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Altitude as a risk factor for the development of hypospadias. Geographical cluster distribution analysis in South America

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Summary

Objective
Hypospadias is the most common congenital anomaly affecting the genitals. It has been established as a multifactorial disease with increasing prevalence. Many risk factors have been identified such as prematurity, birth weight, mother's age, and exposure to endocrine disruptors. In recent decades multiple authors using surveillance systems have described an increase in prevalence of hypospadias, but most of the published literature comes from developed countries in Europe and North America and few of the published studies have involved cluster analysis. Few large-scale studies have been performed addressing the effect of altitude and other geographical aspects on the development of hypospadias. Acknowledging this limitation, we present novel results of a multinational spatial scan statistical analysis over a 30-year period in South America and an altitude analysis of hypospadias distribution on a continent level.

Method
A retrospective review was performed of the Latin American collaborative study of congenital malformations (ECLAMC). A total of 4,020,384 newborns was surveyed between 1982 and December 2011 in all participating centers. We selected all patients with hypospadias. All degrees of clinical severity were included in the analysis. Each participating center was geographically identified with its coordinates and altitude above sea level. A spatial scan statistical analysis was performed using Kulldorf's methodology and a prevalence trend analysis over time in centers below and above 2000 m.

Results
During the study period we found 159 hospitals in six different countries (Colombia, Bolivia, Brazil, Argentina, Chile, and Uruguay) with 4,537 cases of hypospadias and a global prevalence rate of 11.3/10,000 newborns. Trend analysis showed that centers below 2000 m had an increasing trend with an average of 10/10,000 newborns as opposed to those centers above 2000 m that showed a reducing trend with an average prevalence of 7.8 ($p = 0.1246$). We identified clusters with significant increases of prevalence in five centers along the coast at an average altitude of 219.8 m above sea level ($p > 0.0000$). Reduction in prevalence was found in clusters located in two centers on the Andes mountains. Altitude of 2,000 m was associated with hypospadias (Figure), with an OR 0.59 (0.5—0.69). There are ethnic arguments to support our results supported by protective polymorphism distribution in high lands.

Conclusion
Altitude above 2,000 m is suggested to have a protective effect for hypospadias. Specific clusters have been identified with increased risk for hypospadias. Environmental risk factors in these areas need to be further studied given the association seen between altitude and the distribution of more severe cases.

Figure Spatial-temporal analysis. Identified hypospadias clusters with increasing trends in prevalence (red) and clusters with decreasing trends (blue).

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Introduction

Birth defects are the most common cause of morbidity and mortality among infants around the world [1]. Surveillance systems allow a better understanding of the etiology of congenital anomalies, identification of prevalence estimates and trends, and planning and implementation of preventive measures in public health [2]. Some epidemiologic measures such as geographical cluster identification, defined by the EUROCAT as an unusual aggregation of cases in a period of time, and prevalence trend analysis have been shown to be good approaches and techniques in public health systems for studying congenital anomalies [3]. In recent decades multiple authors using surveillance systems have described an increase in prevalence of hypospadias, but most of published literature comes from developed countries in Europe and North America and few have performed cluster analysis [3–6]. Results from these studies have identified associated risk factors in the development of hypospadias, such as birth weight, mother's age at gestation, exposure to endocrine disruptors, and *in vitro* fertilization [7,8].

Nonetheless, not much is known about the effect of altitude on the development of hypospadias. As stated by Castilla et al., altitude might be a risk factor for some congenital anomalies such as craniofacial defects, but protective for others such as hypospadias and neural tube defects [9]. As just mentioned and given the effect of the environment in the development of hypospadias, we believe that geographical and long-term prevalence trend analysis is key to better understand the behavior of hypospadias in our region [10]. Hereby we present novel results of a multinational spatial scan statistical analysis over a 30-year period in South America and an altitude analysis of hypospadias distribution on a continent level.

Method

The Latin American collaborative study of congenital malformations (ECLAMC) is a multicenter project designed to identify associated risk factors in the development of congenital anomalies [11]. For the purpose of the present study we used the ECLAMC methodology and database to analyze our results.

Data collection is performed daily in each participating center in a standardized manner. Every day, all of the newborns are evaluated looking for congenital anomalies. Parents are interviewed and newborns examined by trained personnel. Data are registered by each participating center and sent to the ECLAMC headquarters monthly.

As the ECLAMC is a case-control model, for each patient with a detected congenital anomaly a control is included. Controls are the immediate next newborn, of the same sex as the case. Information gathered for controls is exactly the same as that for cases. For the present study we did not include controls in the analysis. Before each participating center is included in the study it must be accepted by the local investigational review board (IRB).

For the present study we reviewed retrospectively the ECLAMC database from January 1982 to December 2011. Analyzed data included all registered patients diagnosed with hypospadias during the study period. Prevalence was calculated in all hospital newborns registered during the study period. A clinical severity classification was used following Duckett's description (Glanular, Coronal, Penile and Scrotal) [12,13].

We excluded information from centers that did not have a continuous follow-up (periods of more than 5 years without surveillance and data collection) or that had more than 40% of the collected data incomplete. During the study period, 192 centers in 11 countries supplied data. After excluding countries with incomplete information, a final analysis was done in 159 hospitals from six South American countries.

For the altitude variable analysis we used all centers and compared registered prevalences according to clinical severity separating results in two groups, those above and below 2,000 m, as suggested by other authors [9]. Prevalence trend analysis was estimated using a Cochrane Armitage analysis. Registered range of altitude was from 1 to 3,700 m above sea level. Comparison was done using odds ratios (OR) and calculated with the software EpiCalc 2000 version 1.02. The OR and 95% confidence intervals were used to estimate the relative risk [14]. A comparison of prevalence trend over study period was performed between centers above and below 2,000 m and significance was analyzed using a t test.

Geographical variables as potential risk factors were evaluated for each center using registered coordinates as well as altitude above sea level. We used this information following spatial scan statistical analysis under a Poisson model given the size and diversity of the results [15]. The aim was to determine geographical areas with either high or low prevalence rates over time by comparing expected cases with detected cases. The p value for significant differences in prevalence was obtained by the Monte Carlo model of 999 replications and was set up at $p < 0.05$. A multinominal prevalence rate logistic regression was performed using geographic areas as the outcome to establish significant differences between clusters. Identical coordinates were combined into one location. Excluded identified clusters were the ones with no statistically significant results or those where the increase or decrease was identified in a single center. The only restrictions we made before running the data were that the number of captured newborns in a given area did not exceed 10% to reduce overlapping clusters. This change was done to limit overlapping centers with no impact on the significance and power of the results [16]. Results were set up to be translated to Google EarthTM for graphical visual results. This same analysis was then performed selecting cases by clinical severity (glanular, coronal, penile, and scrotal cases).

Results

Between January 1982 and December 2011, participating centers conducted surveillance on 4,020,384 newborns, detecting a total of 4,537 hypospadias cases, and resulting in total prevalence of 11.3 per 10,000 newborns. Trend analysis showed that centers below 2,000 m had an increasing trend with an average trend of 14.9 per 10,000 newborns as opposed to those centers above 2,000 m that

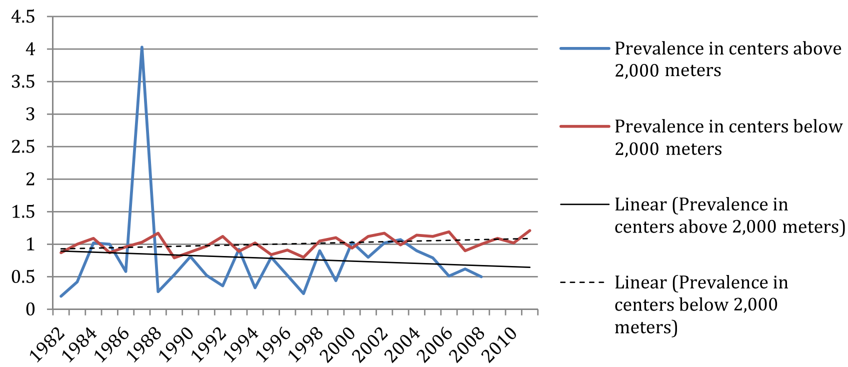

Figure 1 Prevalence trends over study period in centers above and below 2,000 m sea level in South America.

showed a reducing trend with an average prevalence of 0.78 ($p = 0.1246$) (Fig. 1). The spike in 1987 noticed is difficult to interpret because we adjusted data to the number of hospitals and no change was seen. No change in trained personal was reported during this timeframe. Even excluding these years in the analysis, total prevalence trend did not show any significant changes. After separating population results into two groups (centers above and below 2,000 m), we identified significant differences for all grades except for penile and scrotal cases where OR was not statistically significant (Table 1).

Spatial scan statistical analysis performed during the entire study period identified a total of seven clusters with significant changes showed in Table 2. Five of them presented significant increases according to expected cases. The other two showed significant reductions. Average altitude and geographic distribution showed a reducing pattern in areas closer to the Andes mountains as opposed to increasing trends in areas close to the coast on the east side of the continent. The same analysis but adjusted to clinical severity of hypospadias showed similar trends of distribution where increases were identified along centers located below 2,000 m and reductions in high altitudes. For glanular and coronal analysis, totals of eight and six clusters were identified, respectively, with the same distribution as that identified for the entire population.

For cases with penile hypospadias a total of eight clusters was identified, but only two reached statistical significance. These centers showed increases and were located along the coast of Brazil with an average altitude of 18.2 m. For scrotal analysis a total of six clusters was identified, but none were statistically significant.

Discussion

The present study provides epidemiological evidence that altitude, in different countries in South America, presents a pattern that supports a protective effect of altitude in the development of hypospadias. Geographical characteristics

Table 1 Association of altitude and clinical severity of hypospadias.

Clinical severity	Number of cases/non-affected newborns above 2,000 m	Number of cases/non-affected newborns below 2,000 m	OR (95% CI)
Glanular	44/217,452	2,160/3,800,728	0.36 (0.26–0.48)
Coronal	73/217,423	1,724/3,801,164	0.74 (0.59–0.93)
Penile	18/217,478	370/3,802,518	0.85 (0.53–1.37)
Scrotal	12/217,484	136/3,802,752	1.54 (0.86–2.78)
Total	147/217,349	4,390/3,798,499	0.59 (0.5–0.69)

Table 2 Identified clusters with increase (white) or reduction (gray) of cases during the 30-year analysis.

Cluster	Coordinates/radius	Average altitude	Country	Time frame	Detected cases	Expected cases	Relative risk	*p* value
1	21.18S, 47.8 W 288.05 km	718 m	Brazil	1983/1/1 to 1997/12/31	597	322.94	1.98	0.0000
2	27.58S, 48.56W 376.44 km	318 m	Brazil	1993/1/1 to 2007/12/31	536	285.18	2.00	0.0000
3	7.11S, 35.88W 1968.02 km	11.6 m	Brazil	1998/1/1 to 2011/12/31	384	184.24	2.18	0.0000
4	38.73S, 62.26W 314.04 km	45.5 m	Argentina	2002/1/1 to 2003/12/31	29	6.89	4.23	0.0000
5	34.88S, 56.18W 161.09 km	7.6 m	Uruguay	1998/1/1 to 2009/12/31	146	91.64	1.61	0.0034
6	20.21S, 68.16W 1075.52 km	2262 m	Chile/Arg/Bol	1994/1/1 to 2008/12/31	86	234	0.35	0.0000
7	4.45S, 73.83W 1298.58 km	1780 m	Colombia	1982/1/1 to 1994/12/31	67	128.57	0.52	0.0000

of South America are unique compared with other parts of the world where few major cities are located at 2,000 m, or more, above sea level. It is estimated that around 1% of the worldwide population lives above 2,000 m. Some authors have explored the effect of altitude in congenital anomalies, but few have focused their interest on hypospadias [9,16–18]. Castilla et al. [9] addressed the effect of altitude and congenital anomalies. Their results showed a reduction of hypospadias but adjusted analysis failed to reach statistical significance; similar to our prevalence trend analysis. However, Castilla's study did not include glanular cases. A more recent study addressed this geographical prevalence topic without including altitude as a variable and failed to demonstrate a global increase in prevalence but did find some areas prone to higher prevalence rates [19]. Limitations to interpretation of these conclusions are that the period of time analyzed was only 3 years and the study was conducted in only one country [19].

Specific areas in specific periods of time with increases in prevalence as shown in our results also have been reported by other authors [3]. In Sweden a global increase in prevalence of hypospadias was detected over a decade changing from 4.5/10,000 to 8/10,000 newborns, but no geographic distribution was identified [6]. In China, a 12-year follow-up study identified an annual increase of 7.43% in which rural areas had higher increases than urban areas [20]. In North America, results have varied, with some regions with large-scale and long-term follow-up showing a rise in prevalence and others the opposite [5,21,22]. In our region there are previous isolated reports of prevalence at a particular point in time but no long-term results [23,24].

Hypobaric hypoxia may be associated with development of congenital anomalies. Some reports have shown an increase in the prevalence of some craniofacial anomalies in high lands, in support of hypoxia having a damaging effect on cell migration during embryogenesis [16]. Although placental insufficiency is associated with development of hypospadias, there are data showing that the placenta adapts to hypobaric hypoxia reducing the possible effect of hypobaric hypoxia on the newborn [9,25]. The association of altitude and more clinically severe cases might explain and support an environmental effect on development of hypospadias.

Neural tube defects have shown a reduction in prevalence in high lands when compared to lower lands. This could be related to reports of a lower frequency of some susceptible polymorphisms of 5-10-methylenetetra hydrofolate reductase in populations living in high lands [9,24,26]. Along with this genetic argument, an ethnic factor could support our results because other authors have shown a lower frequency of hypospadias in Hispanics compared with Caucasians and African Americans [5,7,27].

Diet has been associated with development of hypospadias, and geographic distribution of different cultures might explain these changes in diet and the relation to a reduction in high lands [8,28]. Nonetheless, vegetarian and low protein diets, which are described as promoters for development of hypospadias, do not have a specific pattern of distribution in our region [8]. Other factors such as endocrine disruptors are more complex to evaluate with our current data. One hypothesis to support these results is related to water contamination. As the majority of rivers are born up in the mountains, there the water is cleaner, whereas close to the coast, where rivers end, the contamination is higher. Future studies need to focus on this topic in our region.

Our methodology, covering a significant amount of surveyed time and included population with a standardized methodology, supports our solid results. To our knowledge, our analysis is one of few large-scale studies to specifically focus on the South American population, and is particularly valuable given the limited information in our region and the novel data about altitude as a risk factor for development of hypospadias [29].

We acknowledge that our findings could be subject to bias triggered by better reporting over time; however, the nature of our methodology reduces this potential issue given the case-control model and the systemized data collection supported as the best methodology for studying congenital anomalies [30].

Conclusion

Altitude above 2,000 m suggests a protective effect for hypospadias. Specific clusters have been identified with increased risk for hypospadias. Environmental risk factors in these areas need to be studied further given the association seen between altitude and the distribution of more severe cases.

Conflict of interest

None.

Funding

None.

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