Original Research Article

Altitude Effect on Birth Weight and Prematurity in the Province of Catamarca (Argentina)

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Objectives: To analyze the effect of altitude on weight and prematurity at birth in the Province of Catamarca (Argentina), between the years 1994 and 2003.

Methods: Records of 22,628 newborns were collected from the vital statistics of the census of Catamarca. Weight was recategorized to include low birth weight (<2,500 g), and gestational age was divided into births that had occurred before or after 37 weeks (preterm or at term births). Altitude was also recategorized (<1,500 m, 1,500–2,000 m, and > 2,000 m). Nonparametric statistical tests were performed.

Results: Differences were found in birth weight between sexes and in the incidence of low birth weight depending on altitude. This pattern changed according to gestational age, because those sexual differences were nonexistent or lower in preterm neonates with certain advantages for females. Moreover, it was found that the effects of hypoxia were not reflected in birth weight until later stages of intrauterine development.

Conclusions: To be female appears to be a benefit under conditions of prematurity and high altitude. The increased incidence of prematurity due to altitude increase may reflect an adaptive advantage of preterm birth under these conditions. Am. J. Hum. Biol. 00:000–000, 2015.

Human populations differ from one another with respect to auxological parameters shaped by certain genetic and environmental characteristics (Bejarano et al., 2009). Body size at birth is the result of the degree of development in the uterus; thus, birth weight is one of the most commonly used variables to study fetal growth during pregnancy because, as discussed by the World Health Organization (WHO), "birth weight summarizes fetal development" (WHO, 2002). Low birth weight (LBW), or newborns weighing less than 2,500 g, with or without prematurity, has historically been the main determinant of infant morbidity and mortality in human populations (UNICEF and WHO, 2004; WHO, 2012). Preterm births are those that occur prior to 37 gestational weeks. At term births take place at 37 weeks or more.

These characteristics of childbirth affect the healthy development of newborns and have an influence on the differential risk of developing chronic diseases later in life (Barker, 1990, 1998; Beck et al., 2010; Crump et al., 2011; Gluckman et al., 2007; Li et al., 2014; Villegas et al., 2009), such as type I and II diabetes (García et al., 2009; Thurner et al., 2013), cardiovascular diseases (CVD), hypertension, insulin resistance (Jaquet et al., 2002) and precocious puberty, with the result of lower than normal adult height (Curcoy et al., 2004). Also, recent research shows that infant body composition has a special relationship with fetal adaptation and developmental programming (Demerath and Fields, 2014). In 2006, the WHO classified the relationship between LBW and adult chronic diseases and CVD under the concept of "Fetal Metabolic Programming" (WHO, 2006).

Fetal development, and the subsequent risk of developing the condition of LBW and/or having a preterm birth, is influenced by many different factors. These can be grouped into four general categories: demographic (social class, ethnicity, maternal education, marital status, maternal age, occupation), medical (pregestational stage: LBW in previous births, nutritional status, parity and chronic diseases; and gestational stage: multiple pregnancy, short interbirth interval, infections and malformations), behavioral (consumption of cigarettes, alcohol and other teratogenic substances) and environmental (season of the year, altitude above sea level) (Bejarano et al., 2009; Bortman, 1998). Given that birth weight is influenced by many complex causes, the evaluation and study of these factors has become one of the main objectives of physical anthropologists, pediatricians and epidemiologists.

Interest in evaluating the factors that affect birth weight increases when the population is located at high altitudes. Environmental conditions in these types of ecosystems are more restrictive than in their lowland counterparts and some specific physiological and cultural adaptations are therefore required. One of the effects on newborns is the reduction in birth weight (Bejarano et al., 2009). The objective of this research is to evaluate the effect of altitude on neonates who were born in the province of Catamarca between 1994 and 2003. This province is located in the northwest of Argentina and is composed of 16 regions, one of which belongs to the "Argentinean Puna," at an altitude of 3,000 m. Thus, populations who live in this region have the right characteristics for the

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TABLE 1. Mean and Standard Deviation (SD) birth weight by altitude[a]

	Male		Female		
Altitude (m)	*N*	Mean weight in grams (SD)	*N*	Mean weight in grams (SD)	Differences
Preterm births (<37 weeks)					
<1,500	362	2,432.13 (633.73)	294	2,444.12 (681.38)	−11.99
1,500–2,000	146	2,849.11 (688.13)	126	2,740.48 (670.25)	108.63
>2,000	126	3,026.98 (547.78)	120	3,034.17 (467.33)	−7.19
At term births (≥37 weeks)					
<1,500	8,271	3,293.23 (466.05)	7,756	3,189.68 (433.92)	103.55
1,500–2,000	2,123	3,281.28 (465.99)	1,994	3,186.40 (433.29)	94.78
>2,000	683	3,205.03 (464.77)	627	3,116.42 (419.48)	88.61

[a]Differences between sexes:
Preterm births: (altitude < 1,500): no significant (NS); (altitude 1,500–2,000): NS; (altitude > 2,000): NS.
At term births: (altitude < 1,500): $Z = 14.853$; $P < 0.001$; (altitude 1,500–2,000): $Z = 6.964$; $P < 0.001$; (altitude > 2,000): $Z = 4.024$; $P < 0.001$.
Preterm and at term birth and male and female are separated. Births to uniparous and primiparous mothers.

TABLE 2. Incidence of LBW by altitude[a]

	Male		Female		
Altitude (m)	*N*	LBW %	*N*	LBW %	Differences
Preterm births (<37 weeks)					
<1,500	202	55.8	166	56.5	−0.7
1,500–2,000	40	27.4	45	35.7	−8.3
>2,000	19	15.1	8	6.7	8.4
At term births (≥37 weeks)					
<1,500	323	3.9	369	4.8	−0.9
1,500–2,000	85	4.0	89	4.5	−0.5
>2,000	38	5.6	36	5.7	−0.1

[a]Differences between sexes:
Preterm: (altitude < 1,500): NS; (altitude 1,500–2,000): NS; (altitude > 2,000): $\chi^2 = 4.452$; d.f. = 1; $P = 0.035$.
At term: (altitude < 1,500): $\chi^2 = 7.039$; d.f. = 1; $P = 0.008$; (altitude 1,500–2,000): NS; (altitude > 2,000): NS.
Preterm and at term birth and male and female are separated. Births to uniparous and primiparous mothers.

study of possible changes caused by altitude in birth weight and prematurity.

METHODS

Data used in this study have been obtained from the vital statistics of the Provincial Directorate of Statistics and Census of Catamarca between 1994 and 2003. After processing the data, the final study sample was composed of 22,628 births, all belonging to primiparous and uniparous mothers.

In the original data, gestational age and birth weight were classified according to the WHO criteria (2012). For this study, weight at birth was reclassified into two new categories: LBW births (<2,500 g) and non LBW births (>2,500 g). The same procedure was used for gestational age; only births between 32 and 41 weeks were considered for inclusion from moderate preterm to post-term neonates: preterm births (<37 gestational weeks) and at term births (≥37 gestational weeks). Finally, altitude was classified into three new categories: less than 1,500 m, between 1,500 and 2,000 m and more than 2,000 m.

The variables did not present a normal distribution, so nonparametric statistical tests were used, such as Student's *T*, Mann-Whitney *U*, and Chi-square. This methodology allows the increase or decrease in the incidence of LBW and prematurity to be evaluated in relation to altitude, and to identify possible association with sex differences. Statistical analyses were performed with the software SPSS Statistics v. 17.0 (IBM Corp.; Somers, New York).

RESULTS

Differences between sexes

Male neonates showed a mean birth weight of 3,250.88 g with a standard deviation (SD) of 501.60 g while female neonates presented values of 3,157.90 g with SD of 463.67 g for the same variable. These findings are for all of the neonates. Significant differences were found between sexes ($Z = 15.651$; $P < 0.001$). When the same comparison was performed for preterm births, nonsignificant results were found (i.e., preterm males were not significantly different from preterm females), but when the weight of births at term was analyzed, male and female neonates were significantly different ($Z = 16.851$; $P < 0.001$). The weight of male newborns was 3,285.48 g with an SD of 466.40 while female newborns averaged 3,184.62 g with an SD of 433.25.

Significant differences were not found between sexes in the incidence of LBW in preterm births; however, the incidence of LBW in male and female neonates who were born at term was significantly different (incidence of LBW in at term males was 4.0% and 4.8% in at term females; $\chi^2 = 6.893$; $P = 0.009$).

Influence of altitude

Table 1 shows the results of comparing birth weight at different altitudes. This table registers the mean birth weight and SD by gestational age (preterm or at term birth) and altitude; likewise, the last column shows the mean difference of birth weight between sexes. Significant differences between altitudes were found only in at term births. Although no significant differences were found in preterm births, it is possible to observe that female neonates weighed more than male neonates in altitudes lower than 1,500 m and higher than 2,000 m. In contrast, in at term births, males weighed more than females at any altitude. Moreover, it is interesting to note that the differences between sexes decreased with increasing altitude. It is important to highlight that both male and female preterm neonates increased in weight with increasing altitude, but in at term male and female births weights decreased with increasing altitude.

Table 2 shows the analyses for LBW by altitude, separating preterm and at term births. As in the previous table, the last column shows the mean difference of birth

TABLE 3. Incidence of prematurity by altitude[a]

Altitude (m)	Male		Female		Differences
	N	Prematurity %	*N*	Prematurity %	
<1,500	362	4.2	294	3.7	0.5
1,500–2,000	146	6.4	126	5.9	0.5
>2,000	125	15.9	120	16.7	−0.5

[a]Differences between sexes:
(Altitude < 1,500): NS; (altitude 1,500–2,000): NS; (altitude > 2,000): NS.
Preterm and at term birth and male and female are separated. Births to uniparous and primiparous mothers.

weight between sexes. These results show significant differences in the incidence of LBW in preterm neonates who were born in altitudes higher than 1,500 m. The greatest rate of LBW is found in female neonates; nevertheless, at altitudes higher than 2,000 m there are male newborns that have high rates of LBW. In at term births, the differences between the sexes decrease as altitude increases.

The last analysis of the present study looks at prematurity at different altitudes. The results show a tendency for the incidence of prematurity to increase with altitude (Table 3).

DISCUSSION AND CONCLUSIONS

Differences between sexes

As described in some studies of the same region, the results show that mean male birth weight was significantly higher than mean female birth weight (Grandi et al., 2013; Lomaglio et al., 2005, 2007; Moreno et al., 2003), with a difference of 93 g that could rise to 100 g in at term births. Nonetheless, we have not found significant differences between the sexes when comparing preterm birth weight.

The results differed in conditions of prematurity because sexual differences in birth weight were nonexistent or lower than for at term births. Preterm births may act as an equalizer between sexes, with lower oscillations in the weight of the female sex. One hypothesis that explains this fact would be the "Feminine Eco-stability Hypothesis." This hypothesis holds that the female sex is less sensitive to external factors which modulate ontogenetic development; in contrast, the male sex would be more negatively affected by environmental factors (Lampl et al., 2010; Volkova, 1988). This phenomenon has been reported by authors in the fields of nutrition and auxology due to its importance when studying growth, development, and human health (Bernis, 2008; Marcoux, 2002; Marrodán et al., 1998; Mata Meneses et al., 2007).

Influence of altitude

The overall results show that at term mean male birth weight was significantly higher than female weight. These results were found in all of the analyses conducted by altitude (i.e., at term mean male birth weight was significantly higher than female weight in altitudes lower than 1,500 m, as well as in altitudes between 1,500 m and altitudes higher than 2,000). Despite this, differences between the sexes decreased with increasing altitude (Table 1). In contrast, although the differences were not significant, at birth preterm females weighed more than males at altitudes lower than 1,500 m and higher than 2,000 m.

An inverse relationship between at term mean birth weight and altitude was found in both sexes. The decrease in weight with increasing altitude is around 100 g for every 1,000 m, as Gwenn et al. (1997) present. These results agree with previous studies (Grandi et al., 2013; Lomaglio et al., 2005, 2007). Surprisingly, preterm neonates show the opposite trend because preterm birth weight increases with increasing altitude.

The results obtained in the analyses of the incidence of LBW show that at term female neonates have greater rates of incidence than males, although the difference between sexes is no greater than 1%. Differences in incidence of LBW decrease with increasing altitude. Looking at rates of LBW in preterm neonates who were born at altitudes higher than 2,000 m, the male sex had a higher rate of LBW than the female sex (8.4%), as shown in Table 2. Recent studies have tested whether restrictions in fetal growth caused by hypoxic situations during intrauterine development are evident from the 32nd gestational week, and these restrictions continue during the third trimester of gestation (Gonzales, 2012). Fetal biometry would not reflect differences caused by altitude between the 20th and 30th gestational weeks (Villamonte and Jerí, 2013; Villamonte et al., 2013).

Moreover, the results of the present study describe how the incidence of prematurity grows with increases in altitude starting with an incidence of 4.2% and 3.7% (males and female neonates, respectively) at altitudes lower than 1,500 m, and rising to 15.9% and 16.7% (male and female neonates, respectively) at altitudes higher than 2,000 m (Table 3). These results may be in concordance with those previously described. Prematurity could be part of an adaptation mechanism where hypoxia conditions favor preterm births as a way of preventing the influence of altitude on intrauterine development.

Finally, there is evidence of birth weight variation in different high altitude ecosystems depending on the ethnic origin of the populations (Moore et al., 2011). The WHO recommends individualized studies of the natal dynamics of each group as the specific socioeconomic, ecological, and ethnic characteristics of a population can influence fetal development patterns (WHO, 1995). The Province of Catamarca, like most Argentine populations, is of mixed origin with a high parental native component (Wang et al., 2008). Some of the results of this research are consistent with other studies conducted on Argentine populations with similar characteristics in that neonates have a lower weight than those observed in national references (Alvarez et al. 2002; Ocampo et al., 1993; San Pedro et al., 2001).

In conclusion, the results of this research show that under conditions of hypoxia (at altitudes higher than 2,000 m), sexual differences in birth weight, and in the incidence of LBW would be unappreciable or females could even have an advantage, thereby strengthening the "Feminine Eco-stability Hypothesis."

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