Association between a Maternal History of Miscarriages and Birth Defects

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ABSTRACT BACKGROUND: Some studies, mainly in the older literature, observed a significant association between miscarriages and birth defects (BDs) occurring in the same sibship. However, few studies examined the BD/miscarriage relationship in depth. In addition nothing has been added to the underlying mechanisms possibly linking both events. The purpose of this work was to identify specific BDs associated with maternal miscarriages. In particular, it examined whether the risk depended on the number of losses, and to suggest the existence of specific factors for each BD/miscarriage association observed. METHODS: The study relied on the Latin American Collaborative Study on Congenital Malformations (ECLAMC) database registries including 26,906 live and stillborn infants with one of 19 selected isolated BDs and 93,853 normal controls. Infants born to primigravid mothers were excluded from the present study. Demographic and reproductive variables were compared between control mothers With and Without previous miscarriages. The number, frequency, and distribution of miscarriages were observed for each BD and controls. A conditional logistic regression was applied to evaluate the miscarriage risk for each BD. RESULTS: Control mothers with previous miscarriages were older, had had more pregnancies, and were less educated. Three risk patterns of miscarriages were observed: a very high risk of miscarriages associated with gastroschisis, omphalocele, and talipes; only one miscarriage associated with spina bifida, and two or more miscarriages associated with hypospadias. CONCLUSION: These three patterns suggest that different factors underly each BD/miscarriage association: infertility for hypospadias, vascular disruption for gastroschisis and talipes, while for spina bifida, the much debated trophoblastic cell residue theory could not be discarded.

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Introduction

Approximately 10 to 15% of all clinically recognized pregnancies results in a miscarriage (Schaeffer et al., 2004).

Most of them occur during the first trimester and are mainly due to chromosome anomalies (Hassold et al., 1980). Other genetic or environmental causes have also been shown to be involved, while for many miscarriages the cause remains unknown.

Recurrent pregnancy losses occur in 1 to 2% of fertile women, often without an identifiable cause (Brigham et al., 1999). A history of abortion may include the birth of a viable malformed fetus, due to the segregation of an inherited chromosome aberration (De Krom et al., 2015).

Some authors have analyzed the association between previous miscarriages and the occurrence of certain birth defects of unknown etiology (Paz et al., 1992; Khoury and Erickson, 1993; Martínez-Frías and Frías, 1997). Several hypotheses have been put forward. For instance, it has been suggested that the same defect observed in the live-born infant could be present (although undetected) in the aborted conceptus, causing the pregnancy loss (Khoury and Erickson, 1993). Martínez-Frías and Frías (1997), who found more abortions in the sibship of infants with more severe defects, reached similar conclusions.

Clarke et al. (1975) hypothesized that residual trophoblastic cells from a previous miscarriage interfered with the embryonic development, causing a neural tube defect. This hypothesis was supported by some authors (Gardiner et al., 1978) and rejected by others (Martínez-Frías and Frías, 1997).

Vascular disruption has been suggested to cause certain defects, such as club foot and gastroschisis (Van Allen, 1981; Lubinsky, 2014), while Rittler et al. (2015) demonstrated an association between miscarriages and gastroschisis and proposed a disruptive mechanism for both.

The purpose of the present study was to determine whether or not some birth defects were associated with a history of miscarriages. In particular, it assessed whether there was a possible effect of the number of miscarriages and it examined whether the miscarriage immediately preceded or not the birth of a newborn with a birth defect. Finally the possible mechanisms involved are discussed.

Material and Methods

The Latin American Collaborative Study on Congenital Malformations (ECLAMC) is a research program dedicated to

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birth defects (BDs) research, relying on a network of maternity hospitals where health care professionals, mainly pediatricians, diagnosed birth defects in live- and stillbirths. Data on socioeconomic and demographic characteristics, previous birth outcomes, and prenatal factors are obtained from medical records and by interviewing, before hospital discharge, the mothers of malformed newborns and healthy controls (infant of the same sex born immediately after each affected newborn). A detailed description of the registry and methodology has been published previously (Castilla and Orioli, 2004). The present study used the ECLAMC data base registries of live- and stillborns with an isolated, major defect and healthy controls born between 1967 and 2013.

Newborns with more than one major defect were excluded, as were cases and controls born to primigravid mothers.

A total of 19 BDs including at least 160 cases were selected (Appendix) to be able to detect with a 80% power and an alpha of 0.05, a 1.5-fold increased risk with a 15% exposure.

The definition of miscarriage was based on the mother's description of a spontaneous first trimester pregnancy loss, without any identifiable fetus.

The following variables were compared between mothers With and Without a previous miscarriage: *Demographic:* maternal and paternal age, gravidity, maternal and paternal education ($<$ 7 years schooling), paternal occupation (unemployed or unqualified worker), and ethnic ancestry (Native American, African American, and European). *Reproductive history and current pregnancy:* short inter-birth interval ($<$ 1 year), chronic maternal illness, and medications during the first trimester of pregnancy.

Analysis of variance and *t* test were applied for continuous variables and a Chi-square test was used for discrete variables. A Bonferroni correction was applied to adjust for the large number of comparisons. Significance level was set at 0.05.

The number of miscarriages, their frequency and their distribution were obtained for each BD and for controls. Cases and healthy controls (four from the total control group per case) were matched by hospital, year of birth and maternal gravidity. To establish the miscarriage risk for each BD, a conditional logistic regression was applied, after adjusting for maternal and paternal ages, native ancestry, maternal education and chronic illness.

The same analysis was performed, taking the newborns with the remaining BDs as controls. The risks between a recent and an ancient miscarriage were compared, using case and control mothers with a history of miscarriages. Data were analyzed with the statistical software StataCorp LP, version 12.0, College Station, Texas.

Results

The study relied on the ECLAMC data base registries including 26,906 newborns with one of the 19 selected BDs and a total of 93,853 healthy controls. The comparison of epidemiologic characteristics of control mothers With and Without a previous miscarriage is shown in Table 1. Mothers with a previous miscarriage showed a higher frequency of some risk factors, such as an older age, an increased number of pregnancies, and a lower education. The impact of these variables increased as the number of miscarriages increased. In Table 2, the number of miscarriages, their frequency, and their distribution are shown for each BD and for controls.

A conditional logistic regression, using healthy controls, showed that mothers with previous miscarriages were at a statistically significant higher risk for 5 of the 19 selected BDs, namely gastroschisis, omphalocele, talipes equinovarus, spina bifida, and hypospadias (Table 3). For gastroschisis and omphalocele, the risk increased with the number of miscarriages.

When comparing to the group of malformed newborns used as controls, the risk remained significant for omphalocele (odds ratio [OR]: 1.83(1.33–2.53); $p < 0.001$), gastroschisis (OR: 2.00(1.51–2.65); $p < 0.001$), and talipes (OR: 1.18(1.04–1.35); $p < 0.01$).

For hypospadias, only mothers with more than one miscarriage were at risk, while for spina bifida, only one previous miscarriage (but not more than one) was a risk factor.

Discussion

Here, we show that among several selected birth defects, five were associated with a maternal history of miscarriages. In support of our findings, Paz et al. (1992) observed a significant association between previous miscarriages and talipes equinovarus. They also found that anencephaly and spina bifida were significantly associated, with stillbirths (not miscarriages). Other methodological differences found in their study were that they considered only the abortion preceding immediately the birth of malformed newborn, while mothers with a miscarriage at any other time were included into the control group and that gastroschisis and omphalocele were included into a global category "other isolated defects," precluding comparisons with the results of the present study.

Khoury and Erickson (1993) evaluated the risk of 57 birth defects in newborns of women with a history of pregnancy losses (miscarriages and stillbirths). In accordance with our work, the authors found a significant risk for positional limb defects and hypospadias, while they did not find a risk for spina bifida, omphalocele, or gastroschisis.

TYPES OF BIRTH DEFECT/MISCARRIAGE ASSOCIATION

The present work revealed three patterns of birth defect/miscarriage association: (1) with only one miscarriage (spina bifida); (2) with two or more miscarriages (hypospadias); and (3) where the risk was very high

TABLE 1. *Epidemiologic Characteristics of Control Mothers with and without Previous Miscarriages*

	Miscarriage						Number of miscarriages							
	No *N* = 76,244		Yes *N* = 17,609				1 *N* = 13534		2 *N* = 3026		3+ *N* = 1049			
Characteristics	***N***	**X ± SD**	***N***	**X ± SD**	**t**	***p*-Value**	***N***	**X ± SD**	***N***	**X ± SD**	***N***	**X ± SD**	**F**	***p*-Value**
Maternal age	74442	26.7 ± 6.3	17564	28.7 ± 6.4	-37.80	<0.001	13497	28.2 ± 6.3	3018	30.3 ± 6.2	1049	31.4 ± 5.9	240.35	<0.001
Gravidity	75872	3.3 ± 1.8	17605	4.5 ± 2.3	-79.40	<0.001	13530	4.1 ± 2.0	3026	5.7 ± 2.3	1049	7.3 ± 2.5	1650.3	<0.001
Paternal age	72213	30.4 ± 7.6	17145	32.1 ± 7.7	-26.34	<0.001	13185	31.6 ± 7.6	2939	33.4 ± 7.9	1023	34.6 ± 7.6	123.85	<0.001
	N	%	*N*	%	χ^2_1	p	*N*	%	*N*	%	*N*	%	χ^2_2	p
Low maternal education	20810	27.3	5062	28.8	15.12	<0.001	3782	27.9	921	30.4	359	34.2	23.829	<0.001
Low paternal education	17995	23.6	4348	24.7	9.37	0.002	3236	23.9	800	26.4	312	29.7	23.798	<0.001
Low paternal occupation	29126	38.2	6161	35.0	62.95	<0.001	4703	34.8	1075	35.5	383	36.5	1.792	0.408
Native	29996	42.1	6636	38.8	60.95	<0.001	5129	39.1	1138	38.7	369	36.6	2.406	0.300
African	15218	21.3	3700	21.6	0.68	0.409	2768	21.1	683	23.2	249	24.7	12.287	0.002
European	26273	36.6	6748	39.6	50.72	<0.001	5236	39.8	1122	38.1	390	38.7	3.355	0.187
Short inter-birth interval	22351	29.3	5526	31.4	29.26	<0.001	4289	31.7	931	30.8	306	29.2	3.513	0.173
Medication	41533	54.5	10483	59.5	148.15	<0.001	7966	58.9	1873	61.9	644	61.4	11.074	0.004
Chronic maternal illness	7930	10.4	2524	14.3	223.53	<0.001	1845	13.6	461	15.2	218	20.8	42.941	<0.001

X ± SD, mean ± standard deviation.

TABLE 2. *Total Number and Distribution of Miscarriages for Each Birth Defect*

	Mothers	Gravidities total	Miscarriages		Mothers by number of miscarriages			
			N	%	0	1	2	3+
Omphalocele	438	1667	166	10.0	329	70	29	10
Hypoplastic left heart	208	756	62	8.2	168	27	7	6
Gastroschisis	864	2525	202	8.0	706	123	30	5
Truncus arteriosus	821	3045	222	7.3	664	114	31	12
Transverse limb reduction	442	1653	120	7.3	368	49	13	12
Diaphragmatic hernia	594	2168	153	7.1	488	75	25	6
Spina bifida	1,739	6718	464	6.9	1,383	267	73	16
Microtia	1,081	4229	281	6.6	880	145	40	16
Cephalocele	461	1826	118	6.5	369	71	18	3
Septal heart defect	2,247	8313	540	6.5	1,858	285	70	34
Esophageal atresia	502	1879	121	6.4	418	60	16	8
Hypospadias	1,179	4211	270	6.4	980	143	45	11
Talipes equinovarus	3,459	12590	808	6.4	2,869	441	109	40
Cleft palate	654	2548	156	6.1	536	97	13	8
Cleft lip +/- cleft palate	3,541	14384	874	6.1	2,896	482	121	42
Preaxial polydactyly	868	3233	198	6.1	716	116	29	7
Postaxial polydactyly	5,397	20610	1258	6.1	4,489	667	175	66
Anencephaly	1,800	7177	417	5.8	1,496	224	58	22
Anorectal atresia	602	2408	122	5.1	511	67	20	4
Controls	93,853	329921	23258	7.0	76,244	13,534	3,026	1,049

%, *N* / total gravidities; +/-, with or without.

(gastroschisis, omphalocele, talipes), and increased with the number of miscarriages (gastroschisis and omphalocele). These findings were expected, if one considers that different mechanisms are presumably involved in birth defects. Therefore, it seemed reasonable to search for specific factors common to each birth defect/miscarriage association.

SPINA BIFIDA

It has been postulated that, within the spectrum of neural tube defects, a miscarriage within the sibship of an infant with spina bifida could represent a previously lost anencephalic embryo (Laurence and Roberts, 1977). Remarkably, our results showed that only spina bifida but not anencephaly was associated with a history of miscarriages.For this observation, the polygenic-multifactorial model of inheritance could provide an explanation, namely an infant with spina bifida would more easily be associated with an anencephaly in its sibship than the opposite, due to the lower genetic threshold of anencephaly than of spina bifida (Carmi et al, 1994). In addition, an embryo with spina bifida within the same sibship of a newborn with anencephaly, would not necessarily be lost, reducing the likelihood to observe a miscarriage/anencephaly association.

On the other hand, Clarke et al. (1975) showed that mothers of infants with NTDs had more miscarriages immediately preceding the observed birth defect case. They hypothesized that residual trophoblastic cells from the preceding abortion interfered with the subsequent developing embryo, leading to anencephaly or spina bifida. This cell rest hypothesis was supported by some authors (Gardiner et al., 1978), some related it to other defects (Sheiner et al., 1998), while others (Martínez-Frías and Frías, 1997) found that the rate of miscarriages preceding immediately the birth of an affected newborn did not differ from a miscarriage occurring at any other time.

Lu et al. (2011) showed that an abortion preceding immediately the birth of a malformed newborn was a risk factor for a subsequent fetus with anencephaly only if the inter-pregnancy interval was short. Todoroff and Shaw (2000) reached a similar conclusion. We analyzed this hypothesis by evaluating the interaction between inter-birth interval and miscarriage on the occurrence of each birth defect and found that for spina bifida such an

TABLE 3. *Previous Miscarriage/s and Risk for Birth Defects*

	Previous miscarriage/s		Number of previous miscarriages			
			1		2 +	
Birth defect	**OR (95% CI)**	***p*-Value**	**OR (95% CI)**	***p*-Value**	**OR (95% CI)**	***p*-Value**
Gastroschisis	1.91 (1.46-2.99)	<0.001	1.76 (1.33-2.33	<0.001	3.04 (1.35-1.72)	<0.001
Omphalocele	1.72 (1.26-2.36)	<0.001	1.49 (1.06-2.10)	<0.001	3.13 (1.79-5.49)	<0.001
Talipes equinovarus	1.48 (1.31-1.68)	<0.001	1.49 (1.30-1.70)	<0.001	1.45 (1.14-1.84)	0.002
Hypoplastic left heart	1.31 (0.78-2.21)	0.306	1.25 (0.72-2.18)	0.434	1.70 (0.60-4.80)	0.313
Spina bifida	1.27 (1.08-1.48)	0.001	1.29 (1.08-1.43)	0.003	1.18 (0.88-1.58)	0.262
Cephalocele	1.23 (0.91-1.28)	0.174	1.17 (0.85-1.62)	0.334	1.65 (0.87-3.10)	0.334
Hypospadias	1.18 (0.97-1.44)	0.089	1.06 (0.86-1.32)	0.578	1.84 (1.27-2.65)	0.001
Esophageal atresia	1.18 (0.85-1.63)	0.326	1.13 (0.79-1.60)	0.498	1.40 (0.75-2.60)	0.293
Preaxial polydactyly	1.14 (0.91-1.44)	0.255	1.14 (0.89-1.46)	0.299	1.17 (0.73-1.89)	0.517
Cleft lip +/- cleft palate	1.13 (1.00-1.27)	0.031	1.10 (0.97-1.25)	0.118	1.26 (0.99-1.59)	0.052
Microtia	1.10 (0.90-1.36)	0.345	1.08 (0.36-1.86)	0.498	1.19 (0.81-1.75)	0.379
Truncus arteriosus	1.09 (0.86-1.39)	0.460	1.07 (0.83-1.38)	0.609	1.22 (0.76-1.94)	0.411
Transverse limb reduction	1.08 (0.73-1.51)	0.677	1.04 (0.71-1.43)	0.838	1.18 (0.66-2.08)	0.574
Anorectal atresia	1.04 (0.77-1.42)	0.788	1.01 (0.73-1.41)	0.940	1.18 (0.65-2.13)	0.583
Diaphragmatic hernia	1.03 (0.77-1.38)	0.839	1.01 (0.74-1.39)	0.928	1.10 (0.64-1.87)	0.736
Cleft palate	1.00 (0.76-1.31)	0.962	1.09 (0.82-1.44)	0.557	0.69 (0.39-1.21)	0.194
Anencephaly	0.98 (0.83-1.16)	0.825	0.99 (0.82-1.19)	0.915	0.96 (0.67-1.30)	0.736
Septal heart defect	0.97 (0.83-1.13)	0.684	0.96 (0.81-1.12)	0.593	1.02 (0.76-1.37)	0.870
Postaxial polydactyly	0.96 (0.89-1.05)	0.365	0.94 (0.85-1.05)	0.273	1.01 (0.84-1.22)	0.903

+/-: with or without.

interaction actually existed. The 1.01 (0.77–1.29) risk observed for a long interval increased to 1.70 (1.11–2.60) if the interval was short.

Based on these results, and the fact that only one previous abortion represented a risk factor for spina bifida, the cell rest theory could not be discarded entirely. However, other factors related to a short inter-pregnancy interval, such as nutritional or vitamin deficiencies (Czeizel, 2009), should be taken into consideration.

HYPOSPADIAS

The present work showed that only women with a history of two or more miscarriages were at risk for hypospadias.

Many studies have demonstrated an association between infertility treatments and hypospadias. Some authors have found such an association with sex hormone medications (Carmichael et al., 2005), suggesting an interference with the development of male genitalia, while others have not (Källén et al., 1991). However, an excess of hypospadias was also observed after treatment with other types of assisted reproductive technology (Heisey et al., 2015). This finding requires further research. Nevertheless it seems reasonable to expect that any such therapy would be applied after a history of at least two miscarriages.

TALIPES EQUINOVARUS

Club foot has been related repeatedly to vascular disruption through factors such as an early amniocentesis (Evans and Wapner, 2005), the loss of a twin fetus (Pharoah, 2005), vasoconstrictive medications (Werler, 2006), or maternal smoking during pregnancy (Skelly et al., 2002). Merrill et al. (2011) identified vascular anomalies in the lower limbs of patients with club foot, in support of a vascular role in the pathogenesis of this defect.

In an epidemiological study on club foot, Werler et al. (2013) observed, among other findings, that case mothers were more often primiparous than control mothers. However, they found that gravidity did not differ between cases and controls. This suggests that case mothers could have had more previous abortions than controls. Unfortunately, previous miscarriages were not included among their analyzed variables.

In further support of vascular disruption, the authors observed associated anomalies, possibly due to the same mechanism, in four of their cases: one with a septo-optic

dysplasia, two with a hydrocephaly, and one with a brain infarct.

Talipes equinovarus is one of the most frequent and conspicuous defects observed in the Moebius sequence, while other findings, such as an expressionless face or neurologic dysfunction, can be missed or not reported. The use of misoprostol as abortifacient, due to its uterotonic property, has often been associated with the Moebius sequence, as well as with other defects related to vascular disruption, such as terminal transverse limb defects (da Silva Dal Pizzol et al., 2006), mainly in regions where a termination of pregnancy is illegal (Pastuszak et al., 1998; Vargas et al., 2000).

It could be hypothesized that abortions preceding the birth of an infant with talipes were in fact terminations of pregnancy (not admitted as such due to their illegal condition), and the current outcome was an attempted although missed abortion. The higher than expected miscarriage frequency in the present population (19 vs. 15%) is consistent with some induced terminations. The observed association between miscarriages and hip dislocation (Paz et al., 1992), often observed in the Moebius sequence, adds further support to this hypothesis.

GASTROSCHISIS

Lubinsky (2014) proposed two disruptive pathogenetic models for gastroschisis. The first one was not age-dependent and acted through vasoconstrictive factors, such as certain medications (Werler, 2006), or smoking (Skarsgard et al., 2015).

The second one was age-dependent, and acted through the thrombotic effect of estrogens, mainly in young women who show higher levels of estrogens at early stages of pregnancy (Lubinsky, 2012). In support of this hypothesis, the association between gastroschisis and endocrine disruptors with an estrogenic effect has been demonstrated (Agopian et al., 2013).

In a previous study (Rittler et al., 2015), we showed that a history of miscarriages was the main risk factor for gastroschisis. To our knowledge, an association between gastroschisis and pregnancy losses has only been mentioned by Getz et al. (2012). Their study, however, was limited to mothers with a short inter-pregnancy interval. They found that the risk factor was the short interval and the risk increased if the previous pregnancy ended in a miscarriage. On the contrary, in the study of Rittler et al. (2015) the identified risk factor was the miscarriage, regardless of the inter-pregnancy interval.

Both hypertension and thrombophilia are recognized risk factors for pregnancy losses (Kutteh and Triplett, 2006). Although to our knowledge the association between thrombophilia and gastroschisis has not been observed, other less frequent hyperthrombotic conditions could be involved.

OMPHALOCELE

In accordance with the observed association between omphalocele and a history of miscarriages, Agopian et al. (2009) found significantly more omphalocele cases among mothers without than with previous livebirths. However, the relationship between omphalocele and miscarriages does not seem to point toward any straight forward hypothesis. The chances of misdiagnosing omphalocele for gastroschisis were low in our sample as all abdominal wall defect cases had been previously reviewed (Castilla et al., 2008).

One possible explanation could be that omphalocele is often observed in syndromes, mainly due to chromosome anomalies (Stoll et al., 2001), and couples carrying a chromosome rearrangement may be at risk for malformed fetuses as well as for recurrent miscarriages (De Krom et al., 2015). Although in the present study only infants with isolated defects were included, chromosome studies, which are not requested as part of the ECLAMC protocol, were not always performed. Consequently, the inclusion of some cases with a chromosome anomaly cannot be ruled out entirely, even though this explanation does not seem able to account for the observed number of cases.

On the other hand, some authors (Reefhuis and Honein, 2004; Marshall et al., 2015) observed that both old and young ($<$ 20 years) maternal age was associated with omphalocele. Given the well-recognized association between gastroschisis and young maternal age, factors similar to those responsible for gastroschisis could be involved in the occurrence of omphalocele.

All the above findings and their interpretation show that the association of miscarriages with BDs may occur through different mechanisms. For instance, with hypospadias, the miscarriage acted as a trigger, leading to a sequence of events, while with gastroschisis or talipes, it rather represents the consequence of a common underlying factor.

STRENGTHS AND WEAKNESSES

The main strengths of this study resided in the magnitude of the ECLAMC series of newborns with birth defects, to have adjusted by the number of pregnancies, and the use of malformed controls, thereby reducing memory bias in mothers of malformed versus healthy newborns. A further strength was that ascertainment and reporting was performed by pediatricians trained in the diagnosis and the description of birth defects, providing homogeneity to the data.

Limitations were those related to retrospective case control studies, such as the recall bias for data obtained by interviewing the mothers. Information on abortions, whether spontaneous or induced, might be unreliable, especially in countries, such as in South America, where termination of pregnancy is illegal.

CONCLUSIONS

The present work revealed three patterns of birth defect/miscarriage association: (1) A very high risk associated with gastroschisis, omphalocele, and talipes and a risk increasing as the number of miscarriages increased for gastroschis and omphalocele, (2) with only one miscarriage (spina bifida), and (3) with two or more miscarriages (hypospadias).

These findings and their possible explanations indicate that associations between birth defects and miscarriages can occur through different mechanisms.

The recognition of such associations may increase the chances of identifying underlying causes of birth defects.

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References

Agopian A, Marengo L, Mitchell LE. 2009. Descriptive epidemiology of nonsyndromic omphalocele in Texas, 1999-2004. Am J Med Genet A 149A:2129–2133.

Agopian AJ, Langlois PH, Cai Y, et al. 2013. Maternal residential atrazine exposure and gastroschisis by maternal age. Matern Child Health J 17:1768–1775.

Brigham SA, Conlon C, Farquharson RG. 1999. A longitudinal study of pregnancy outcome following idiopathic recurrent miscarriage. Hum Reprod 14:2868–2871.

Carmi R, Gohar J, Meizner I, Katz M. 1994. Spontaneous abortion high risk factor for neural tube defects in subsequent pregnancy. Am J Med Genet 51:93–97.

Carmichael SL, Shaw GM, Laurent C, et al. 2005. Maternal progestin intake and risk of hypospadias. Arch Pediatr Adolesc Med 159:957–962.

Castilla EE, Orioli IM. 2004. ECLAMC: The Latin American Collaborative Study of Congenital Malformations. Community Genet 7: 76–94.

Castilla EE, Mastroiacovo P, Orioli IM. 2008. Gastroschisis: international epidemiology and public health perspectives. Am J Med Genet C Semin Med Genet 148C:162–179.

Clarke C, Hobson D, McKcndrick OM, et al. 1975. Spina bifida and anencephaly: Miscarriage as possible cause. Br Med J 4:743–746.

Czeizel AE. 2009. Periconceptional folic acid and multivitamin supplementation for the prevention of neural tube defects and other congenital abnormalities. Birth Defects Res A Clin Mol Teratol 85:260–268.

da Silva Dal Pizzol T, Knop FP, Mengue SS. 2006. Prenatal exposure to misoprostol and congenital anomalies: systematic review and meta-analysis. Reprod Toxicol 22:666–671.

De Krom G, Arens YH, Coonen E, et al. 2015. Recurrent miscarriage in translocation carriers: no differences in clinical characteristics between couples who accept and couples who decline PGD. Hum Reprod 30:484–489.

Evans MI, Wapner RJ. 2005. Invasive prenatal diagnostic procedures 2005. Semin Perinatol 29:215–218.

Gardiner A, Clarke S, Cowen J, et al. 1978. Spontaneous abortion and fetal abnormalities in subsequent pregnancy. Br Med J 1:1016–1018.

Getz KD, Anderka MT, Werler MM, Case AP. 2012. Short interpregnancy interval and gastroschisis risk in the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol 94:714–720.

Hassold T, Chen N, Funkhouser J, et al. 1980. A cytogenetic study of 1000 spontaneous abortions. Ann Hum Genet 44(Pt 2):151–178.

Heisey AS, Bell EM, Herdt-Losavio ML, Druschel C. 2015. Surveillance of congenital malformations in infants conceived through assisted reproductive technology or other fertility treatments. Birth Defects Res A Clin Mol Teratol 103:119–126.

Källén B, Mastroiacovo P, Lancaster PA, et al. 1991. Oral contraceptives in the etiology of isolated hypospadias. Contraception 44:173–182.

Khoury MJ, Erickson JD. 1993. Recurrent pregnancy loss as an indicator for increased risk of birth defects: a population-based case-control study. Paediatr Perinat Epidemiol 7:404–416.

Kutteh WH, Triplett DA. 2006. Thrombophilias and recurrent pregnancy loss. Semin Reprod Med 24:54–66.

Laurence KM, Roberts CJ. 1977. Spina bifida and anencephaly: are miscarriages a possible cause? Br Med J 2:361–362.

Lu QB, Wang ZP, Gao LJ, et al. 2011. Previous abortion and the risk of neural tube defects. A case-control study. J Reprod Med 56:431–436.

Lubinsky M. 2012. Hypothesis: Estrogen related thrombosis explains the pathogenesis and epidemiology of gastroschisis. Am J Med Genet A 158A:808–811.

Lubinsky M. 2014. A vascular and thrombotic model of gastroschisis. Am J Med Genet A 164A:915–917.

Marshall J, Salemi JL, Tanner JP, et al. 2015. Prevalence, correlates, and outcomes of omphalocele in the United States, 1995-2005. Obstet Gynecol 126:284–293.

Martínez-Frías ML, Frías JL. 1997. Are blastogenetic anomalies sporadic? Am J Med Genet 68:381–385.

Merrill LJ, Gurnett CA, Siegel M, et al. 2011. Vascular abnormalities correlate with decreased soft tissue volumes in idiopathic clubfoot. Clin Orthop Relat Res 469:1442–1449.

Pastuszak AL, Schüler L, Speck-Martins CE, et al. 1998. Use of misoprostol during pregnancy and Möbius' syndrome in infants. N Engl J Med 338:1881–1885.

Paz JE, Otaño L, Gadow EC, Castilla EE. 1992. Previous miscarriage and stillbirth as risk factors for other unfavourable outcomes in the next pregnancy. Br J Obstet Gynaecol 99:808–812.

Pharoah PO. 2005. Causal hypothesis for some congenital anomalies. Twin Res Hum Genet 8:543–550.

Reefhuis J, Honein MA. 2004. 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 70:572–579.

Rittler M, Campaña H, Ermini ML, et al. 2015. Gastroschisis and young mothers: What makes them different from other mothers of the same age? Birth Defects Res A Clin Mol Teratol 103:536–543.

Schaeffer AJ, Chung J, Heretis K, et al. 2004. Comparative genomic hybridization-array analysis enhances the detection of aneuploidies and submicroscopic imbalances in spontaneous miscarriages. Am J Hum Genet 74:1168–1174.

Sheiner E, Katz M, Fraser D, et al. 1998. The relationship between congenital cardiovascular malformations and spontaneous abortion in preceding pregnancy. Paediatr Perinat Epidemiol 12:128–135.

Skelly AC, Holt VL, Mosca VS, Alderman BW. 2002. Talipes equinovarus and maternal smoking: a population-based case-control study in Washington state. Teratology 66:91–100.

Skarsgard ED, Meaney C, Bassil K, et al. 2015. Maternal risk factors for gastroschisis in Canada. Birth Defects Res A Clin Mol Teratol 103:111–118.

Stoll C, Alembik Y, Dott B, Roth MP. 2001. Risk factors in congenital abdominal wall defects (omphalocele and gastroschisis): a study in a series of 265,858 consecutive births. Ann Genet 44: 201–208.

Todoroff K, Shaw GM. 2000. Prior spontaneous abortion, prior elective termination, interpregnancy interval, and risk of neural tube defects. Am J Epidemiol 151:505–511.

Van Allen MI. 1981. Fetal vascular disruptions: mechanisms and some resulting birth defects. Pediatr Ann 10:219–233.

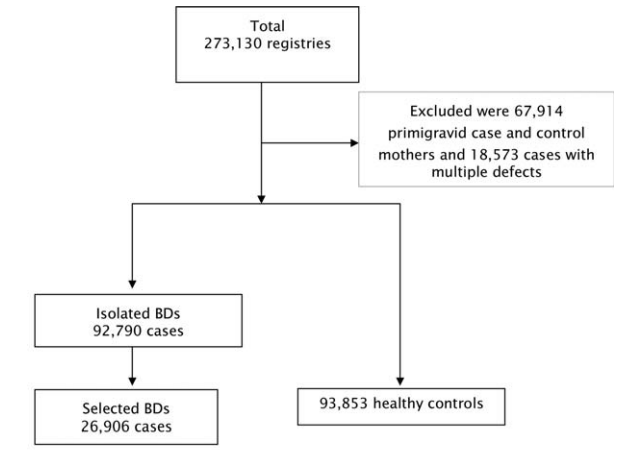
Vargas FR, Schuler-Faccini L, Brunoni D, et al. 2000. Prenatal exposure to misoprostol and vascular disruption defects: a case-control study. Am J Med Genet 95:302–306.

Werler MM. 2006. Teratogen update: pseudoephedrine. Birth Defects Res A Clin Mol Teratol 76:445–452.

Werler MM, Yazdy MM, Mitchell AA, et al. 2013. Descriptive epidemiology of idiopathic clubfoot. Am J Med Genet A 161A:1569–1578.

Appendix

ECLAMC Data Base: 209 Participating Hospitals in 10 South American Countries, 1967 to 2013



Birth defect	N
Omphalocele	438
Gastroschisis	864
Anencephaly	1,800
Spina bifida	1,739
Cephalocele	461
Microtia	1,081
Cleft palate	654
Cleft lip +/- cleft palate	3,541
Esophageal atresia	502
Ano-rectal atresia	602
Truncus arteriosus	821
Septal defects	2,247
Hypoplastic left heart	208
Hypospadias	1,179
Transverse limb reduction	451
Talipes equinovarus	3,459
Preaxial polydactyly	868
Postaxial polydactyly	5,397
Diaphragmatic hernia	594