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RESEARCH ARTICLE

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A case-control study characterizing polydactyly risk factors in Bogotá and Cali, Colombia between 2002 and 2020

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Abstract

Background: Polydactyly is a congenital abnormality characterized by the presence of additional fingers on one or more extremities. In Colombia, polydactyly accounted for 17% of musculoskeletal congenital abnormalities in 2021, with a prevalence of 6.03 per 10,000 live births. The purpose of this study was to determine the prevalence of polydactyly and identify associated risk factors in Bogotá and Cali, Colombia, from 2002 to 2020.

Methods: A retrospective case-control study design was employed, analyzing data from birth defect reports provided by the Program for the Prevention and Follow-up of Congenital Defects and Orphan Diseases surveillance system. Cases included live births or stillbirths with polydactyly, while controls consisted of infants without congenital abnormality, matched in terms of birth date and hospital. Prevalence of polydactyly was calculated and risk factors were assessed through odds ratios obtained by logistic regression models, considering a 95% confidence interval.

Results: Among the 558,255 births included in the study, 848 cases of polydactyly were identified, resulting in a prevalence rate of 15.19 per 10,000 live births. Risk factors associated with polydactyly included male newborn sex, pregestational diabetes, and a family history of malformation among first-degree relatives.

Conclusion: These findings highlight the importance a surveillance system aimed to characterize populations with congenital abnormalities, providing a better option for analyzing risk factors, help improving prevention, diagnosis, notification, and optimal treatment in patients.

KEYWORDS

congenital abnormality, musculoskeletal, polydactyl, risk factor, surveillance

1 | INTRODUCTION

Polydactyly (PD) is a congenital abnormality characterized by the presence of more than five fingers on at least one extremity. It is one of the most common congenital abnormality of a musculoskeletal nature and the most common limb anomaly (Benjamin et al., 2022; Farrugia & Calleja-Agius, 2016; Phadke & Sankar, 2010). The global prevalence of PD is estimated to be 3.0 to 36.0 per 10,000 live births (LB) (Umair et al., 2018). In Latin America, countries like Argentina reported a prevalence of preaxial PD at a rate of 1.50 per 10,000 LB and postaxial PD at a

rate of 5.29 per 10,000 LB for 2016. The prevalence was found to be higher in public healthcare hospitals (Bronberg et al., 2021).

In Colombia, according to the National Public Health Surveillance System (SIVIGILA for its acronym in Spanish), PD represented 17% of all congenital abnormalities in the musculoskeletal system in 2021, with a prevalence of 6.03 per 10,000 LB (Instituto Nacional de Salud, República de Colombia, 2022). Preaxial PD in Bogotá between 2001 and 2010 showed a prevalence of 3.04 per 10,000 LB (Zarante, Gracia, & Zarante, 2016), and all types of PD showed a prevalence of 16.84 per 10,000 LB during 2006–2015 (Zarante, Sarmiento, et al., 2016).

Polydactyly is not typically associated with serious health complications on its own; however, it has been observed to occur frequently in over 90 genetic syndromes, including Smith-Lemli-Opitz syndrome, Greig syndrome, and trisomy 13 (Phadke & Sankar, 2010).

Currently, several risk factors are known to be associated with the development of polydactyly, including the use of methylphenidate during pregnancy (Bolea-Alamanac et al., 2014; Lopez-Leon et al., 2020), and exposure to toxic substances during pregnancy (Luo et al., 2009). Additionally, social factors such as low educational level and average annual income (Luo et al., 2009; Materna-Kiryluk et al., 2013), and maternal factors such as age, infections during the first trimester of pregnancy, multiparous mother, and family history of the malformation have also been identified (Cifuentes et al., 2007; Wang et al., 2021).

The aim of our study was to conduct an epidemiological characterization of the prevalence and associated risk factors associated with polydactyly in Bogotá and Cali, Colombia between 2002 and 2020, utilizing data from the Program for the Prevention and Follow-up of Congenital Defects and Orphan Diseases of Bogotá and Cali (PREVERDEC).

2 | MATERIALS AND METHODS

2.1 | Study design

A retrospective case–control study was conducted following the Latin American Collaborative Study of Congenital Malformation approach (ECLAMC by its acronym in Spanish). In which all major and minor congenital abnormalities present at birth in infants weighing ≥500 g were systematically documented using a standardized manual of procedures and guideline, that were used by certified physicians to perform standardized physical examinations on newborns to identify and report congenital abnormalities. Additionally, the subsequent four babies born without congenital abnormalities, matched by newborn sex, were selected as control subjects to establish a cases-and-controls cohort. Further data on prenatal, pregnancy-related, and newborn-related variables were obtained through direct interviews with the mothers of the newborns after birth (Poletta et al., 2014). Data collection took place across 43 hospitals in Bogotá and Cali and was reported to the PREVERDEC surveillance system. The collected data were classified based on medical criteria and stored on servers provided by the Bogotá Secretary of Health and Pontificia Universidad Javeriana.

Remarkably, 44% of the included hospitals are classified as low complexity-hospital, 2.3% of the hospitals are designated as low-mild complexity, 39.5% displaying mild complexity, 4.7% mild-high complexity, and 9.3% high complexity hospitals. This distribution underscores the comprehensive representation of hospitals with diverse complexity levels in our study, thereby offering a realistic perspective on the healthcare settings scrutinized. Hospitals under consideration yield a representative sample of our population, as they encompass varying levels of complexity, involve both the public and private sectors, and span across the majority of geographical areas in our society dedicated to the identification of birth defects.

Cases were defined as LB or stillbirths presenting PD, weighing ≥500 g, and born in a hospital affiliated with the surveillance program between January 2002 and March 2020. Controls were LB without congenital abnormalities, born on the same day as the reported case, and from the same hospital, with a 1:4 case-to-control ratio.

Further classification of cases was established as follows: isolated cases were defined as those presenting only PD; isolated complex cases were defined as those presenting PD along with another musculoskeletal congenital abnormality; polymalformed cases were defined as those presenting PD along with other major congenital abnormalities besides musculoskeletal anomalies; and syndromic cases were defined as those presenting PD along with a recognizable genetic pattern (such as Down syndrome). Malformations were classified as preaxial, postaxial or combined PD, and were further classified based on whether they affected the lower limbs, upper limbs, or both. Timing of the included variables was determined at birth, considering data were obtained from surveillance records provided by PREVERDEC.

2.2 | Statistical analysis

The data were analyzed using IBM SPSS Statistics for Mac (Version 29). The prevalence of PD was calculated per 10,000 LB and a 95% confidence interval was

TABLE 1 Distribution and prevalence of polydactyly cases.

Case group	Male	Female	Indeterminate	Total	Prevalence per 10,000 (95% confidence interval
Isolated	410	285	1	696	12.47 (11.56–13.43)
Complex Isolated	21	16		37	0.66 (0.47–0.91)
Polymalformed	57	42	4	103	1.85 (1.51–2.24)
Syndromic	6	5	1	12	0.21 (0.11–0.38)
Total	494	348	6	848	15.19 (14.18–16.25)

established using Poisson distribution. LB are used as a denominator in the calculation of prevalence of birth defects as a consensus was previously established among studies (Mason et al., 2005). For risk factors, the odds ratios were calculated using frequency distribution, and adjusted odds ratios were obtained using a logistic regression model in order to estimate the risk for PD given the values of the following independent variables: newborn sex, maternal and paternal age >35 years, family history of malformation, multiparity of the mother, pregestational and gestational diabetes, folic acid use, drug use, tobacco use during pregnancy. For social characteristics, we classified income according to the National Administrative Department of Statistics, which classifies individuals based on housing characteristics and findings within its community (public services access and transport facility). We compare groups 1 and 2 (low income) against 3–6 (medium-high income). Considering educational level, we considered low educational level if incomplete secondary or lower. Missing data were excluded for the analysis. Additional logistic regression model was made restricting non-syndromic cases of PD. In order to understand the impact of the inclusion of syndromic cases in the estimates of risk factors overall.

As the critical exposure window for PD generally occurs before the eighth week of gestation, some variables included in the analysis are detected before in this period, such as pregestational diabetes, male sex determination, and family history of polydactyly, which must be considered for the logistic regression analysis.

3 | RESULTS

A total of 558,255 births were identified between 2002 and 2020, out of which 848 were diagnosed with PD. Among these cases, 833 were live births, while 15 were stillbirths. The distribution of the total cases is as follows: 82.07% ($n = 696$) were isolated cases, 4.36% ($n = 37$) were complex isolated cases, 12.15% ($n = 103$) were polymalformed cases, and 1.42% ($n = 12$) were syndromic cases (Table 1).

Considering PD distribution; seven cases presented postaxial PD distribution, three with preaxial, one had combined PD, and one non-specified PD. For syndromic cases, Patau syndrome was found to be the most common with eight cases, followed by Down syndrome with two cases.

In terms of limb involvement, the majority of cases exhibited upper limb malformations ($n = 570$), followed by lower limb malformations ($n = 135$), non-specified malformations ($n = 84$), and involvement of both limbs ($n = 59$). Among the reported cases, the postaxial configuration was the most prevalent, accounting for 67% ($n = 564$) of the total. The preaxial configuration accounted for 21% ($n = 176$), while non-specified and combined configurations were observed in 9% ($n = 84$) and 3% ($n = 24$) of the cases, respectively (Table 2).

We observed a general prevalence of PD to be 15.19 per 10,000 LB (95% CI 14.18–16.25) between 2002 and 2020. In Bogota, a total of 474,946 births were recorded during the same period, and the prevalence of PD was found to be 14.44 per 10,000 LB (95% CI 13.38–15.57) with 686 cases out of 848. In Cali, 83,309 births were registered, and the prevalence of PD was 19.45 per 10,000 LB (95% CI 16.57–22.68) with 162 cases.

Male newborn sex was found to increase the odds for PD (aOR: 1.47; 95% CI: 1.05–2.04). Neither maternal nor paternal age >35 years showed any significant association with PD (Table 3). The presence of family history of PD in first-degree relatives or consanguinity was found to be strongly associated with the development of PD in the newborn (aOR: 709.30; 95% CI: 97.09–5181.94). Similar findings were observed for the presence of maternal pregestational diabetes (aOR: 3.69; 95% CI: 1.24–10.99). However, no significant association was found between PD and gestational diabetes (aOR: 0.52; 95% CI: 0.17–1.62).

In relation to the mother's pregnancy, consumption of folic acid did not show statistical significance with the odds of PD (aOR: 0.80; 95% CI 0.55–1.16). Similarly, no significant association was found between the consumption of drugs (aOR: 4.93; 95% CI 0.83–29.35) or tobacco (aOR: 0.70; 95% CI 0.37–1.32) and the odds of PD.

Regarding social variables, no association was found between low income (aOR: 1.01; 95% CI 0.72–1.42) or

TABLE 2 Classification of polydactyly cases.

	Limb involvement				
	Upper limb	Lower limb	Both	Non specified	Total
Malformation configuration	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Preaxial	153 (27)	20 (15)	3 (5)		176 (21)
Postaxial	397 (70)	111 (82)	56 (95)		564 (67)
Combined	20 (3)	4 (2)			24 (3)
Non Specified				84 (100)	84 (9)
Total	570 (100)	135 (100)	59 (100)	84 (100)	848 (100)

low educational level of the mother (aOR: 0.78; 95% CI 0.52–1.16) and the risk of PD presentation.

Considering the additional logistic regression model performed for non-syndromic cases, we obtained similar findings that do not deviate from risk factors when including all cases, with changes observed only in the odds ratio values (Table 3).

4 | DISCUSSION

The study centered on the characterization of prevalence and risk factors associated with PD presentation in Bogotá and Cali between 2002 and 2020 in different hospitals linked into the PREVERDERC surveillance system.

The observed prevalence of PD is higher compared to the prevalence reported by European countries from 2002 to 2020, which was 9.48 per 10,000 LB (95% CI 9.34–9.62) according to EUROCAT's database (adapted from European Surveillance Of Congenital Anomalies, 2022). The higher prevalence in our study could be attributed to PD being an inherited condition, with families in regions like South America and other middle-to-low-income countries typically having larger numbers of children compared to European countries and North America (Maralani, 2008). However, other explanations should also be considered.

Our study revealed that male newborns have a heightened risk for PD (aOR: 1.47; 95% CI: 1.05–2.04). This finding aligns with the current body of literature, which consistently indicates a higher prevalence of PD cases among males (Materna-Kiryluk et al., 2013; Rayan & Frey, 2001). It is noteworthy, however, that no specific genetic factor contributing to the increased risk of PD in males, as compared to females, has been identified to date.

A family history of PD among first-degree relatives has been identified as a significant risk factor for PD (aOR: 709.30; 95% CI: 97.09–5181.94). Numerous studies have elucidated the hereditary nature of PD, establishing a link between new PD cases and a family history within first-degree relatives (Malik, 2014). Notably, the existing literature demonstrates that well-characterized PD cases typically follow an autosomal dominant pattern of inheritance rather than an autosomal recessive pattern, as primarily observed in non-syndromic postaxial PD (Bubshait, 2022; Comer et al., 2018). Consequently, it could be hypothesized that the relatively higher prevalence of PD, compared to other congenital musculoskeletal defects, may be partially attributed to its autosomal dominant nature (Comer et al., 2018). Nevertheless, further research is warranted to establish a robust correlation between these two factors.

Pregestational diabetes is a well-known risk factor for congenital abnormalities, typically involving cardiovascular, gastrointestinal, and central nervous system malformations (Chen et al., 2019; Garne et al., 2012; Øyen et al., 2016). Our study revealed that pregestational diabetes in the mother increases the risk of PD in the newborn (aOR: 3.69; 95% CI: 1.24–10.99). Hyperglycemia has been identified as the primary factor contributing to the pathogenesis of PD. It is considered to have a teratogenic effect due to its ability to elevate reactive oxygen species and induce intracellular stress during embryological development (Loeken, 2006; Yang et al., 2008). Notably, preaxial hallucal polydactyly has been recognized as a marker for diabetic embryopathy (Adam et al., 2009).

Our findings did not demonstrate an association between folic acid consumption during pregnancy and the risk of PD presentation (aOR: 0.80; 95% CI 0.55–1.16). However, folic acid has been established as a protective factor against congenital abnormalities in various systems (Feng et al., 2015; Jenkins et al., 2007; Li et al., 2016). Thus, it is crucial to enhance public health policies aimed at ensuring optimal levels of folic acid prior to embryonic morphogenesis, this can be achieved through direct supplementation or even macroscopic fortification of foods, such as rice. Fortification with folic acid is currently implemented in Colombia, specifically in wheat flour; however, there is no mandatory preconception supplementation (Murphy &

TABLE 3 Risk factors for polydactyly using a logistic model regression.

Variables	Cases ($n = 848$)		Controls ($n = 3368$)		Odds ratio (95% CI)	*p*-value	Adjusted odds ratio[a] (95% CI)	*p*-value	Adjusted odds ratio[a] (95% CI) for NSC	*p*-value
	Outcome	% Missing	Outcome	% Missing						
Male newborn sex	494	0	1827	0.30	1.17 (1.01–1.36)	0.044	1.47 (1.05–2.04)	0.024	1.48 (1.06–2.07)	0.023
Maternal age >35 years	87	6.96	296	9.44	1.15 (0.90–1.49)	0.270	1.41 (0.80–2.47)	0.232	1.27 (0.71–2.28)	0.416
Paternal age >35 years	113	9.08	654	3.68	0.99 (0.79–1.24)	0.946	0.95 (0.61–1.48)	0.806	0.98 (0.63–1.54)	0.933
Family history of malformation	186	0	15	0	62.81 (36.87–106.98)	<0.001	709.30 (97.09–5181.94)	<0.001	728.270 (99.71–5318.91)	<0.001
Multiparity of the mother	331	8.61	1863	1.72	1.05 (0.88–1.26)	0.567	0.78 (0.56–1.09)	0.147	0.76 (0.54–1.06)	0.110
Pregestational diabetes	7	0	29	0	0.96 (0.42–2.20)	0.920	3.69 (1.24–10.99)	0.019	3.83 (1.29–11.41)	0.016
Gestational diabetes	25	0	100	0	0.99 (0.64–1.55)	0.974	0.52 (0.17–1.62)	0.260	0.55 (0.17–1.71)	0.298
Gestational folic acid use	423	0	2277	0	0.48 (0.41–0.56)	<0.001	0.80 (0.55–1.16)	0.230	0.82 (0.56–1.19)	0.290
Gestational drug use	3	8.96	11	2.73	1.05 (0.29–3.79)	0.936	4.93 (0.83–29.35)	0.080	4.91 (0.83–29.17)	0.080
Gestational tobacco use	34	8.73	257	1.90	0.50 (0.34–0.71)	<0.001	0.70 (0.37–1.32)	0.272	0.72 (0.38–1.36)	0.310
Low income	160	11.20	848	2.40	1.09 (0.83–1.44)	0.528	1.01 (0.72–1.42)	0.944	0.98 (0.70–1.39)	0.927
Low educational level	152	8.61	871	2.05	1.00 (0.82–1.23)	0.987	0.78 (0.52–1.16)	0.215	0.79 (0.52–1.18)	0.244

Abbreviations: CI, Confidence interval; NSC, Non-syndromic cases.

[a]Each model is adjusted for all other variables.

Westmark, 2020). Clinical practice guidelines recommend prenatal folic acid supplementation during pregnancy, typically commencing at week 12. We posit that the initiation of supplementation at this stage does not likely exert a significant influence on limb development.

Maternal tobacco use during pregnancy has been recognized as a potential risk factor for various adverse health outcomes in children (Baldacci et al., 2018). Previous studies have established an association between cigarette use during pregnancy and congenital digital abnormalities (Man & Chang, 2006). However, our study did not find a significant association between gestational tobacco use and the risk of PD presentation (aOR: 0.70; 95% CI 0.37–1.32). It is important to note that, despite our results, tobacco use during pregnancy is not recommended due to its association with the occurrence of pregnancy-related complications and other congenital abnormalities (Boyd et al., 2022; Rogers, 2009). Further research is warranted to explore potential mechanisms underlying the development of PD.

Recent studies have drawn attention to the association between parental education and the occurrence of congenital abnormalities. For instance, a previous hospital-based case-control study found a link between the educational level of parents and the prevalence of PD and syndactyly (Luo et al., 2009). Similarly, a study utilizing data from the Polish Registry of Congenital Malformations suggested that lower paternal education levels may act as a potential risk factor for sporadic preaxial PD type I, thereby supporting the hypothesis that non-genetic factors contribute to the etiology of PD (Materna-Kiryluk et al., 2013). Although our study did not establish an association between low educational levels and the occurrence of PD (aOR: 0.78; 95% CI 0.52–1.16), it remains imperative to investigate non-genetic risk factors for congenital abnormalities to enhance our understanding of their etiology and gain valuable insights into potential interventions aimed at reducing their prevalence.

Following the implementation of a secondary logistic regression model focused exclusively on non-syndromic cases, we derived results consistent with our initial findings. This congruence is likely influenced by the restricted number of syndromic cases incorporated into the study. Nevertheless, caution remains imperative in the analysis of syndromic cases and their correlated risk factors. Distinguishing whether a congenital defect stems from a particular risk factor or arises due to the mechanisms inherent in the genetic syndrome can pose significant challenges (Tinker et al., 2015).

The observed limitations of this study primarily stemmed from missing data discovered in the national surveillance system registry. Incomplete reporting of records results in a deficient report for certain variables, thereby compromising risk factors statistical analysis. As well as memory bias that occurs during mother's interview, on behalf it is a retrospective study. Moreover, the COVID-19 pandemic disrupted the data registration process of the PREVERDEC surveillance system in Colombia, thereby constraining our dataset to the temporal span from January 2002 to March 2020.

5 | CONCLUSIONS

Our study examined various variables associated with the onset of PD. We identified male newborn sex, pregestational diabetes, and a family history of PD among first-degree relatives as risk factors. Additionally, we observed a higher prevalence of PD among individuals with a low birth weight (<2500 g). However, due to the timing of its manifestation after birth, low birth weight cannot be considered a direct risk factor. These findings suggest the importance of a surveillance system aimed to characterize populations with congenital abnormalities, providing a better option for analyzing risk factors, help improving prevention, diagnosis, notification, and an optimal treatment. Such measures will ultimately lead to better prognoses and an improved quality of life.

AUTHOR CONTRIBUTIONS

Esteban Portilla-Rojas: Study design; literature review; writing and editing manuscript. **Lina Ramírez:** Study design; literature review; writing manuscript. **Camilo Moreno:** Study design; literature review; writing manuscript. **Juliana Lores:** Editing manuscript; final manuscript approval. **Karen Sarmiento:** Editing manuscript; final manuscript approval. **Ignacio Zarante:** Editing manuscript; final manuscript approval.

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CONFLICT OF INTEREST STATEMENT

No potential conflict of interest was reported by the authors.

DATA AVAILABILITY STATEMENT

Due to confidentiality of patient records, data analyzed are not publicly available.

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