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Original article

Prenatal risk factors for selected congenital anomalies development: a case-control pilot study in postpartum women from Argentina

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Abstract

Introduction: Congenital anomalies (CAs) are abnormalities in intrauterine development and are one of the main causes of burden disease, especially in low- and middle-income countries. Many environmental and maternal risk factors could lead to these pathologies. The aim of this study was to identify different types of CAs, determine their frequency and identify their possible association with maternal sociodemographic and lifestyle risk factors among patients from Santa Fe Province, Argentina.

Material and methods: An observational cases and control pilot study was conducted in 2018 and 2019 on 280 postpartum mothers of newborn babies with any CA (cases, n = 64) and without a CA (controls, n = 216) attending public hospitals. A face-to-face questionnaire was completed, and clinical histories were required to obtain information on maternal sociodemographic factors, gynecological events, health state, lifestyle habits and child diagnoses.

Results: Polymalphormations and neural tube defects were the most frequent CA observed. Differences between cases and control groups, as well as between places of residence, were given by gestational age, type of delivery and newborn birth weight, all of which are preventable variables. A slight association between maternal diabetes and the occurrence of cases was found.

Discussion: Maternal place of origin is a factor of inequity in terms of gynecology variables which describes a deeper background in sanitary reality from Santa Fe Province that would have a large impact on future adults born preterm. The results highlight the necessity of generating both sanitary tools

for maternal-child health policies and environmental evaluations, which remains a permanent challenge of the Argentine public health system.

Keywords

Birth defects, perinatal medicine, lifestyle, public health, risk factors, mother-child relationship.

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Introduction

Congenital anomalies (CAs), also known as birth defects (BDs), are structural or functional abnormalities that develop during uterine life and can be identified before, during or after delivery [1]. They represent one of the main causes of the global burden of disease and contribute to life-long disability, especially in low- and middle-income countries [1]. Low socioeconomic level is a risk factor for CAs due to different situations such as malnutrition, exposure to teratogenic agents and young maternal age. Moreover, it is associated with lower detection of CAs due to a lack of prenatal diagnosis or postnatal detection in lower complexity hospitals [2].

Approximately 6% of babies worldwide are born with a BD, and every year 303,000 newborns die before reaching 4 weeks of age due to these pathologies and associated complications [1]. In 2018, the infant mortality rate in children less than 1 year old in Argentina was 8.8 per 1,000 live-born infants, and the perinatal mortality rate was 11.3 per 1,000 live-born infants. CAs were responsible for 28% of all infant deaths during this period [3]. The National Network for Congenital Anomalies (RENAC) [4] in Argentina covered 38% of the deliveries registered in the whole country and reported a total CA prevalence of 1.68%, according to its most recent report in 2019. In Santa Fe Province, they covered 29% of deliveries and found a prevalence of 1.53% [4]. Prenatal diagnosis facilitates timely referrals of pregnant women to an adequate level of complexity hospital. Further, it enables the early planning of medical or surgical treatment to reduce the risk of early neonatal death [5].

The course of gestation originates in the periconception period, which has a time frame of 5 to 6 months around conception [6]. This time is critical since the developing gametes, embryo and placenta are susceptible to changes due to maternal conditions and environmental factors, like nutritional state and lifestyle factors [7]. An estimated 25% of CAs could be due to genetic factors [8]. Meanwhile, 25% could be multifactorial (a combination of environmental and genetic factors); 47% could be due to unknown factors, like socioeconomic and demographic features (age, educational level) [9], maternal health and lifestyle habits; and just 3% arise in the aftermath of acute infections and physical or chemical agents [10].

Environmental pollutants could cause CAs by periconceptional teratogenic actions [11]. Maternal exposure to certain contaminants, including pesticides, as well as certain medications, alcohol, tobacco and radiation during pregnancy, may increase the risk for birth defects. The health implications of chronic exposure for pregnant women and their children are an ongoing concern and inquiry for scientists and regulators [12]. In this sense, epidemiological studies suggest an association between proximity to agricultural lands and a wide range of associated adverse health outcomes [13-15].

The main economic activity of Argentina is the extensive production of grains and oilseeds (mainly soybean and corn) [16]. Most of this production occurs in the Pampas region, one of the largest flatlands in the world, where Santa Fe Province is located. This model of agricultural production is characterized by an increase in the use of pesticides [17], both in the farming belt of Santa Fe City [18] and in the extensive agricultural area of Santa Fe Province [19]. In the first case, the most frequently used pesticides are cypermethrin, λ-cyhalothrin, chlorpyrifos, dimethoate, methamidophos and imidacloprid, among others [18]. Meanwhile, in extensive agriculture, insecticides like fipronil and endosulfan; herbicides such as atrazine, ammonium glufosinate and dicamba; and fungicides, including carbendazim and picoxystrobin, were mentioned. Moreover, of these, 46.875% were class IV (probably without toxicological hazard), 9.375%

were class III (slightly toxic), 34.375% were class II (moderately toxic), 6.25% were class Ib (highly toxic), and 3.125% were class Ia (extremely toxic) [19].

On the other hand, non-communicable chronic diseases (NCCDs), such as pregestational diabetes, are associated with a markedly increased risk for many specific birth defects, like congenital heart diseases (CHDs) and CAs of the kidney and the urinary tract [20, 21].

A diet rich in vegetable oil and fish is associated with improved embryonic development [22]. Maternal diet during gestation is an important target for intervention, and it may influence the likelihood of developing CHDs [23]. Furthermore, a lack of folic acid supplement intake during this period is related to CAs and even impaired embryonic growth [24]. In this sense, in Argentina, Law 25630 for the prevention of anemias and neural tube defects (NTDs) [25] demands the incorporation of folic acid into wheat flour sold for consumption in the national market.

Alcohol intake and smoking during pregnancy can produce fetal abnormalities and disorders in prenatally exposed children [26]. The dual risk of prenatal alcohol and tobacco exposure is particularly concerning because of the synergistic effect of the concurrent use of both substances on pregnancy outcomes [27]. Furthermore, some acute maternal infections during the gestation period are also significant risk factors for birth defects [28]. Finally, in many instances, mothers of affected babies have no family history of CAs or risk factors. Therefore, it is thought that genetics, the environment, or some combination of both, play a role in the development of CAs.

Based on the above discussion and the lack of information about this topic in Santa Fe Province, Argentina, the aim of this work was to identify different types of CAs and determine their frequencies and other neonatal variables. Moreover, this study aimed to evaluate maternal sociodemographic, health and lifestyle risk factors and their possible associations with the prevalence of CA in a pilot study to generate valuable data and sanitary tools for maternal-child health policies.

Materials and methods

Study area and period

The present study was conducted in Santa Fe Province, in the centre of Argentina, in 2018 and 2019. This province belongs to the so-called Pampa Húmeda Region, which is an important area of agricultural activities. The biggest cities of the province are Rosario and Santa Fe, both of which are surrounded by ports, industrial areas and horticultural lands (the so-called Cinturón Hortícola Santafesino). La Capital Department, where Santa Fe City is located, is a productive zone of approximately 3,100 ha, 1,200 ha of which are cultivated in intensive form and contribute 1.2% to the national market of products. Historically, horticulture has been an agricultural activity of great economic importance for the region [29].

Design of the study

An analytical observational study of cases and controls was designed to evaluate the exposure status of associated risk factors for CAs in newborns at 9 public hospitals in Santa Fe Province. Participants were divided into 2 groups: mothers of newborn babies with any CA (cases, n = 64) and those without a CA (controls, n = 216). The sample size was calculated using a case-control ratio of 1:4. That is, for each mother of a case, we aimed to include 4 mothers of control babies. For all mothers, inclusion criteria were having a baby under 45 days old and being willing to participate in the survey and sign the informed consent. Inclusion criteria for mothers of cases were the delivery of a baby with any major CA (except those for which cause was already determined, like chromosomic ones). For mothers of control babies, the inclusion criteria were to have lived out their pregnancy in the same department as the mother of a case and have delivered a baby unaffected by any CAs ± 15 days since the delivery of the case.

Data collection and variables analyzed

Newborns' births at the collaborative public hospitals during the study period were evaluated for the presence of CAs by pediatricians and a neonatologist. Mothers were contacted during their stay after delivery or during the medical treatments of their children, helped by collaborative sanitary staff from public hospitals. During recruitment, a face-to-face questionnaire was completed to obtain various types of information from participants: socio-demographical factors (age, educational level, place of residence and maternal occupation),

gynecological events (history of miscarriage, prenatal care, number of previous deeds and gestational age), maternal health status (acute infection during pregnancy or NCCDs – such as diabetes mellitus, hypertension and thyroid disease), and lifestyle habits (fruit and vegetable intake, alcohol and drug use, medications, iron-folic supplementation, antibiotics, physical activity, active or passive smoking status and exposure to domestic pesticides). Maternal age was categorized by lustrums within the fertile age of women. Educational level was recorded from incomplete primary school to completed university studies and dichotomized for the analysis by incomplete high school or less or complete high school or more due to the compulsory schooling until high school. Regarding place of residence, La Capital and Rosario Departments (LC&R) were considered together due to representing almost half of the population surveyed; all other participants were categorized as being from the rest of the province (RP). Gestational age and newborn weight were dichotomized by term (≥ 37 weeks) and preterm newborns (< 37 weeks) and by < 2,500 g or ≥ 2,500 g, respectively.

The questionnaire was designed by the research team, validated by experts and adjusted based on a pilot study (data not published). Standardized training was provided to all researchers to ensure the quality of the interview. Other variables, such as type of delivery – vaginal or caesarean surgery (CS) –, sex and birth weight of the neonate, and the presence of acute infection during pregnancy, were taken from the women's clinical histories (CHs), which were available at the time of recruitment. Because some of the CHs were unavailable or incomplete, the variable "acute infection during pregnancy" was considered negative when there was information for both infections (toxoplasmosis and syphilis), and they were negative; the variable was considered positive when there was information for at least 1 of those infections as positive. The type and description of CAs in newborns were taken from each child's CHs and classified by the system affected and by newborn diagnoses (control, isolate CA, multiple CA and syndrome) [4].

Ethical issues

The study was conducted in accordance with the Declaration of Helsinki guidelines for the protection of human subjects [30]. The study protocol was approved by the Research Ethics Committee of Santa Fe Province on 30 November 2017 and the Advisory Committee on Research Ethics and Security of the Faculty of Biochemistry and Biological Science of the University of the Littoral (Acta 03/16) on 17 November 2017. The aim of the study was explained to each participant, and a written informed consent was obtained from each of them.

Statistical analysis

Data were analyzed using SPSS® software. Categorical variables were described according to their frequency and expressed as percentages or dichotomized to compare different groups using odds ratios and Pearson's Chi^2 test. Continuous variables statistics were summarized by means and standard error and analyzed by the Mann-Whitney U test. Statistical significance was considered at $p = 0.01$-0.05 and highly significant at $p < 0.01$. The grouping variables were newborn diagnosis (case/control) and maternal place of residence (LC&R/RP). The covariables were maternal age, educational level, gynecological events, health status and lifestyle habits.

Results

Regarding the newborn participants, the sample consisted of 65 babies with CAs (including a pair of twins) and 219 without CAs (including 3 pairs of twins). Eight types of CAs were identified by organ system: craniofacial anomalies, limb defects, gastrointestinal defects, urogenital defects, NTDs, CHDs, abdominal wall defects and polymalphormations. Of all newborns, 48.24% (137/284) were male and 48.94% (139/284) were female, while the sex of 2.82% (8/284) was not present in their medical records. Regarding the clinical RENAC scores, about 73.85% (48/65) of the CAs identified were isolated, whereas 23.08% (15/65) were multiple and 3.08% (2/65) were syndromes. The prevalence of CAs in Santa Fe was 15.33 per 1,000 births in 2018 and 15.6 per 1,000 births in 2019 [4]. In 2018 and 2019, RENAC notified 237 and 280 cases of CAs in Santa Fe Province, respectively. The present study included 44 and 21 cases, respectively, representing 18.57% (44/237) and 7.5% (21/280) of the information already described by RENAC for each year. The frequency of CAs in the present study by organ system is shown in **Tab. 1**.

Table 1. Frequency of congenital anomalies (CAs) by organ/organ system among newborns in Santa Fe, Argentina, 2018-2019.

Type of CAs	Frequency (n)	%
Polymalphormations	13	20.0
NTDs	12	18.4
Abdominal wall defects	10	15.3
Limbs defects	9	13.8
Craniofacial anomalies	6	9.2
Urogenital defects	5	7.6
CHDs	4	6.1
Gastrointestinal defects	4	6.1
Syndrome	2	3.0
Total	65	100

CAs: congenital anomalies; CHD: congenital heart disease; NTD: neural tube defect.

Sociodemographic characteristics of the mothers of newborns

In total, 280 mothers of newborn babies participated in the study – specifically, 64 mothers of cases and 216 mothers of controls. These mothers were 27.66 ± 6.09 years old. The frequency of age group for both groups are shown in **Tab. 2**. In terms of educational level, results revealed that 4.64% of the women had not finished primary school, 15.71% had only completed primary school, 55.71% did not complete high school, 18.21% had finished compulsory education, 5.00% did not complete university degree, and 0.71% had a university degree. Educational level was dichotomized by compulsory education, as shown in **Tab. 2**. Considering the place of residence, women came from 13 of the 19 departments of the province; specifically, 47.85% (134/280) were from LC&R, and 52.14% (146/280) were from RP. Among the mothers of cases, 45.31% (29/64) came from LC&R, and 54.68% (35/64) came from RP. Among all the participants, 72.14% (202/280) were housewives, 10% (28/280) were employed, 8.21% (23/280) were students, and 9.64% (27/280) had other activities.

Considering gynecological events, about 18.57% (52/280) of the patients had a history of spontaneous abortion; the frequencies by mothers of cases and controls and by place of residence are shown in **Tab. 2**. Although the difference between the groups was not statistically significant, an association between a history of abortion and the use of domestic pesticides was found (OR: 1.91; 95% CI: 1.00-3.64; Chi^2: 3.82; p = 0.050). It is important to highlight that 79% of women realized they were pregnant within the first trimester, 20% within the second trimester and 1% within the third; meanwhile, 3.57% (10/280) of the mothers had no prenatal care visits, as shown in **Tab. 2**. Previous deeds were 1.60 ± 0.10 in average, and descriptive statistics for each group are shown in **Tab. 2**. Gestational age mean was 36.48 ± 0.22; 48.57% (136/280) were preterm births, and 51.43% (144/280) were term births. For preterm births, 70.31% (45/64) of the cases and 42.13% (91/216) of the controls were born before 37 weeks, as seen in **Tab. 2**. Gestational age was associated with newborn diagnosis and maternal place of residence. In the first case, having a baby with a CA has more than 3 times the chances of being a preterm birth (OR: 3.25; 95% CI: 1.79-5.90; Chi^2: 15.70; p = 0.0001). Gestational age was also related to maternal place of residence (OR: 2.89; 95% CI: 1.78-4.69; Chi^2: 18.74; p = 0.0001), as women who came from RP had almost a three times greater risk of preterm births.

Regarding the type of delivery, 37.5% (105/280) were vaginal, 51.79% (145/280) were CS, and information was missing for about 10.71% (30/280) of the participants. **Tab. 2** shows this by case and controls and by maternal place of residence. An association between CS and cases was found (OR: 2.11; 95% CI: 1.13-3.94; Chi^2: 5.51; p = 0.01). Moreover, there was an association between maternal place of residence and type of delivery (OR: 2.23; 95% CI: 1.34-3.73; Chi^2: 9.45; p = 0.0021). Women from RP have double the chance of having a CS than women from LC&R. There was also an association between preterm births and CS (OR: 3.13; 95% CI = 1.85-5.29; Chi^2: 18.26; p < 0.0001).

Newborns' birth weight mean was 2,845.09 ± 53.95 g, with a range from 440-4,530.00 g (n = 271), and 30.63% (83/271) of them were born with a low weight (< 2,500 g). Cases' and newborns from RP's birth weights were significantly lower than controls (p = 0.01) and from LC&R (p = 0.004). Moreover, low birth weight was associated with those from RP (OR: 2.90; 95% CI: 1.68-4.98; Chi^2: 15.09; p = 0.0001).

State of health involves not only acute infections but also NCCDs during pregnancy. Overall, NCCDs showed no significant difference between cases and controls or between LC&R and RP. However, when these pathologies were considered separately, there was a slight association between maternal diabetes and cases (OR = 2.36; 95% CI = 0.99-5.64; Chi^2: 3.76; p = 0.052). In this sense, diabetes mellitus was observed in 8.21% (23/280) of the participants, hypertension was observed in 18.57% (52/280), and 10% (28/280) had some type of thyroids disease.

Table 2. Frequency, mean and standard error of maternal sociodemographic factors, gynecological events and state of health by newborn diagnoses and place of residence. Santa Fe Province, Argentina, 2018-2019.

Variables			Newborn diagnosis			Maternal place of residence		
			Case (n = 64)	Control (n = 216)	p	LC&R (n = 134)	RP (n = 146)	p
Socio-demographic factors	Age (years)	Mean ± SD	27.28 ± 6.38	27.78 ± 6.01	0.38	28.16 ± 5.77	27.21 ± 6.36	0.10
		≤ 20 years old	8% (5/64)	7% (15/216)		4% (5/134)	10% (15/146)	
		21-25 years old	39% (25/64)	38% (81/216)		37% (49/134)	39% (57/146)	
		26-35 years old	39% (25/64)	43% (93/216)		46% (62/134)	38% (56/146)	
		≥ 36 years old	14% (9/64)	13% (27/216)		13% (18/134)	12% (18/146)	
	Educational level	Incomplete high school or less	72% (46/64)	77% (167/216)	0.37	71% (95/134)	81% (118/146)	0.0518
		Complete high school or more	28% (18/64)	23% (49/216)		29% (39/134)	19% (28/146)	
	Maternal occupation	Housewife	64% (41/64)	75% (161/216)	-	74% (99/134)	71% (103/146)	-
		Employed	16% (10/64)	8% (18/216)		10% (14/134)	10% (14/146)	
		Students	13% (8/64)	7% (15/216)		7% (10/134)	9% (13/146)	
		Others	8% (5/64)	10% (22/216)		8% (11/134)	11% (16/146)	
Gyneco-logical events	History of miscarriage		20% (13/64)	18% (39/216)	0.68	18% (24/134)	19% (28/146)	0.78
	No prenatal care		6% (4/64)	3% (6/216)	0.18	5% (7/134)	2% (3/146)	0.15
	No. of previous deeds	Mean ± SD	1.45 ± 1.63	1.65 ± 1.66	0.38	1.60 ± 1.61	1.60 ± 1.70	0.73
		0-1	69% (44/64)	55% (118/216)		54% (72/134)	62% (90/146)	
		2-3	22% (14/64)	32% (69/216)		35% (48/134)	24% (35/146)	
		≥ 4	9% (6/64)	13% (29/216)		10% (14/134)	14% (21/146)	
	Gestational age (weeks)	Mean ± SD	35.89 ± 3.15	36.66 ± 3.78	**0.0016** [b]	37.41 ± 3.10	35.65 ± 3.92	**0.0001** [b]
		Preterm	70% (45/64)	42% (91/216)	**0.0001** [b]	35% (47/134)	61% (89/146)	**0.0001** [b]
		Term	30% (19/64)	58% (125/216)		65% (87/134)	39% (57/146)	
	Type of delivery (n = 250)	Vaginal	29% (17/59)	46% (88/191)	**0.01** [a]	51% (67/131)	32% (38/119)	**0.0021** [b]
		CS	71% (42/59)	54% (103/191)		49% (64/131)	68% (81/119)	
	Newborn sex (n = 276)	Male	50% (32/64)	50% (105/112)	0.94	49% (65/133)	50% (72/143)	0.80
		Female	50% (32/64)	50% (107/112)		51% (68/133)	50% (71/143)	
	Newborn weight (n = 271)	Mean ± SD	2,683.14 ± 755.74	2,895.16 ± 921.04	**0.01** [a]	3,029.73 ± 771.06	2,679.96 ± 958.62	**0.004** [a]
		< 2,500 g	39% (25/64)	28% (58/207)	0.09	20% (26/133)	41% (57/138)	**0.0001** [b]
		≥ 2,500 g	61% (39/64)	72% (149/207)		80% (107/133)	59% (81/138)	
State of health	Acute infections during pregnancy (n = 213)		11% (5/47)	11% (18/166)	0.96	7% (7/105)	16% (17/108)	0.055
	• Toxoplasmosis IgM (n = 208)		0% (0/46)	2% (4/162)		1% (1/104)	3% (3/104)	
	• Syphilis (n = 261)		8% (5/61)	7% (14/200)		5% (6/127)	10% (13/134)	
	NCCDs		30% (19/64)	28% (61/216)	0.82	25% (33/134)	32% (47/146)	0.16
	• Diabetes mellitus		14% (9/64)	6% (14/216)	0.052	9% (12/134)	8% (11/146)	0.36
	• Hypertension		17% (11/64)	19% (41/216)	0.74	16% (22/134)	21% (30/146)	0.57
	• Thyroids disease		8% (5/64)	11% (23/216)	0.50	7% (10/134)	12% (18/146)	0.17

CS: caesarean surgery; LC&R: La Capital and Rosario Department; NCCDs: non-communicable chronic diseases; RP: rest of the province.
[a] Statistical significance was considered at p = 0.01-0.05; [b] highly significant was considered at p < 0.01.

Moreover, preterm births were associated with maternal NCCD (OR: 2.56; 95% CI: 1.50-4.38; Chi^2: 12.10; p = 0.0005) and maternal hypertension (OR: 2.33; 95% CI: 1.25-4.35; Chi^2: 7.23; p = 0.0072).

According to a summary by newborn diagnoses and by maternal place of residence, there were differences between groups in gynaecological events like gestational age, type of delivery and newborn weight but not in terms of sociodemographic factors (age, educational level), state of health or lifestyle habits (**Tab. 2**).

Associated risk factors with congenital anomalies

Lifestyle habits are described by case and control mothers and by place of residence in **Tab. 3**. In the total population surveyed, the frequency of fruit and vegetable consumption was around 90%, and physical activity before pregnancy was 40.71% (114/280), which decreased to 23.21% (65/280) in the first trimester of pregnancy. Furthermore, 56.43% (158/280) of women drank alcohol before pregnancy, and during the first trimester, it was reduced to 50.35% (141/280). Active and passive smoking (35% and 50%, respectively) remained almost unchanged between both periods. Exposure to domestic pesticides was observed in 59.14% (165/279) of the mothers.

The frequency of physical activity and alcohol intake decreased from before pregnancy to the first trimester, while active and passive smoking remained almost unchanged. Moreover, fruit and vegetable intake, as well as antibiotic consumption, increased from before gestation to the first trimester. Diet supplementation with iron and folic acid increased since the first trimester in all groups.

Discussion

The aetiology of most CAs is not completely understood, but genetic, environmental and socio-demographic factors could be involved. Their prevalence can be decreased by identifying modifiable factors and preventing maternal exposure to harmful habits like smoking and drug and alcohol consumption. Some birth defects can also be avoided through screening, vaccination, fortification with nutrients such as folic acid and iodine and adequate prenatal care, among other practices [1].

Considering RENAC's report [4], the prevalence (by 10,000 born 95% CI) of major CAs in Santa Fe were lip and palate clef (18.98%), NTDs (11.72%),

Table 3. Frequency of lifestyle habits during the period before pregnancy to delivery, by trimester, in groups classified by diagnosis and maternal place of residence. Santa Fe Province, Argentina, 2018-2019.

Lifestyle habits		Case group (n = 64)		Control group (n = 216)		LC&R (n = 134)		RP (n = 146)	
		Before pregnancy	1st trimester	Before pregnancy	1st trimester	Before pregnancy	1st trimester	Before pregnancy	1st trimester
Fruits and vegetables intake		92% (59/64)	95% (61/64)	88% (189/216)	94% (202/216)	89% (119/134)	95% (127/134)	88% (129/146)	93% (136/146)
Physical activity		41% (26/64)	22% (14/64)	41% (88/216)	24% (51/216)	37% (49/134)	25% (33/134)	45% (65/146)	22% (32/146)
Alcohol intake		59% (38/64)	55% (35/64)	56% (120/216)	49% (106/216)	50% (67/134)	43% (58/134)	62% (91/146)	57% (83/146)
Active smoking		28% (18/64)	28% (18/64)	38% (81/216)	38% (82/216)	36% (48/134)	36% (48/134)	35% (51/146)	36% (52/146)
Passive smoking		47% (30/64)	47% (30/64)	51% (111/216)	51% (110/216)	53% (71/134)	52% (70/134)	48% (70/146)	48% (70/146)
Ilicit drugs		5% (3/64)	5% (3/64)	6% (12/216)	6% (12/216)	5% (7/134)	5% (7/134)	5% (8/146)	5% (8/146)
Pesticides indoor exposure (n = 279)		59.37% (38/64)		59.06% (127/215)		55.97% (75/134)		62.06% (90/145)	
Medication	Folic acid	8% (5/64)	53% (34/64)	4% (9/216)	56% (120/216)	5% (7/134)	54% (72/134)	5% (7/146)	56% (82/146)
	Iron	8% (5/64)	56% (36/64)	5% (10/216)	50% (108/216)	5% (7/134)	49% (65/134)	5% (8/146)	54% (79/146)
	Antibiotics	6% (4/64)	16% (10/64)	5% (11/216)	17% (36/216)	1% (1/134)	17% (23/134)	10% (14/146)	16% (23/146)

LC&R: La Capital and Rosario Department; RP: rest of the province.

CHDs (10.60%), abdominal wall and limb defects (6.14%) and talipes (5.58%), among others. In the present pilot study, the most prevalent cases were polymalphormations, followed by NTDs and abdominal wall and limb defects. Although CHD is one of the most frequent CAs in Argentina [4], we found a relatively low prevalence, perhaps because such cases are usually very serious and need an urgent delivery at higher complexity hospitals in big cities. Thus, these mothers were not available to participate in the present study.

Regarding maternal sociodemographic factors, the present study showed no difference between the controls and cases, even when considering maternal place of residence, demonstrating the homogeneity of the population surveyed.

Gynaecological events revealed different associations between CAs and preterm birth, as well as CS, as was also described in Brazil [31, 32]. The frequency of preterm births was about 8.9% in 2019 in Argentina [33], 12-13% in the USA and 5-9% in other developed countries [34]. Surprisingly, the prevalence in the present study was 49%, 6 times higher than that reported for Argentina [33]. One of the most common risk factors for preterm births and low birth weight is maternal periodontal disease [35]. Considering the high percentage of late, incomplete or lacking pregnancy control registered in CHs, the high frequency of preterm births is not surprising. At this point, it is important to highlight that this high prevalence of preterm births could lead to a generation of adults born preterm. As it was already described, there is a wide spectrum of long-term health risks which are associated with being born preterm at a low birth weight, including metabolic syndrome, hypertension [36], diabetes mellitus [37], reduced lung function and psychiatric disorders [38].

On the other hand, when the type of delivery was considered, there was an association not only between CS and CAs but also between CS and place of residence. In the first case, it could indicate antenatal care and a previous diagnosis, which led to a scheduled delivery, especially in cases, to decrease any risk factors for both the mother and the baby, according to medical criteria. On the other hand, an association between CS and RP and the high general prevalence of this kind of delivery method, were already found in a multicenter study in Latin American countries, including Argentina [39], in which increasing rates of CS were described, both for medical convenience and for maternal request [40, 41]. This procedure, which is performed without a medical indication, is not advised by the World Health Organization because CS rates higher than 10% are not associated with reduced maternal and newborn mortality rates [42]. The Perinatal Informatic System registered 34.7% of CS in Argentina and 36% in Santa Fe in 2017 [43]. These values are lower than shown in the present study (52%). However, the higher frequency of preterm births and CAs related to CS should be taken into account.

Argentinian statistics about newborns' low birth weights have described that 7.3% of births were under 2,500 g and two-thirds of them were preterm [44]. However, in the present study, more than 30% of the newborns had a low birth weight. This was also associated with the cases group, as was already found by Vanassi et al. [31] in Brazil, and with those who come from RP, showing that differences still exist in terms of health care and accessibility to the sanitary system between big cities like Santa Fe and Rosario and other smaller cities in the province [45].

Regarding the state of health, it is well known that pregestational diabetes increases the risk of specific non-chromosomal CAs and multiple CAs [46]. In the present study, one-third of the population surveyed have some NCCDs. The association between diabetic mothers and cases of CA found in the present work is subtle, but similar associations were already described in previous studies in Cuba [47], Argentina [48] and the USA [49]. In Argentina, almost 10% of pregnancies are affected by gestational diabetes mellitus (GDM), which is associated with increased fasting glucose and increased GDM prevalence [48].

It is important to note that just more than half of the mothers had their first pregnancy control during the first trimester, which is a higher proportion than recorded in Argentina and Santa Fe Province by the Ministry of Health [3]. This appointment is very important for counselling women and detecting possible harmful lifestyle habits to avoid during this susceptible period. That is why, a delay in getting it could delay the reception of medical advice and support for mothers in their new stage of life. The face-to-face questionnaire showed how those habits present different patterns of behaviour as gestation goes by. In this sense, the difference in frequency of folic acid and iron intake between before pregnancy period and the first trimester could show not only a later diagnosis of pregnancy or unplanned pregnancies but also the absence of preconceptionally counselling for knowing the

importance of folic acid for optimal pregnancy outcomes. Unplanned pregnancies have reached 59.3% in Argentina and 52.6% in Santa Fe Province despite the high frequency (94.7%) of sexual and reproductive health counselling declared by the Ministry of Health [3]. On the other hand, while alcohol intake and drug consumption decreased from the period before pregnancy to the first trimester, active smoking and passive smoking remained constant, perhaps due to a lack of risk perception of the possible harmful effects on women and baby health.

Regarding alcohol intake, in the present study, even when the frequency of drinking decreased as long as the pregnancy developed, more than 15% of the patients maintained the habit until the end of gestation. On the other hand, considering tobacco consumption, there is no safe level or safe trimester for maternal smoking during pregnancy [50]. La Fauci et al. [51] found that 14% of pregnant women in Italy continue smoking despite their pregnancy, like in the present study. The combined use of alcohol and smoking not only exposes fetuses to a risk for perinatal adversities but also increases the risk of delayed acquisition of fine motor skills in motor and cognitive development [27].

The very low percentage of drug consumption declared could be due to the fact that illicit drug consumption is forbidden in Argentina, and they could be afraid to reveal it in a face-to-face questionnaire. Moreover, Fish et al. [52] described how cannabinoids can exacerbate the teratogenesis effect of alcohol and produce CAs. Unlike other risk factors, medication use increases as gestation grows. Lutz et al. [53] showed that women who had 3 or more health problems during pregnancy demonstrated a more frequent use of medicines. Health education campaigns focused on encouraging and supporting women to quit those harmful habit that represent a current public health challenge in Argentina are needed to improve the awareness of women (especially those in the reproductive age) about all these risk factors.

The global prevalence of latent toxoplasmosis in pregnant women from South America is 56.2% [54]. In the present study, the data obtained from the CHs reached 45%, lower than that reported in South America. Some of this information could not be included in the study because of its absence during contact with the volunteer mothers, incomplete CHs or uncontrolled pregnancies. A similar seroprevalence study developed in pregnant females from Chascomús (Argentina) revealed a significant difference between urban (26.8%) and rural (36.4%) areas [55].

In conclusion, this descriptive fieldwork is the first such study conducted on a population of postpartum mothers of newborn babies with CAs, from Santa Fe Province, Argentina, focusing on the identification of potential maternal and environmental risk factors for those pathologies and settling a health situation analysis of this vulnerable group. It was revealed that the most differences between groups were found regarding gestational age, type of delivery and newborn birth weight, all of which are preventable variables. These indicators show a lack of maternal health care in periconceptional time and during pregnancy, that would also have a large impact on future adults born preterm, adversely affecting their health and quality of life. Improvements to lifestyle habits and maternal health education are as important as the awareness of a suitable and healthy environment to live in, which will enhance maternal and child health, which is a permanent challenge of the Argentine public health system today and in the future.

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Declaration of interest

The Authors declare no conflict of interest.

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