Adverse social determinants and risk for congenital anomalies

Mariela S. Pawluk, M.D.[a,d], Hebe Campaña, M.D.[a,d,e], Juan A. Gili, B.S.[a,c], Belén Comas, B.S.[a,c], Lucas G. Giménez, B.S.[a,c], María J. Villalba, B.S.[a,d], Sandra C. Scala, B.S.[a,d], Fernando A. Poletta, M.D.[a,b,c] and Jorge S. López Camelo, M.D.[a,b,c,d]

ABSTRACT

Introduction. Different studies have related familiar and regional adverse social conditions to perinatal outcome (neonatal mortality, low birth weight and prematurity); however, few studies have studied the effect of poverty on congenital anomalies.

Objective. To assess the hazard ratio of 25 congenital anomalies and adverse social determinants as per the socioeconomic level of families and regions.

Population and methods. Exploratory, case-control study using data from the Latin-American Collaborative Study of Congenital Malformations (*Estudio Colaborativo Latinoamericano de Malformaciones Congénitas*, ECLAMC). The sample consisted of 3786 live newborn infants with a single malformation and 13 344 controls selected among 546 129 births occurred in 39 hospitals from Argentina in the 1992-2001 period. Both direct and indirect (residence) risks (OR) were estimated, together with the interaction between the individual and residential socioeconomic levels for each of the 25 congenital anomalies.

Results. Cleft lip with/without cleft palate (OR= 1.43) and ventricular septal defect (OR= 1.38) showed a significantly higher risk in the lower socioeconomic level. Low socioeconomic levels were significantly associated with a higher frequency of parental sibship (blood relationship), native descent, maternal age younger than 19 years old, more than four pregnancies, a low number of antenatal care visits, and residence in deprived regions.

Conclusion. Cleft lip with/without cleft palate and ventricular septal defects were significantly associated with a lower socioeconomic level. Lack of family planning and antenatal care, and exposure to environmental or teratogenic agents may account for these findings.

Key words: *congenital anomalies, inequities, cleft lip, ventricular septal defect.*

a. Latin-American Collaborative Study of Congenital Malformations (ECLAMC) at Clinical Research and Medical Education Center, CONICET.
b. National Institute of Medical Population Genetics (INAGEMP), Brazil.
c. Clinical Research and Medical Education Center (CEMIC).
d. Multidisciplinary Institute of Cell Biology (IMBICE), CICPBA-CONICET.
e. Scientific Research Commission of Buenos Aires Province (CICPBA).

E-mail Address:
Jorge S. López Camelo, M.D.: jslc@eclamc.org

Conflict of interest:
None.

Received: 9-10-2013
Accepted: 1-2-2014

INTRODUCTION

Literature referring to the impact of adverse social conditions on specific congenital anomalies is scarce, except for publications related to neural tube defects which have been shown to have a strong relationship with poverty levels.[1] Poverty is a multidimensional concept and is usually measured using observable variables combined into a single index. In general, poverty indices measure the proportion of families within a defined geographical unit with a combination of circumstances indicating fewer resources or a great need of basic services, or both.[2]

Different studies have studied familiar and regional adverse social determinants in relation to perinatal outcome, such as neonatal mortality,[3] low birth weight[4] and prematurity,[5] but not in relation to congenital anomalies. Among the few reported causes on this issue, a low maternal socioeconomic level (SEL) has been associated with a higher risk of having a newborn infant with cleft lip,[6,9] neural tube defects,[7] and heart diseases.[8,9]

The etiology of poverty in relation to congenital anomalies is varied, indirect and non-specific, and includes environmental conditions (pollution, violence, stress, etc.), lack of antenatal care, adverse reproductive behavior,[10] difficulties to access health services during pregnancy,[11] lack of information on prevention during pregnancy, and exposure to tobacco and alcohol as part of their lifestyle.[12]

Our hypothesis was that adverse social conditions directly or indirectly might increase the hazard ratio of some specific congenital anomalies.

The aim of the present study is to evaluate the hazard ratio of 25 congenital anomalies and adverse social determinants as per the socioeconomic level of families and regions.

MATERIAL AND METHODS

This is an exploratory, case-control study, matched by time and place of birth using the data obtained from the Latin-American Collaborative Study of Congenital Malformations (*EstudioColaborativoLatinoamericano de MalformacionesCongénitas*, ECLAMC).[13]

Twenty-five congenital anomalies were studied. These had been selected because of their clinical and biological relevance and/or because of their impact on neonatal morbidity and mortality (*Table 1*), that were diagnosed before hospital discharge.

Development of the family socioeconomic level index

The family socioeconomic level (f-SEL) index was created using the factor analysis methodology based on different outcome measures directly or indirectly related to the socioeconomic level. The included outcome measures were maternal age, multigravidity, maternal and paternal education level, maternal and paternal employment modality, and health insurance system (no insurance or some insurance). All possible combinations among the studied outcome measures were evaluated, and the most

TABLE 1. *Number of cases and controls distributed by family socioeconomic level (f-SEL) as per the regional SEL (r-SEL) index*

	Middle and low r-SEL (UBNs <18%)					High r-SEL (UBNs ≥18%)					
f-SEL	**Q1-low**	**Q2**	**Q3**	**Q4**	**Q5-high**	**Q1-low**	**Q2**	**Q3**	**Q4**	**Q5-high**	**Total**
Anomaly	N	N	N	N	N	N	N	N	N	N	N
Omphalocele	7	3	6	7	7	4	2	2	4	2	44
Gastroschisis	6	9	11	21	27	6	3	6	6	2	97
Anencephaly	28	29	32	54	54	35	17	24	33	16	322
Spina bifida	33	31	29	52	72	24	16	7	26	18	308
Hydrocephalus	42	26	25	52	63	25	8	10	18	12	281
Cephalocele	11	5	7	11	13	8	10	0	10	5	80
Microtia	20	8	10	29	35	11	8	9	15	12	157
Cleft lip	60	31	54	76	83	62	41	39	46	27	519
Cleft palate	8	6	9	13	22	4	5	13	12	7	99
Esophageal atresia	6	5	6	14	17	3	3	6	4	2	66
Imperforate anus	12	3	5	20	26	9	8	8	10	5	106
Truncus arteriosus	15	26	17	26	39	5	7	5	16	9	165
ASD	5	4	3	6	12	4	1	1	6	4	46
VSD	41	28	35	49	69	29	18	23	23	12	327
Hypospadias	19	14	8	22	62	10	7	9	5	3	159
Postaxial polydactyly	73	37	37	80	108	26	20	34	30	21	466
Preaxial polydactyly	23	13	6	21	23	12	9	8	8	5	128
Terminal transverse limb reduction	7	7	3	6	17	5	5	3	3	1	57
Preaxial limb reduction	2	2	1	2	2	4	1	1	2	1	18
Diaphragmatic hernia	17	6	12	14	14	12	6	6	6	6	99
Pectoralis major agenesis	1	0	0	2	3	5	5	3	3	1	23
Ambiguous genitalia	1	0	3	2	6	1	0	1	3	1	18
Renal agenesis	2	2	0	4	8	0	1	0	0	0	17
Renal polycystosis	10	7	11	18	23	3	2	3	1	5	83
Hydronephrosis	9	7	8	17	42	2	1	2	5	8	101
Total anomalies	458	309	338	618	847	309	204	223	295	185	3786
Controls	1532	1109	1210	2201	2929	878	808	792	1228	657	13 344

ASD: atrial septal defect. VSD: ventricular septal defect.

consistent and reliable combination was selected using Cronbach's alpha coefficient. The best combination was the one that included maternal and paternal education level and paternal employment modality, with a Cronbach's alpha of 0.80. Maternal and paternal education levels were grouped into eight categories: 1. does not read, 2. able to read and write, 3. incomplete primary school, 4. complete primary school, 5. incomplete secondary school, 6. complete secondary school, 7. incomplete university, and 8. complete university. Paternal employment modality was defined using eight categories: 1. household chores, 2. unemployed, 3. unskilled worker, 4. skilled worker, 5. autonomous worker, 6. employee, 7. employer, 8. professional. The three outcome measures for each newborn infant family were added and the resulting score ranged between 3 and 24. Given that such score did not have a normal distribution, it was divided into quintiles, thus generating the definitive f-SEL, where the first quintile (Q1) corresponded to the lowest SEL and the fifth quintile (Q5) accounted for the highest SEL (*Table 1*).

Regional socioeconomic level index

Geographic regions were identified and a regional socioeconomic level (r-SEL) index was allocated to each region using census data from the unmet basic need (UBN) index obtained during the 2001 National Population, Households and Housing Census conducted by the National Statistics and Censuses Institute (*Instituto Nacional de Estadísticas y Censos de la Argentina*, INDEC).

An UBN value was assigned to each of the 25 Argentine municipalities/districts where the 39 maternity centers in the ECLAMC network are located.

In order to identify geographic regions with UBNs significantly higher than those observed for the total sample, an analysis was conducted using the StatScan software and the method developed by M. Kulldorff and N. Nagarwalla.[14]

Adverse social determinants

The following outcome measures were selected as possible independent risk factors and/or confounding factors associated with the poverty index and the congenital anomaly: paternal age, parental sibship, maternal and paternal native descent (defined as those cases that have a Latin American descent, as far as the family memory recalls, including American Indian and creole origin), maternal age, number of pregnancies, impaired fecundity (fertility treatments: YES/NO), number of months with parents living together before the mother got pregnant, a different father compared to the previous pregnancy, exposure to acute or chronic conditions during the first trimester of gestation, use of medications, and number of antenatal care visits during pregnancy.

Confounding factors were controlled using a statistical technique called propensity scores.[15] For this, the combination of outcome measures defined above was analyzed, obtaining the most adequate propensity score. Risk analysis for the 14 congenital anomalies due to exposure to a low socioeconomic level were adjusted stratifying the sample by the obtained propensity scores.

An ordinal regression was used to assess the outcome measures associated with the f-SEL: eachf-SEL quintile was considered a dependent outcome measure, and the adverse social determinants defined above were considered independent outcome measures.

The f-SEL dose/response effect on the congenital anomaly was assessed using the Woolf's test,[16] which analyzes the odds ratio(OR) trend with a chi-square with one degree of freedom.

The risk for a low f-SEL considering the level of development of the region was assessed using a multilevel logistic regression,[17] which recognizes data hierarchical organization. Associations were estimated calculating the OR and the corresponding 95% confidence intervals. The interactions between the f-SEL and the r-SEL were evaluated by grouping individuals into four categories: 1. mothers with low f-SEL (quintiles 1 and 2) who live in high r-SEL regions (OR_{11}), 2. mothers with a low f-SEL (quintiles 1 and 2) who live in low r-SEL regions (low f-SEL effect, OR_{12}), 3. mothers with a non-low f-SEL (quintiles 3, 4 and 5) who live in high r-SEL regions (residence region effect, OR_{21}), and 4. mothers with a non-low f-SEL (quintiles 3, 4 and 5) who live in low r-SEL regions (reference group, OR_{22}). Direct and indirect effects of a low f-SEL on the congenital anomaly were estimated.[18] Synergy was measured using Rothman's index (S).[19] Synergy is considered to be present when the risk of a mother with a low SEL who lives in a deprived region is higher than the individual sum of both risks:

$$S = \frac{OR_{11} - 1}{OR_{12} + OR_{21}}$$

Anomalies selected were those with an occurrence of at least 100 cases. The sample size was estimated for a risk factor with an exposure of at least 20% and that would allow to detect a minimum risk at least two times higher, with an 80% power (beta) and an alpha significance level of 5%.

RESULTS

The sample consisted of 3786 live newborn infants with a single congenital anomaly and 13 344 live newborn infants with no congenital anomalies (controls) selected out of a total of 546 129 births occurred in 39 hospitals from Argentina (*Annex I*) examined in the 1992-2001 period.

Four regions were identified; three had high levels of UBNs (between 19% and 21%) and corresponded to the following districts: 1) Bariloche and Futaleufú (south of Argentina); 2) Esteban Echeverría, Lomas de Zamora and Almirante Brown (Province of Buenos Aires); 3) Dr. Manuel Belgrano, San Miguel de Tucumán and La Rioja (northwest region of Argentina), and other region with a low level of UBNs (7.8%), the Autonomous City of Buenos Aires. The remaining 16 districts had a middle level of UBNs (13%). The definitive r-SEL was established by grouping the 25 municipalities/districts into the three resulting categories: 1. high r-SEL (districts with UBNs between 19% and 21%), 2. middle r-SEL (UBNs= 13%) and 3. low r-SEL (UBNs= 7.8%). *Table 1* shows the number of cases for each congenital anomaly by family socioeconomic level (quintiles) for two geographic regions according to the level of development: high and middle r-SEL and low r-SEL.

The f-SEL index showed that low socioeconomic levels were significantly associated with a higher frequency of parental sibship, native descent, maternal age younger than 19 years old, more than four pregnancies, low number of antenatal care visits, and residence in deprived regions (*Table 2*).

In relation to maternal conditions during the first trimester of gestation, a higher rate of scabies, AIDS, syphilis, use of quinine and abortion medications (Hipofisina, Cristerona, unspecified hormones) were observed in lower SELs.

The propensity score that showed the most adequate matching degree between cases and controls included maternal age, gravidity order,

TABLE 2. *Social adverse determinants by family socioeconomic level (f-SEL) in controls (percentage)*

Quintiles f-SEL		**Low Q1**	**Q2**	**Q3**	**Q4**	**High Q5**	**Trend**	
N		2410	1917	2002	3429	3586	b	p
Median		9	11	12	13	16		
		%	**%**	**%**	**%**	**%**		
f-SEL index	Low maternal education level	67	19	11	5	1	-3.16	-
	Low paternal education level	66	16	9	4	1	-3.00	-
	Low paternal employment modality	90	77	42	20	4	-3.61	-
Demographic characteristic	Paternal age ≤ 19 years old	7	9	10	7	4	-0.19	0.297
	Paternal age ≥ 39 years old	16	10	11	10	10	-0.02	0.839
	Sibship	0.4	0.4	0.25	0.4	0.2	-1.30	0.002
Ethnic descent	Native	95	95	94	90	71	-1.20	<0.001
Reproductive behavior	Maternal age ≤ 19 years old	23	25	24	21	13	-0.52	<0.001
	Maternal age ≥ 35 years old	15	10	11	9	11	0.09	0.241
	Primigravidity	19	26	27	29	37	0.00	-
	Multigravidity ≥ 4	49	36	36	30	21	-0.38	<0.001
	Impaired fecundity	6	8	10	12	10	0.05	0.545
	Period living together < 1 year	4	2	4	3	3	0.24	0.070
	Different father	14	13	13	13	13	-0.10	0.185
Antenatal care	Antenatal care ≤ 5	47	41	36	31	22	-0.24	<0.001
Exposure during the first trimester	Acute conditions	23	25	29	29	31	-0.05	0.358
	Chronic conditions	11	11	13	13	14	-0.09	0.202
	Use of medications	37	40	45	47	54	0.21	<0.001
Regional development level (r-SEL)	Low	36	42	40	36	18	-0.31	<0.001
	Middle	58	48	45	46	51	-	-
	High	5	10	15	18	31	0.40	<0.00

number of antenatal care visits, and native descent.

Significant differences were observed between cases and controls for a low f-SEL (Q1), maternal age ≥35, gravidity order ≥4, low number of antenatal care visits (≤5), higher rate of acute conditions during the first trimester of gestation, chronic conditions, and use of medications during the first trimester of gestation *(Table 3).*

Cleft lip with/without cleft palate and ventricular septal defect showed a dose/response effect in relation to the f-SEL. For both defects, the risk of having an anomaly was statistically significant in a lower SEL. When both direct and indirect f-SEL effects were analyzed, both defects showed a significant direct effect, but only cleft lip with/without cleft palate had a significant risk for the indirect effect. Out of the total effect of a f-SEL risk on cleft lip (OR= 1.43), an OR= 1.42 corresponded to a direct effect, while an OR= 1.01 corresponded to an indirect effect. Only cleft lip with/without cleft palate showed a significant OR in deprived regions, independent from the f-SEL. That is to say, out of the total effect of the f-SEL on cleft lip, 3.4% may be due to the conditions ofthe place of maternal residence *(Table 4).* Likewise, both anomalies showed increased and significant ORs among mothers with a low f-SEL who live in regions with a high r-SEL (interaction effect: cleft lip S= 1.37, ventricular septal defect S= 6.21) *(Table 5).*

DISCUSSION

Lack of family planning and poor antenatal care were the most relevant characteristics of mothers with a low f-SEL based on the outcome measures associated with this risk group: high number of pregnancies, few antenatal care visits, parental age (≤19 years old or ≥35 years old), higher frequency of urinary tract infections, and higher use of abortion medications. In Argentina, approximately 50% of pregnancies are not planned,[20] and this study confirms the risks of such reproductive behavior.

A higher risk for cleft lip with/without cleft palate and ventricular septal defects was observed

TABLE 3. *Distribution of adverse social determinants by cases and controls. Propensity scores for adjusted social determinants*

		Cases		Controls	
Outcome measures		**N**	**%**	**N**	**%**
Family SEL index	Q1 - low SEL	954	21	2410	18
	Q2	610	13	1917	14
	Q3	681	15	2002	15
	Q4	1072	24	3429	26
	Q5 - high SEL	1228	27	3586	27
Demographic characteristics	Paternal age ≤19 years old	332	7	953	7
	Paternal age ≥39 years old	754	16	1484	11
	Sibship	26	0.5	50	0.4
Ethnic descent	Native	4223	87	11 519	87
Reproductive behavior	Maternal age ≤19 years old	920	18	2703	20
	Maternal age ≥35 years old	963	19	1515	11
	Primigravidity	1339	26	3794	28
	Multigravida≥4	1920	38	4375	33
	Impaired fecundity	395	8	1268	10
	Period living together <1 year	168	5	300	3
	Different father	473	15	1141	13
Antenatal care	Antenatal care visits ≤5	1521	42	3065	33
Exposure during the first trimester	Acute conditions	1711	35	3717	28
	Chronic conditions	840	17	1693	13
	Use of medications	2587	53	6116	46
Regional development level (r-SEL)	Low	1745	34	4363	33
	Middle	2353	46	6643	50
	High	989	19	2338	17
Propensity scores (X ± SD)	Maternal age	25.7 ± 4.5		25.6 ± 5.4	
	Gravidity order	3.1 ± 2.0		3.0 ± 1.9	
	Antenatal care visits	5.8 ± 2.5		5.9 ± 2.4	
	Native descent	89.4%		88.9%	

among mothers with a low f-SEL who live in high r-SEL regions, regardless maternal age, number of pregnancies, number of antenatal care visits, and native descent. This last observation is greatly relevant given that ventricular septal defect has been related to a higher risk of native descent,[21] gravidity order,[22] and few antenatal care visits.[23] Similarly, the effect of maternal age has been reported in connection with this defect.[24]

After adjusting for the propensity score, cases and controls presented, in average, the same maternal age, gravidity order, number of

TABLE 4. *Risk for 14 congenital anomalies by f-SEL and r-SEL*

	Family socioeconomic level							SEL effect		
	Ql	**Q2**	**Q3**	**Q4**	**Q5**	**Tendency**		**Direct**	**Indirect**	
Anomaly	OR	OR	OR	OR	OR	OR	p	OR	OR	%
Gastroschisis	0.86	0.79	0.97	1.00	1.00	0.93	0.390	0.84	0.99	5.4
Anencephaly	1.20	1.42	1.40	1.11	1.00	1.05	0.346	1.20	1.00	0.1
Spina bifida	0.79	0.94	0.84	0.87	1.00	0.96	0.517	0.79	0.99	3.9
Hydrocephalus	1.36	0.81	0.73	0.79	1.00	1.06	0.271	1.37	0.98	0.0
Microtia	1.09	0.71	0.89	1.18	1.00	0.97	0.736	1.09	1.00	5.7
Cleft lip	1.43*	1.16	1.36	1.09	1.00	1.08	0.067	1.42*	1.03*	3.4
Cleft palate	0.44	0.78	1.85	1.14	1.00	0.89	0.256	0.42	1.01	0.0
Imperforate anus	0.64	0.84	0.80	0.93	1.00	0.92	0.357	0.63	1.01	0.0
Truncus arteriosus	0.85	2.08	1.45	1.38	1.00	1.05	0.512	0.86	0.99	8.1
Ventricular septal defect	1.39*	1.19	1.42	0.95	1.00	1.11	0.045	1.38*	1.01	2.3
Hypospadias	0.96	0.86	0.58	0.97	1.00	1.00	0.983	0.96	0.99	12.1
Postaxial polydactyly	1.08	0.63	0.95	0.80	1.00	1.00	0.851	1.08	1.00	0.1
Preaxialpolydactyly	1.65	1.67	0.89	1.11	1.00	1.14	0.095	1.66	0.99	0.0
Hydronephrosis	0.45	0.43	0.40	0.52	1.00	0.79	0.021	0.46	0.98	2.4

Low f-SEL: Q1; high f-SEL: Q5 (reference group).
* $p < 0.01$.

TABLE 5. *Risk for 14 congenital anomalies by interaction between a low f-SEL + a high r-SEL and each individually*

Effects	**Low f-SEL + high r-SEL**		**High r-SEL**		**Low f-SEL**		
Anomaly	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**S**
Gastroschisis	1.10	0.42-2.83	0.64	0.34-1.19	0.53	0.21-1.34	-0.120
Anencephaly	1.27	0.73-2.24	0.93	0.65-1.34	0.77	0.46-1.28	-0.900
Spina bifida	0.72	0.36-1.45	0.76	0.52-1.10	0.83	0.52-1.35	0.683
Hydrocephalus	1.58	0.92-2.70	0.50	0.32-0.79	1.18	0.75-1.83	-1.813
Microtia	1.06	0.41-2.74	1.21	0.73-1.99	1.25	0.65-2.40	0.130
Cleft lip	1.74	1.14-2.64	1.32	1.01-1.73	1.22	0.85-1.76	1.370
Cleft palate	0.31	0.42-2.32	1.69	0.96-2.96	0.62	0.21-34.99	-2.226
Imperforate anus	0.84	0.25-2.78	1.27	0.73-2.20	0.81	0.33-1.94	-2.000
Truncus arteriosus	0.55	0.19-1.53	0.73	0.44-1.20	0.62	0.30-1.27	0.692
VSD	1.87	1.14-3.05	1.06	0.76-1.49	1.08	0.69-1.70	6.214
Hypospadias	1.29	0.54-3.05	0.74	0.44-1.26	1.04	0.54-2.00	-1.318
Postaxial polydactyly	1.02	0.59-1.77	1.07	0.79-1.44	1.37	0.95-1.97	0.045
Preaxialpolydactyly	1.26	0.55-2.88	0.97	0.57-1.66	1.39	0.76-2.55	0.722
Hydronephrosis	0.30	0.04-2.20	0.57	0.28-1.13	0.78	0.33-1.86	1.077

r-SEL: high UBNs (UBNs >19%).
Low r-SEL: Q1.
VSD: ventricular septal defect.

antenatal care visits and rate of native descent; therefore, these outcome measures would not interfere with the interpretation of results. However, a residual effect cannot be ruled out.

There have been reports in the literature indicating an association between a low f-SEL and cleft lip with/without cleft palate[25,10]with a moderate risk 1.5-1.7 times higher, and within the range observed in this study.

When the outcome measures that make up the f-SEL are analyzed independently, only paternal education level showed an increased risk. The paternal employment modality was reported in the literature as a risk factor for cleft lip[26] given that they are often farmers and painters who are exposed to agrochemicals and solvents, which may result in an indirect exposure for mothers. Other likely explanation may be maternal lifestyle which entails a higher degree of exposure to alcohol and tobacco[27,28] or environmental contaminants[29] during pregnancy because they live in regions subjected to poor regulation regarding toxic agent management and safety.

Heart diseases are characterized by a low heritability, an environmental etiology and for occurring at an early stage during embryogenesis. A higher risk was reported for different types of congenital heart diseases[30] among lower social strata.[31,32] Mothers of newborn infants with a ventricular septal defect have a lower socioeconomic level and a higher percentage of tobacco and alcohol use.[33]

When analyzed independently, none of the outcome measures that make up the f-SEL index showed an increased risk for ventricular septal defect.

Most congenital anomalies have a multifactoral etiology, and the greatest vulnerability to environmental agents takes place over the first days or months of gestation while women generally are not aware they are pregnant. This implies that the risk observed in lower socioeconomic levels may be the direct result of lack of parental information during antenatal care or an indirect effect of the region of residence (lack of access to hospitals with adequate technology to detect and diagnose diseases, regions of greater violence, pollution, etc.) or the maternal lifestyle (higher degree of exposure to alcohol, tobacco, other drugs, etc.), which have not been assessed in this study but are obviously closely related to the poverty index.

Strengths

The relevance and innovation of this study lie on the number of assessed congenital anomalies, the large sample size, the evaluation of the SEL effect using two hierarchy levels, and the implementation of a comprehensive methodological approach.

The study was conducted as per the operational rules of the ECLAMC, a South American hospital database. In addition to collecting information on more than 50 risk factors, the diagnostic definition of congenital anomalies was performed by trained professionals.

The methodology employed was the most appropriate so as to respect the hierarchal structure of data at the analysis level (familiar and regional) and to control confounding factors using the propensity score technique, therefore ensuring that the distribution of confounding outcome measures was equal between cases and controls.

The reason for selecting the study period was that, in Argentina, the 1990s were characterized by financial and social instability leading to the 2001 economic crisis, an adequate period for this type of study.

Weaknesses

It is not possible to rule out possible information and confounding biases, which are inherent to case-controls studies. The definition of social heterogeneity regions implies an ecological fallacy bias, which means inferring individual risks from grouped data. That is to say, middle class families living in poor regions are classified as poor families.

In spite of this, a wrong classification would make no difference (for cases and controls). Other possible information bias is the use of the hospital where the birth occurred as an approximate indicator of the place of residence; however, deviation in risk estimations may occur when including severe cases referred to hospitals to higher complexity. Certain confounding factors were not measured, such as smoking, alcohol consumption or other factors related to the lifestyle during pregnancy, so they could have a residual effect on risk estimations.

CONCLUSION

Out of 14 analyzed congenital anomalies, cleft lip with/without cleft palate and ventricular septal defect were significantly associated with the two poverty levels analyzed after adjusting

the values for maternal age, gravidity order, number of antenatal visits and native descent. There was a higher risk for both anomalies among low socioeconomic level families who live in high r-SEL regions.

It has been observed that mothers with a low socioeconomic level and who live in less developed regions (high r-SEL) are exposed to risk factors related to pregnancy planning, a higher frequency of chronic and infectious diseases during pregnancy, which are probably not treated, and exposure to teratogenic agents.

Additional studies are necessary to analyze the risk factors herein described according to a causative hypothesis so as to better and more specifically understand the effects of adverse social determinants on congenital anomalies.■

REFERENCES

1. Little J, Elwood H. Socio-economic status and occupation. En: Elwood JM, Little J, Elwood H, eds. Epidemiology and control of neural tube defects. Oxford: Oxford University Press; 1992.
2. Bartley M, Blane D. Socioeconomic deprivation in Britain. Appropriateness of deprivation indices must be ensured. *BMJ* 1994;309(6967):1479.
3. Singh GK, Kogan MD. Widening socioeconomic disparities in us childhood mortality, 1969-2000. *Am J Public Health* 2007;97:1658-65.
4. Buka S, Brennan R, Rich-Edwards J, Raudenbush S, et ál. Neighborhood support and the birth weight of urban infants. *Am J Epidemiol* 2003;157:1-8.
5. O'Campo P, Burke J, Culhane J, Elo I, et ál. Neighborhood Deprivation and Preterm Birth among Non-Hispanic Black and White Women in Eight Geographic Areas in the United State. *Am J Epidemiol* 2008;167:155-63.
6. Clark J, Mossey P, Sharp L, Little J. Socioeconomic status and orofacial clefts in Scotland, 1989 to 1998. *Cleft Palate-Craniofac J* 2003;40:481-5.
7. Grewal J, Carmichael SL, Song J, Shaw GM. Neural tube defects: an analysis of neighbourhood- and individual-level socio-economic characteristics. *Paediatr Perinat Epidemiol* 2009;23:116-24.
8. Vrijheid M, Dolk H, Stone D, Abramsky L, et ál. Socioeconomic inequalities in risk of congenital anomaly. *Arch Dis Child* 2000;82:349-52.
9. Carmichael SL, Ma C, Shaw GM. Socioeconomic measures, orofacial clefts, and conotruncal heart defects in California. *Birth Defects Res A Clin Mol Teratol* 2009;85:850-7.
10. Departamento de Salud Reproductiva e Investigación de la Organización Mundial de la Salud (OMS/RHR) y Johns Hopkins Bloomberg School of Public Health/ Center for Communication Programs (CCP), Project INFO. Planificación familiar: Un manual mundial para proveedores. Baltimore y Ginebra: CCP y OMS; 2007.
11. Wehby GL, Murray JC, Castilla EE, López-Camelo JS, et ál. Prenatal care demand and its effects on birth outcomes by birth defect status in Argentina. *Econ Hum Biol* 2009;7:84-95.
12. Wehby GL, Prater K, McCarthy AM, Castilla EE, et ál. The impact of maternal smoking during pregnancy on early child neurodevelopment. *J Hum Cap* 2011;5:207-54.
13. Castilla EE, Orioli IM. ECLAMC: The Latin-American collaborative study of congenital malformations. *Community Genetics* 2004;7:76-94.
14. Kulldorff M, Nagarwalla N. Spatial disease clusters: Detection and inference. *Stat Med* 1994;14:799-810.
15. Imbens GW. The role of the propensity score in estimating dose-response functions. *Biometrika* 2000;87(3):706-10.
16. Woolf B. On estimating the relation between blood group disease. *Ann Hum Genet* 1995;19:251-3.
17. Khan H, Shaw E. Multilevel logistic regression analysis applied to binary contraceptive prevalence data. *J Data Sc* 2011. Págs.93-110.
18. Erikson R, Goldthorpe JH, Jackson M, Yaish M, Cox DR. On class differentials in educational attainment. *Proceed Nat Acad Sc* 2005;102:9730-3.
19. Rothman KJ. Synergy and antagonism in cause-effect relationships. *Am J Epidemiol* 1974;99:385-8.
20. Gadow EC, Paz JE, López-Camelo JS, Dutra MG, et ál. Unintended pregnancies in women delivering at 18 South American hospitals. NFP-ECLAMC Group. Latin American Collaborative Study of Congenital Malformations. *Human Reprod* 1998;13(7):1991-5.
21. Mossey PA, Little J. Epidemiology of oral clefts: an international perspective. En: Cleft Lip & Palate. New York: Oxford University Press; 2002. Págs.127-58.
22. Gili JA, Poletta FA, Campaña H, Comas B, et ál. Is gravidity 4+ a risk factor for oral clefts? A case-control study in eight South American countries using structural equation modeling. *Cleft Palate-Craniofacial J* 2013;50(5);591-6.
23. Nyarko KA, López-Camelo J, Castilla EE, Wehby GL. Does the relationship between prenatal care and birth weight vary by oral clefts? Evidence using South American and United States samples. *J Pediatr* 2013;162(1):42-9.
24. Reefhuis J, Honein MA. Maternal age and non-chromosomal birth defects, Atlanta - 1968-2000: Teenager or thirty-something, who is at risk? *Birth Defects Res A Clin Mol Teratol* 2004;70:572-9.
25. Yang J, Carmichael S, Canfield M, Song J, et ál. Socioeconomic status in relation to selected birth defects in a large multicentered US case - control study. *Am J Epidemiol* 2008;167:145-54.
26. Qi L, Liu J, Zhang Y, Wang J, et ál. Risk factors for non-syndromic oral clefts: a matched case-control study in Hubei Province, China. *Oral Dis* 2013.
27. Munger RG, Romitti PA, Daack-Hirsch S, Burns TL, et ál. Maternal alcohol use and risk of orofacial cleft birth defects. *Teratology* 1996;54(1):27-33.
28. Lieff S, Olshan AF, Werler M, Strauss RP, et ál. Maternal cigarette smoking during pregnancy and risk of oral clefts in newborns. *Am J Epidemiol* 1999;150:683-94.
29. Croen LA, Shaw GM, Sanbonmatsu L, Selvin S, Buffler PA. Maternal residential proximity to hazardous waste sites and risk for selected congenital malformations. *Epidemiology* 1997;8(4):347-54.
30. Kučienė R, Dulskienė V. Maternal socioeconomic and lifestyle factors during pregnancy and the risk of congenital heart defects. *Medicina (Kaunas)* 2009;45:904-9.
31. Olshan F, Baird PA, Lo KH. Socioeconomic status and the risk of birth defects. *Am J Epidemiol* 1991;134:778-9.
32. Correa-Villaseñor A, McCarter R, Downing J, Ferencz C. White-black differences in cardiovascular malformations in infancy and socioeconomic factors. The Baltimore-Washington Infant Study Group. *Am J Epidemiol* 1991;134:393-402.
33. Vereczkey A, Kósa Z, Csáky-Szunyogh M, Urbán R, Czeizel AE. Ventricular septal defects in function of maternal sociodemographic aspects. *Cent Eur J Med* 2012;7(4):511-22.

Annex I

Thirty-nine hospitals from Argentina participating in the Latin-American Collaborative Study of Congenital Malformations and level of unmet basic needs, 1992-2001 period

Name of the Hospital	District/municipality/school district	Province	% of UBN
Suizo-Argentino	District I	CABA (Autonomous City of Buenos Aires)	7.1
Fernández	District I	CABA (Autonomous City of Buenos Aires)	7.1
Sardá	District VI	CABA (Autonomous City of Buenos Aires)	11.4
Italiano	District VI	CABA (Autonomous City of Buenos Aires)	11.4
Santojanni	District XX	CABA (Autonomous City of Buenos Aires)	7.9
Materno Infantil "Ana Goitia"	Avellaneda	Bs. As.	10.7
Lucio Meléndez	Almirante Brown	Bs. As.	19.3
Ricardo Finochietto	Almirante Brown	Bs. As.	19.3
Sofía de Santamarina	Esteban Echeverría	Bs. As.	20.4
Privado de Comunidad	General Pueyrredón	Bs. As.	10.9
Interzonal Materno Infantil	General Pueyrredón	Bs. As.	10.9
Del Niño y de la Madre	General Pueyrredón	Bs. As.	10.9
Eva Perón	General San Martín	Bs. As.	13.0
Italiano	La Plata	Bs. As.	12.8
Narciso López	Lanús	Bs. As.	11.7
Luisa de Gandulfo	Lomas de Zamora	Bs. As.	17.2
Materno Provincial	Capital City	Córdoba	12.2
Ntra. Sra. de la Misericordia	Capital City	Córdoba	12.2
Tránsito Cáceres de Allende	Capital City	Córdoba	12.2
Concepción	Capital City	Córdoba	12.2
Materno Neonatal	Capital City	Córdoba	12.2
Andrés Ísola	Viedma	Chubut	13.8
Zonal de Esquel	Futaleufú	Chubut	21.6
Centenario	Gualeguaychú	Entre Ríos	12.7
Mat. Inf. San Roque	Paraná	Entre Ríos	11.3
Pablo Soria	Dr. Manuel Belgrano	Jujuy	20.9
San Roque	Dr. Manuel Belgrano	Jujuy	20.9
Regional Dr. Vera Barros	Capital City	La Rioja	17.6
Fleming	Capital City	Mendoza	8.3
Italiano	Guaymallén	Mendoza	13.5
Regional Alfredo Perrupato	San Martín	Mendoza	16.2
Madariaga	Capital City	Misiones	20.8
Área El Bolsón	Bariloche	Río Negro	20.3
Complejo Sanitario San Luis	Capital City	San Luis	13.2
Rivadavia	Capital City	San Luis	13.2
Martin	Rosario	Santa Fe	14.7
Roque Sáenz Peña	Rosario	Santa Fe	14.7
Ntra. Sra. de las Mercedes	Capital City	Tucumán	17.5
Regional de Ushuaia	Ushuaia	T. del Fuego	17.6

UBNs: unmet basic needs.