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Spatial distribution and secular trend (1991–2014) of small for gestational age infants born in Jujuy

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ABSTRACT

Introduction. A fetus that does not reach the expected growth potential *in utero* is considered small for gestational age (SGA). Such restriction depends on genetic and/or environmental factors, being altitude a very relevant factor. This study analyzes the spatial distribution of the prevalence of SGA and its secular trend in Jujuy (1991–2014).

Materials and methods. The records of 308 469 live births in Jujuy (Health Statistics and Information Department) were analyzed. The prevalence of SGA (weight/gestational age < P10 and < P3) was estimated for sex according to the INTERGROWTH-21st standard in the ecoregions of Jujuy (Valle and Ramal –less than 2000 MASL–, Puna, and Quebrada) across 3 periods (1991–2000, 2001–2009, 2010–2014) and proportions were compared. The secular trend was assessed using the Joinpoint regression analysis.

Results. The overall prevalence of SGA was 2.3% (< P3) and 7% (< P10). Significantly higher values were observed in Puna and Quebrada in both SGA categories and across all periods. Only in Valle, significant differences were observed between sexes across all periods. The prevalence of SGA showed a significant downward secular trend at a provincial and regional level, and this was greater in Quebrada (5.2% < P3 and 3.5% < P10).

Conclusions. A consistent and significant decrease in the prevalence of SGA has been observed since the 1990s in Jujuy, where altitude is itself a determining factor of size at birth, since the Puna and Quebrada regions showed the highest prevalence of SGA during the entire period.

Key words: *small for gestational age infant; medical geography; prevalence; secular trend; Jujuy.*

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INTRODUCTION

The size of a newborn infant (NBI) is the result of the growth, from conception to birth, and reflects both the duration of gestation and the growth rate of the fetus. Therefore, birth size should be considered in relation to gestational age (GA) to avoid confusion between growth and maturation.[1] Growth is a biological process determined by the increase in body mass due to the increase in the number and size of cells. Maturation refers to the level of development reached at a given moment, a process by which living beings achieve the greater functional capacity of their tissues, organs, and systems.[2]

The most common indicator used to analyze size at birth establishes a relation between birth weight (BW) and GA. When a fetus does not reach the expected growth potential *in utero* due to genetic or environmental factors, this is called intrauterine growth restriction (IUGR). The small for gestational age (SGA) category, which is determined based on the 10th percentile (P10) of BW for GA and sex, is a reflection of such restriction.[3] The 3rd percentile (P3), which defines severe SGA, is also used because it is a category more predictive of adverse perinatal outcomes than the < P10 cutoff point.[4,5]

Since IUGR is difficult to measure, there is consensus on the use of SGA data as the equivalent of IUGR for epidemiological purposes.[6,7] Considering that SGA estimates vary substantially depending on the reference population and the social and environmental setting, having a single universal growth standard is encouraged over local/national growth references. Argentina has adopted the INTERGROWTH-21st standard for the assessment of size at birth and postnatal growth of preterm infants.[8–11]

There are only a few records of SGA assessments using the INTERGROWTH-21st standard in the Argentine population in general, and in the Jujuy population in particular. However, a higher number of studies have been conducted focused on BW in the province of Jujuy, which revealed a differential regional pattern, where a significantly lower average weight, a higher prevalence of low birth weight (LBW < 2500 g), and a lower prevalence of very low birth weight (VLBW < 1500 g) were observed in the highlands. These results are related to the influence of altitude as one of the most relevant environmental factors conditioning size at birth. The physiological effects of hypobaric hypoxia on body size begin at 1500 meters above sea level (MASL) and increase progressively with altitude.[12]

Only few countries have an altitudinal gradient like those located in the Andes mountain range. Plenty of the studies that have analyzed the variation of BW in relation to altitude correspond to Peru and Bolivia;[13–18] whereas studies that have analyzed the size at birth in these extreme environments are scarce.

In Argentina, most studies were carried out in relation to the province of Jujuy, due to its location on the Andean foothills, with ecoregions located on an altitudinal gradient (Puna ≈3000 MASL, Quebrada ≈2000 MASL, Valle ≈1000 MASL, and Ramal ≈500 MASL) and their own demographic, socioeconomic, and cultural characteristics.[12,19–22]

Taking into account the aforementioned topographic features of the province of Jujuy and having a continuous registration of births for approximately 25 years, the objective of this study was to analyze the spatial distribution of the prevalence of SGA and its secular trend (1991–2014).

MATERIALS AND METHODS

This was a descriptive, retrospective, eco-epidemiological, cross-sectional, time-series study. The data were obtained from the certificates of live NBIs in the province of Jujuy from 1991 to 2014, provided by the Health Statistics and Information Department of the National Ministry of Health of Argentina. Exclusion criteria were records indicating a GA < 24+0 and > 42+6 weeks, missing weight or sex, twin pregnancy, and those where the mother's place of residence was outside the province of Jujuy.

Statistical analysis

Prevalence values and 95% confidence intervals (CIs) of SGA < P3 and < P10 (weight for GA and sex) were estimated using the INTERGROWTH-21st standard,[9] by region and department, by year, and by period (1991–1999, 2000–2008, 2009–2014). Sex, spatial, and temporal differences were analyzed using tests for the comparison of proportions. Maps were developed to show the spatial distribution of prevalence by department and period, using geographic information systems (Quantum GIS).

The secular trends of SGA categories, with their respective 95% CIs, were estimated using spline functions adjusted with the Stata V.15 software. The changes in the trends of each SGA category across the entire period were identified adjusting Joinpoint regression analysis, which allowed estimating the annual percent change (APC) and the corresponding 95% CI for the total for the province and by region. The Joinpoint software was used for this analysis.

Ethical considerations

This study adheres to the Declaration of Helsinki (WMA, 2013), Law no. 25326 on Personal Data Protection, Resolution no. 1480/2011 by the National Ministry of Health, and Resolution no. 012565 by the Ministry of Health of the Province of Jujuy. It was also assessed by the Provincial Health Research Ethics Committee of the Ministry of Health of Jujuy and approved by Resolution no. 2872-S-2018.

RESULTS

During the entire period studied, 322 742 live births were registered. After applying the exclusion criteria, the sample was made up of 308 469 live births, with an average of approximately 13 000 births per year. The spatial distribution was heterogeneous, both at the departmental and regional level. The Puna and Quebrada regions (highlands ≥ 2000 MASL) accounted for less than 15% of births in the province in the entire period studied.

The prevalence of SGA < P3 and < P10 in Jujuy between 1991 and 2014 was 2.3% (CI: 2.25–2.36) and 7% (CI: 6.88–7.06), respectively, with a significant decrease ($p < 0.05$) over time, both at the provincial and regional level (*Table 1*). The prevalence was significantly higher in both categories in Puna and Quebrada, and reached a value similar to the baseline value of the lowland regions towards the end of the period.

Although at the provincial level the prevalence of SGA was significantly higher in female NBis across all periods, at the regional level, this was

Table 1. Prevalence of small for gestational age infants < P3 and < P10 (95% CI) by region and period. Jujuy 1991–2014

SGA	Region	Period							
		1999-2000*		2001-2008*		2009-2014*		Total	
		n	%	n	%	n	%	n	%
<P3	Puna	403	4.36	272	3.01	149	2.68	824	3.45
		(3.96-4.79)		(2.67-3.38)		(2.28-3.13)		(3.23-3.69)	
	Quebrada	346	5.16	206	3.28	94	2.17	646	3.73
		(4.65-5.7)		(2.86-3.74)		(1.77-2.64)		(3.46-4.02)	
	Valle	1652	2.47	1359	2	813	1.71	1824	2.14
		(2.35-2.59)		(1.9-2.11)		(1.60-1.83)		(2.05-2.24)	
	Ramal	850	2.6	638	2.04	336	1.59	3824	2.1
		(2.44-2.78)		(1.89-2.2)		(1.42-1.76)		(2.03-2.17)	
	Jujuy	3252	2.81	2475	2.16	1392	1.77	7118	2.31
		(2.72-2.91)		(2.08-2.25)		(1.68-1.87)		(2.25-2.36)	
<P10	Puna	1234	13.35	971	10.74	526	9.45	2731	11.45
		(12.67-14.05)		(10.12-11.39)		(8.70-10.24)		(11.05-11.86)	
	Quebrada	978	14.57	654	10.42	329	7.61	1961	11.33
		(13.74-15.43)		(9.68-11.19)		(6.85-8.43)		(10.86-11.81)	
	Valle	5027	7.51	4229	6.24	2398	5.05	5162	6.07
		(7.31-7.71)		(6.06-6.42)		(4.86-5.25)		(5.91-6.23)	
	Ramal	2317	7.1	1876	6	969	4.57	11654	6.4
		(6.82-7.38)		(5.74-6.27)		(4.30-4.86)		(6.28-6.51)	
	Jujuy	9556	8.27	7730	6.76	4222	5.38	21508	6.96
		(8.11-8.43)		(6.61-6.90)		(5.22-5.54)		(6.88-7.06)	

**Significant differences between sexes (p < 0.05) among periods for < P3 and < P10 in Jujuy and its regions.*
CI: confidence interval.
SGA: small for gestational age.
n: number.

only observed in Valle, while in Quebrada and Ramal, it was only observed for one category and one period (*Tables 2 and 3*).

At the departmental level, it was observed that the behavior of SGA in both categories was similar to that of their region of origin. In the last period, all departments reached a prevalence of SGA < P3 and < P10 below the clinical and epidemiological cutoff points (3% and 10%, respectively), except in Cochinoca in both categories (3.4% and 11%, respectively) and in Rinconada for SGA < P3 (3.5%) (*Figure 1*).

The analysis of the secular trend of the prevalence of SGA < P3 and < P10 using the median spline smoothing method showed a downward trend in both categories in the 4 regions and at the provincial level. The Joinpoint analysis corroborated such reduction with an APC of 2.5% (< P3) and 2.3% (< P10) for the total at a provincial level, while at the regional level it ranged from 1.9% (Valle) to 5.2% (Quebrada) per year of SGA < P3 (*Figure 2*). For SGA < P10, the APC ranged from 1.9% (Puna) to 3.5% (Quebrada) per year (*Figure 3*). No significant inflection points were noted in the models for each region, i.e., the best fit was observed with a single downward trend or at 0 joinpoint.

DISCUSSION

Despite the importance of analyzing IUGR –given that, compared to NBIs with normal intrauterine growth, those with IUGR have an increased risk for adverse effects in early childhood and childhood in terms of mortality, morbidity, growth, obesity, hypertension, diabetes, heart and lung disease, and stroke in adulthood,[23,24]– there are scarce records of SGA assessment using the INTERGROWTH-21st standard.[4,7,9,22]

Table 2. Prevalence of small for gestational age infants < P3 (95% CI) by sex. region, and period. Jujuy 1991–2014

Region	Sex	1999-2000 n	1999-2000 %	2001-2008 n	2001-2008 %	2009-2014 n	2009-2014 %	Total n	Total %
Puna	Male	191	4.07 (3.53-4.66)	132	2.87 (2.42-3.38)	75	2.68 (2.13-3.32)	398	3.2 (2.98-3.62)
	Female	212	4.66 (4.07-5.3)	140	3.15 (2.67-3.7)	74	2.68 (2.12-3.33)	426	3.62 (3.3-3.97)
Quebrada	Male	147	4.34* (3.69-5.07)	106	3.36 (2.77-4.03)	47	2.17 (1.62-2.85)	300	3.44* (3.08-3.84)
	Female	199	5.99* (5.22-6.83)	100	3.2 (2.63-3.86)	47	2.18 (1.63-2.86)	346	4.02* (3.62-4.45)
Valle	Male	907	2.65* (2.48-2.83)	705	2.04 (1.89-2.19)	452	1.88* (1.71-2.05)	962	2.21* (2.07-2.35)
	Female	745	2.27* (2.12-2.44)	654	1.97 (1.83-2.13)	361	1.55* (1.39-1.71)	862	2.08* (1.94-2.22)
Ramal	Male	442	2.63 (2.4-2.88)	336	2.1 (1.89-2.33)	184	1.7 (1.47-1.96)	2064	2.22 (2.13-2.32)
	Female	408	2.57 (2.34-2.83)	302	1.98 (1.77-2.21)	152	1.47 (1.25-1.71)	1760	1.97 (1.88-2.06)
JUJUY	Male	1687	2.86 (2.72-2.99)	1279	2.19 (2.07-2.31)	758	1.9* (1.77-2.04)	3724	2.37* (2.29-2.44)
	Female	1564	2.77 (2.64-2.91)	1196	2.14 (2.02-2.26)	634	1.64* (1.52-1.77)	3394	2.25* (2.17-2.32)

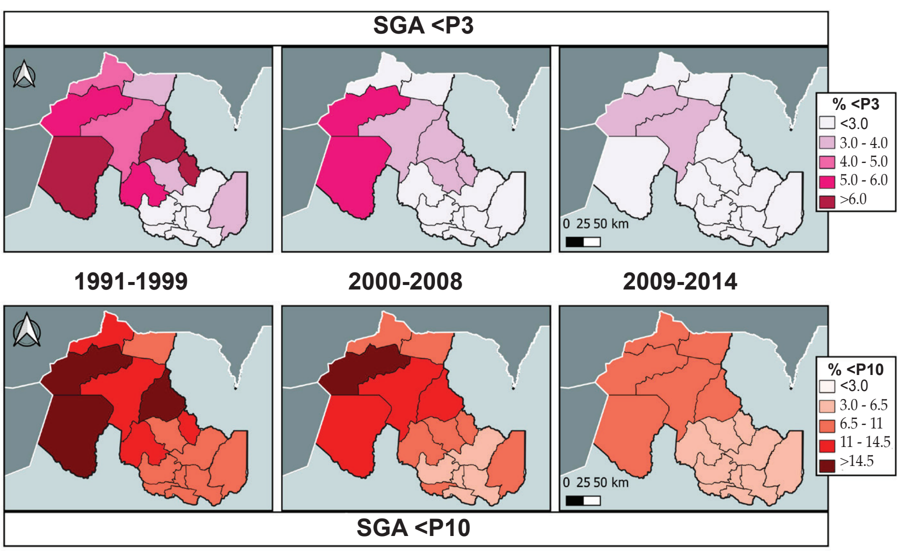
**Significant differences between sexes (p < 0.05).*
CI: confidence interval.
SGA: small for gestational age.
n: number.

Table 3. Prevalence of small for gestational age infants < P10 (95% CI) by sex, region, and period. Jujuy 1991–2014

Region	Sex	1999-2000 n	1999-2000 %	2001-2008 n	2001-2008 %	2009-2014 n	2009-2014 %	Total n	Total %
Puna	Male	614	13.1 (12.14-14.07)	491	10.7 (9.80-11.59)	269	9.6 (8.55-10.73)	1374	11.4 (10.8-11.93)
	Female	620	13.6 (12.64-14.64)	480	10.8 (9.93-11.75)	257	9.3 (8.26-10.43)	1357	11.6 (10.98-12.13)
Quebrada	Male	479	14.1 (13-15.35)	335	10.6 (9.58-11.73)	166	7.65 (6.59-8.83)	980	11.3 (10.6-11.93)
	Female	499	15.0 (13.83-16.26)	319	10.2 (9.19-11.31)	163	7.56 (6.50-8.74)	981	11.4 (10.74-12.09)
Valle	Male	2713	7.93* (7.65-8.22)	2236	6.46* (6.20-6.72)	1304	5.41* (5.13-5.70)	2734	6.27* (6.05-6.5)
	Female	2314	7.06* (6.79-7.35)	1993	6.01* (5.76-6.27)	1094	4.69* (4.42-4.96)	2428	5.85* (5.63-6.08)
Ramal	Male	1232	7.34 (6.95-7.74)	972	6.08 (5.72-6.46)	530	4.9* (4.50-5.32)	6253	6.73* (6.57-6.89)
	Female	1085	6.84 (6.46-7.24)	904	5.92 (5.55-6.30)	439	4.24* (3.86-4.64)	5401	6.05* (5.9-6.21)
JUJUY	Male	5038	8.53* (8.3-8.76)	4034	6.91* (6.71-7.12)	2269	5.69* (5.46-5.92)	11341	7.2* (7.08-7.34)
	Female	4518	8.0* (7.78-8.22)	3696	6.6* (6.4-6.81)	1953	5.06* (4.84-5.28)	10167	6.72* (6.60-6.85)

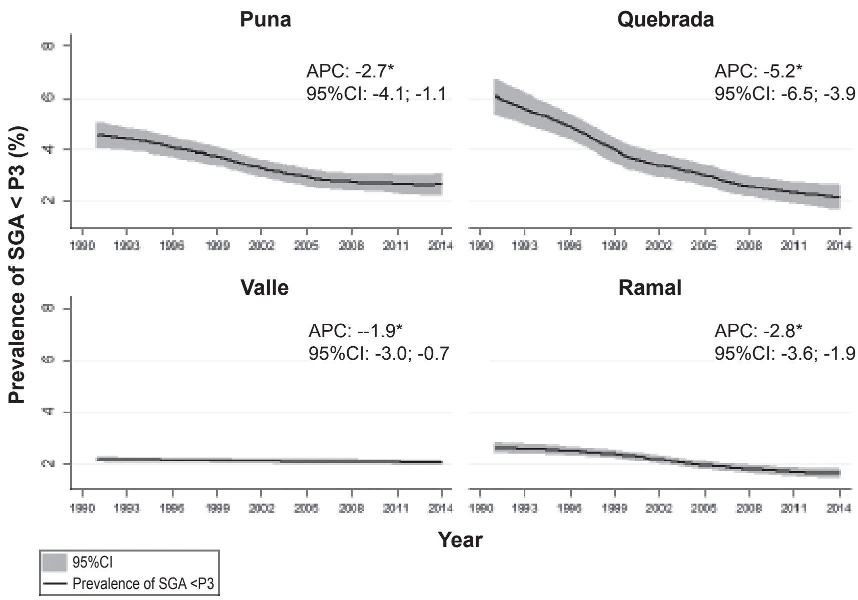
**Significant differences between sexes (p < 0.05).*
CI: confidence interval.
SGA: small for gestational age.
n: number.

Figure 1. Spatial distribution of small for gestational age infants (SGA < P3 and < P10) by department and period. Jujuy 1991–2014



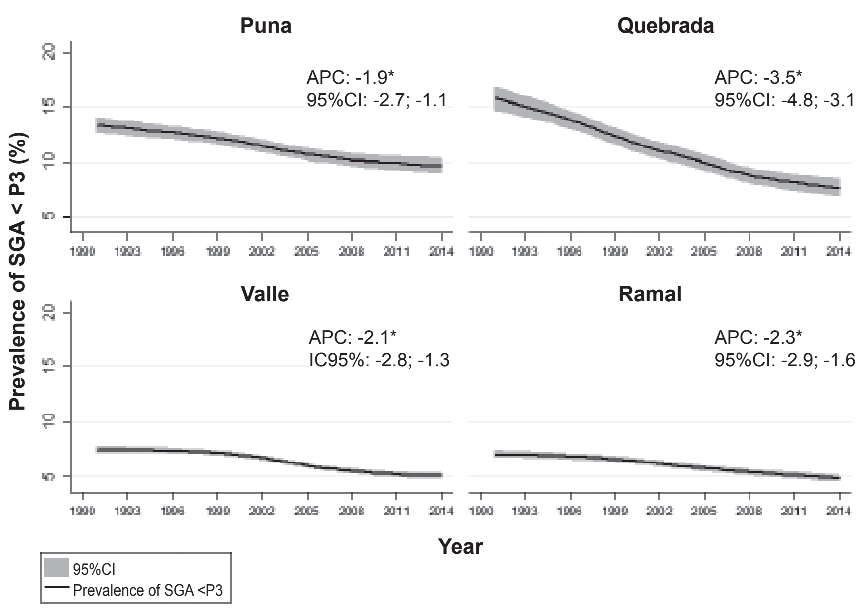
SGA: small for gestational age.

Figure 2. Secular trend (1991–2014) of the prevalence of small for gestational age infants < P3 (95% CI) by region



APC: annual percent change.
SGA: small for gestational age.
CI: confidence interval.

Figure 3. Secular trend (1991–2014) of the prevalence of small for gestational age infants < P10 (95% CI) by region



APC: annual percent change.
SGA: small for gestational age.
CI: confidence interval.

In this study, the prevalence of SGA in Jujuy was 7% (P10) and 2.3% (P3) for the entire study period. In a global study of this indicator, for 2010, the prevalence of SGA (< P10) observed in Latin America and the Caribbean (12.5%, CI: 9.4–16.3) and in Argentina (11.3%, CI: 8.2–15) was higher than that found in this study, both at the provincial and regional level. Only in the Puna region and for the last period (2009–2014), the prevalence (9.5%) observed met the CIs indicated in the study mentioned above.[25] In another global study, for 2012,[7] the authors estimated that the prevalence of SGA was 19.3% (CI: 17.6–31.9) in low- and middle-income countries, as well as in Latin America and the Caribbean. Although the prevalence values reported were lower, 8.6% (CI: 6.7–19.3) for Latin America and the Caribbean and 7.6% (CI: 6.3–16.6) for Argentina, compared to 2010, they continue to be higher than those observed in this study for Jujuy and its regions.

The only national data analyzing the category of SGA < P3 are those provided in the studies by Revollo et al.,[4] and Martinez et al.[26] The former found a higher prevalence of LBW (SGA < P3) at a regional level, almost twice as high, among preterm infants compared to term NBIs.[4] While the study by Martínez et al., conducted based on the records of the Perinatal Information System of Jujuy in the 2009–2014 period, found a prevalence of SGA < P3 slightly lower (1.27%) than that observed in this study (1.8%) for the same period, they also reported a 1.3 times higher rate of the same indicator in the highlands (> 2000 MASL) compared to the lowlands.[26]

Across all the periods analyzed, the prevalence of SGA (< P10, < P3) was higher in the Puna and Quebrada regions; although this could be conditioned by unfavorable socioeconomic factors, it is not possible to rule out its relation to growth characteristics imposed by high-altitude hypoxia. This means that the distribution of BW deviates towards the left of the curve in the Puna and Quebrada regions, and that, therefore, any of the percentiles used to diagnose SGA would capture a greater number of NBIs with this condition. On the other hand, it has been well-established that a decreased BW with altitude is accompanied by a higher prevalence of SGA.[21,22,27]

The prevalence of SGA, in both categories, showed a significant decrease over time throughout Jujuy. Although there are not many records of the secular trend of SGA (< P10 and < P3), available studies show disparate results and refer to very few countries.[28–31] In Utah, USA, between 2000 and 2008, a decrease in BW was observed along with an increase in the prevalence of SGA.[31] In France, between 1972 and 2003, BW fluctuated until 1995 and then remained constant, while the prevalence of SGA decreased until 1995 and then increased until the end of the period.[32] In both studies, the authors did not find an explanation to identify the factors responsible for such discordant changes.

The significant decrease in the prevalence of SGA observed in this study in the province of Jujuy and its regions can be interpreted as an improvement in living conditions, reflected in the decrease in unmet basic needs (UBN) at the departmental and regional level in the past 3 national censuses of population and housing (1991, 2001, and 2010). In 1991, by comparison, inequalities were greater in Jujuy: the Puna region and its departments had the highest UBN values. In 2001, in general, there was a decrease in this indicator with less interdepartmental heterogeneity, but it persisted in the Puna departments of Susques and Rinconada, with high UBN values. The downward trend continued in 2010.[33] According to Golovanevsky et al., such dynamic of living conditions would be influenced by agricultural activities and the strong urbanization process experienced by the province of Jujuy since 1960.[33]

The regional evolution of UBNs is similar to that of SGA found in this study (*Figure 2*), although a sharper decline in the prevalence of SGA was observed here, with APC values higher than those observed at the provincial level and at the remaining regions, both in terms of SGA < P10 and < P3, as observed in the Quebrada region. This region, which joins the Puna with the valleys of the province of Jujuy, has historically been an outstanding tourist destination, which became even more popular when it was declared a World Cultural and Natural Heritage site by UNESCO in 2003, which has undoubtedly had an impact on local development.

Although Quebrada showed the greatest decrease in the prevalence of SGA, it continues to be one of the highest in the province, together with Puna, compared to the Valley and Ramal regions. This is consistent with the results reported by Revollo et al. (2017) based on Argentine birth certificates from 2013, where the lowest SGA prevalence was observed in the Central and Patagonia regions (the most developed regions of Argentina). These comparisons support the idea that socioeconomic disadvantage remains one of the main determinants of SGA, even in developed countries.[34,35]

The relationship between SGA and socioeconomic conditions studied here would indicate that its analysis could become a proxy for socioeconomic development; however, this assumption requires validation through other socioeconomic and morbidity and mortality indicators. The main strength of this study is its prolonged time coverage (24 years) and the large volume of data analyzed, accounting for all births in the province of Jujuy that occurred between 1991 and 2014. The main limitation of this study is working with secondary data, which highlights the importance and value of data recording.

CONCLUSIONS

The prevalence of SGA, regardless of the cut-off point used to establish it (< P3 or < P10), decreased significantly in the study period, both at the provincial and regional level.

It was observed that altitude is itself a determining factor of size at birth, since the Puna and Quebrada regions always show the highest prevalence of SGA and that, only at the end of the study period, such prevalence reached the baseline value of SGA found in Valle and Ramal. ■

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