64–2.80</td>
</tr>
<tr>
<td>Maternal age</td>
<td>279</td>
<td>91,586</td>
<td>91,865</td>
<td>30.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>46</td>
<td>16,231</td>
<td>16,277</td>
<td>28.26</td>
<td>1.11</td>
<td>0.63–1.96</td>
</tr>
<tr>
<td>20–24</td>
<td>80</td>
<td>29,511</td>
<td>29,591</td>
<td>27.04</td>
<td>1.06</td>
<td>0.62–1.82</td>
</tr>
<tr>
<td>25–29</td>
<td>73</td>
<td>23,453</td>
<td>23,526</td>
<td>31.03</td>
<td>1.22</td>
<td>0.71–2.10</td>
</tr>
<tr>
<td>30–34</td>
<td>54</td>
<td>14,716</td>
<td>14,770</td>
<td>36.56</td>
<td>1.44</td>
<td>0.82–2.51</td>
</tr>
<tr>
<td>35–39</td>
<td>16</td>
<td>6265</td>
<td>6281</td>
<td>25.47</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥40</td>
<td>10</td>
<td>1410</td>
<td>1420</td>
<td>70.42</td>
<td>2.77</td>
<td>1.26–6.13b</td>
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<tr>
<td>Health insurance</td>
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<td>91,662</td>
<td>30.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Government</td>
<td>169</td>
<td>62,551</td>
<td>62,720</td>
<td>27.12</td>
<td>1</td>
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<td>Private</td>
<td>110</td>
<td>28,832</td>
<td>28,942</td>
<td>38.01</td>
<td>1.41</td>
<td>1.11–1.80b</td>
</tr>
</tbody>
</table>

OR = odds ratio.
a Per 10,000 male live births.
b Significant at 95% confidence interval (CI).
Figure 2  Spatial distribution of hypospadias prevalence for the Puerto Rican archipelago, 2007–10. (A) Municipalities below the average value of hypospadias prevalence are shown in white whereas municipalities above the average value of hypospadias prevalence are shown in gray and black. Puerto Rico is the largest island of the Puerto Rican archipelago followed by the island municipality of Vieques. Culebra is the smallest island municipality of this archipelago within the Caribbean region. North cardinal point applies to (A–C). Geographic scale (size in km) and legend for hypospadias prevalence are shown (see text for details). (B) Six contiguous municipalities in the north-central region of the mainland with the highest prevalence of hypospadias are shown in black. Two municipalities identified as spatial outliers (High Low) are shown in the darkest gray tone. Three municipalities identified as spatial outliers (Low Low) are shown in the lightest gray tone. Geographic scale (size in km) and legend for Anselin Local Moran’s I values are shown (see text for details). (C) Cold spots for low hypospadias prevalence are shown in white or hatched lines. Hot spots for high hypospadias prevalence are shown in black. Municipalities between cold and hot spots are shown in gray tones. Geographic scale (size in km) and legend for Getis–Ord G values are shown (see text for details).
The prevalence and epidemiologic profile of hypospadias in Puerto Rico further supports the notion that cases are not particularly different from other regions of the world. Our study is also consistent with most recent studies, which report stable or declining prevalence of hypospadias [5,10–15]. Australia [16] and Denmark [17] are noted as exceptions. We found an association between hypospadias and low birthweight, as has been shown particularly for severe hypospadias [18–20]. But the strong association between birthweight and gestational age in our sample, and the lack of information on severity for low birthweight cases, does not allow us to determine which of the two is the proxy variable that underlies hypospadias cases. Nevertheless, in agreement with recent studies, we also found that gestational age is associated with hypospadias [20,21]. Strong evidence for early delivery as a risk factor for congenital urogenital conditions is provided by Jensen et al. [20], suggesting that prenatal factors that affect relative fetal growth restriction can also produce hypospadias. However, it is important to note that global growth deficits among hypospadiac boys do not seem to persist through infancy [22]. Other reports have shown that younger [23] or older [24] paternal age is associated with increased hypospadias risk. In our sample, we found a strong positive linear correlation between maternal and paternal age, which confirms the plausible contribution of each as a risk factor for the condition. According to several studies, older maternal age has been identified as a risk factor for hypospadias [10,25,26], but it has been difficult to pinpoint the relevance of this association with hypospadias etiology. For instance, is age associated with underlying genetic defects associated with aging or with subfertility? We did not conduct analyses for multiple births (n = 6) or gestational diabetes mellitus (n = 6) due to the small number of cases in the sample.

We found that private health insurance is associated with the condition. Our multivariate logistic regression analysis indicates that the effect of health insurance status persists after controlling for age of mother. Therefore, it will be advantageous for further lines of inquiry to determine social class differences following a social theory-based model beyond traditional socioeconomic status measures [27,28]. In this context, it will be important for future studies to inquire about the use of assisted reproductive technologies among women with private health insurance. In addition, further analyses by type and place of employment may reveal patterns of significant population mobility on a daily basis, which adds to the complexity of plausible environmental factors associated with the condition.

Our study indicates that hypospadias prevalence according to the mother’s residence is not distributed uniformly across the island of Puerto Rico as identified with prevalence values. The cluster of hypospadias cases in the north-central region of Puerto Rico was detected by using two separate approaches: Moran’s Global I and Getis-Ord G. The first one identifies statistically significant spatial clusters and spatial outliers, while the second one detects locations with high or low prevalence (hot and cold spots, respectively). While Anselin Local Moran’s I analysis identified six contiguous municipalities in the north-central region of Puerto Rico with high hypospadias prevalence, Getis-Ord G identified a gradient pattern across the mainland from north to south with the hot spot in the north-central region as well. Getis-Ord G is based on inferential statistics where results of the analysis are interpreted within the context of the null hypothesis, which states that there is no spatial clustering of feature values. But if the z-score is positive or negative, it indicates that high values or low values are clustered in the study area, respectively. The use of Global Moran’s I becomes particularly important when both high and low values produce clusters as these may cancel each other out because Global Moran’s I provides a spatial autocorrelation analysis which identifies the spatial distribution of high values when surrounded by low values, and vice versa. In this study, the spatial autocorrelation refers to the relationship of computed I values with neighboring municipalities. Taken together, both GIS methods do not require data filtering and both methods assume complete spatial randomness; that is, values are randomly distributed among the features in the dataset which assumes random spatial processes at work. In our case, the total number of hypospadias cases and the total number of male live births without a congenital condition per municipality per year were submitted to built-in analytical algorithms of each method without making assumptions about frequency of cases nor space. The fact that both methods detected spatial clustering of hypospadias provides strong evidence that such spatial distribution was not produced by an artifact introduced by the number of hypospadias cases nor from the geographical units that were used in the analyses.

According to four local and federal government reports (data not shown), the following environmental contaminants are found in discrete regions of the island: chlorinated pesticides, polychlorinated biphenyls, phthalates, and dioxins; all of which have been associated with hypospadias [29]. It is of interest for future studies to determine whether there is a correlation between the spatial distribution of these contaminants and hypospadias clusters according to severity of the condition.

It remains as a tenet in the field that most hypospadias cases are idiopathic. In spite of great research efforts, it is plausible that the etiology of the condition has remained elusive because studies that screen for risk factors are not conducted according to severity [19]; for a recent review see Ref. [30]. Therefore, it remains as a challenge for future studies to determine the distribution of hypospadias prevalence for the Puerto Rican archipelago according to severity type.

Conclusion
The clustering of hypospadias prevalence provides an opportunity to assess the underlying causes of the condition and their relationships with geographical space.

Conflict of interest
None.
Funding
None.

Ethical approval
This study was approved by the Institutional Review Board (IRB) Committee.

References