Gastroschisis and Young Mothers: What Makes Them Different from Other Mothers of the Same Age?

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Background: Although young maternal age has been identified as a risk factor for gastroschisis, its role remains undisclosed. To our knowledge, the differences between young mothers of infants with gastroschisis and young mothers of infants with other pregnancy outcomes have not been established. The aim of this work was to compare characteristics of young mothers whose newborn had gastroschisis with same aged mothers of malformed and nonmalformed control infants, diagnosed within the ECLAMC maternity hospital network. **Methods:** Data base records of live and stillborn infants of one of three groups (with isolated gastroschisis, with 1 of 5 other isolated birth defects, and nonmalformed), and whose mothers were younger than 20 years, were selected. Secular trends were obtained for all birth defects; frequencies and odds ratios (OR) of demographic and reproductive variables were compared among the 3 groups. Significantly associated variables were adjusted with a multivariate regression. **Results:** The association was higher with gastroschisis 1) than with other birth defects for African ancestry, smoking, adequate prenatal control and diagnosis 2) than with nonmalformed controls for maternal illnesses and alcohol 3) and than both for previous pregnancy loss and medication, mainly sex hormones. After adjustment, only previous pregnancy loss maintained its significance when compared with malformed (OR = 2.34; 1.37–3.97; $P = 0.002$), as well as with nonmalformed (OR = 3.43; 2.07–5.66; $P < 0.001$) controls. **Conclusion:** A previous pregnancy loss was identified as the main risk factor for gastroschisis, while an increased use of sex hormones, perhaps related to the previous loss, could trigger a disruptive mechanism, due to their thrombophilic effect.

Birth Defects Research (Part A) 00:000–000, 2015.

Key words: gastroschisis; maternal age; ECLAMC; risk factors; previous pregnancy loss; sex hormones; thrombosis

Introduction

Gastroschisis is an abdominal wall defect whose birth prevalence is rising in most of the birth defects reporting registries worldwide (Vu et al., 2008; Castilla et al., 2008; Chabra et al., 2011; Loane et al., 2011). Although this increase is not restricted to young mothers (Loane et al., 2007), no doubt seems to exist that young maternal age is associated with gastroschisis, and several lifestyle and biological factors related to young mothers have been studied (Werler et al., 1992; Rasmussen and Frías, 2008, Feldkamp et al., 2008a,b; Burdan et al., 2012), without reaching any conclusive results. However, and despite the amount of literature, we are not aware of any study which, by comparing risk factors, attempted to establish differences between young mothers of infants with gastroschisis and same aged mothers of infants with other birth defects. The purpose was to identify specific epidemiological characteristics and risk factors of young (< 20 years) mothers of infants with gastroschisis, by comparing them with same aged mothers of infants with other birth defects and of nonmalformed infants.

Material and Methods

The study was carried out with data of infants diagnosed in 155 maternity hospitals of the ECLAMC network. ECLAMC, a program aimed at the research and surveillance of birth defects, is in operation since 1967 through a network of maternity hospitals in 10 South American countries. Participation is voluntary, complying with operational guidelines and periodically assessing the minimum data quality criteria. Ascertainment and reporting of birth defects in live and stillborn infants are performed by specially trained pediatricians. Miscarriages with congenital anomalies and pregnancy terminations, which are illegal in South America, are not recorded (Castilla and Orioli, 2004; Castilla et al. 2008).

ECLAMC data base records of live and stillborn infants with gastroschisis (cases) and those with the following birth defects (malformed controls) were selected: omphalocele, spina bifida, hydrocephaly, cleft lip with or without cleft palate, and Down syndrome. The selection of these five birth defects was based on similarities and differences with gastroschisis of certain epidemiological or biological characteristics that were considered useful for comparison.

Supported by Agencia Nacional de Promoción Científica y Tecnológica (MINCyT), Argentina.; contract grant numbers: PICT 2008-0429; PICT 2010–2798.
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Published online 0 Month 2015 in Wiley Online Library (wileyonlinelibrary.com). Doi: 10.1002/bdra.23374

Infants without birth defects were taken as nonmalformed controls.

To confirm the association between gastroschisis and young maternal age, the frequencies of mothers aged < 20 years were compared between cases and controls of the whole ECLAMC database for the 1982 to 2010 period (3,390,212 total births). For the rest of the study, only cases and controls with maternal age < 20 years were selected, while those aged ≥ 20 years were excluded.

Prevalence at birth over time of the selected birth defects was calculated by using a Poisson regression.

To ensure certain homogeneity in the use of prenatal ultrasound, the period January 1, 1995, to December 31, 2010, was taken for comparison of the following variables between mothers of infants with gastroschisis, and of malformed and nonmalformed controls: *Demographic:* Young paternal age (< 24 years), low maternal and paternal education (< 7 years schooling), low paternal occupation (unemployed or unqualified worker), parental consanguinity, and maternal and paternal ancestry (Native American, African American, Latin European). *Reproductive:* Previous pregnancy loss (miscarriage or fetal loss), short inter-birth interval (< 1 year), change in paternity (different partner than of previous pregnancy). *Current pregnancy:* gravidity (primigravid, multigravid), short time of cohabitation with current partner (< 1 year), poor prenatal control (< 5 visits), specific prenatal diagnosis of the defect, medication, maternal illnesses (acute or chronic), smoking, alcohol, and use of illicit drugs at any time during pregnancy.

Information was obtained by pediatricians who interviewed the mothers before their discharge from the hospital, as part of the standard ECLAMC procedure. The frequency of each variable was compared among the 6 birth defects (chi square test, 5 degrees of freedom) and the contribution of each birth defect to the overall chi square was established.

Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained for each risk factor to identify variables significantly associated with gastroschisis when compared with nonmalformed and with the total of malformed controls. A multivariate logistic regression was performed with the variables previously shown to be significantly associated with gastroschisis, and with at least 90% of specified data. To increase sensitivity, for this step, the limit of significance was set at 10%. To detect a minimum two-fold risk, with an approximately 10% exposure, a 20% beta- and a 5% alpha-errors, the calculated sample size was of at least 200 for each cases and controls.

As ECLAMC is a hospital based program and many of its hospitals are referral centers, both analyses were adjusted by hospital and year of birth. Data were analyzed with the statistical software StataCorp LP, version 12.0, College Station, TX.

Results

The association between gastroschisis and young maternal age, as well as an increase over time for gastroschisis were confirmed (Appendix and Fig. 1). Of the six birth defects under study, only infants with gastroschisis showed a significant excess of mothers younger than 20 years, while only gastroschisis and hydrocephaly showed an increasing secular trend during the period under study (12% and 4% per year, respectively).

The frequency of several variables was heterogeneous among mothers of infants with birth defects (Table 1). When compared with mothers of the other selected birth defects, mothers of infants with gastroschisis were more often of African and less of Native ancestry; they had had more previous pregnancy losses, predominantly miscarriages, adequate prenatal control (5 or more visits), had taken more medication, and prenatal diagnosis of the defect was more often made.

In Table 2, the comparisons of risk factors between mothers of cases and controls are shown. For the following variables, the association with gastroschisis was significantly higher than with the other birth defects: African ancestry, previous pregnancy losses, adequate prenatal control, prenatal diagnosis of the defect, and medication and smoking during pregnancy, while the risk of Native ancestry was lower.

The following variables were of significant risk for gastroschisis when compared with nonmalformed controls: previous pregnancy losses, medication, maternal illnesses, and alcohol drinking. Among the medications and illnesses, mothers who had taken sex hormones and antacids, and those who had had urinary tract infections showed a higher risk for gastroschisis than for other birth defects (OR = 1.94, 95% CI, 1.14–3.24; OR = 2.55, 95% CI, 1.17–5.54; OR = 1.48, 95% CI, 1.12–1.95, respectively).

After adjusting for the significantly associated variables, only previous pregnancy losses maintained its significance when compared with malformed, as well as with nonmalformed controls (OR = 2.34, 95% CI, 1.37–3.97, $P = 0.002$; OR = 3.43, 95% CI, 2.07–5.66, $P < 0.001$, respectively). The association with prenatal diagnosis was also higher for gastroschisis than for other birth defects (OR = 3.53, 95% CI, 2.05–6.08, $P < 0.001$). When gastroschisis mothers were classified according to gravidity and previous pregnancy losses, a risk gradient was observed, showing that the risk was highest for multigravid mothers with a previous pregnancy loss, followed by primigravidae, and lowest for multigravid mothers without a previous loss (Table 3).

Discussion

The present study revealed a pattern for young mothers of infants with gastroschisis, that was different from mothers of the same age but with different pregnancy outcomes (newborns either not malformed or with other birth defects).

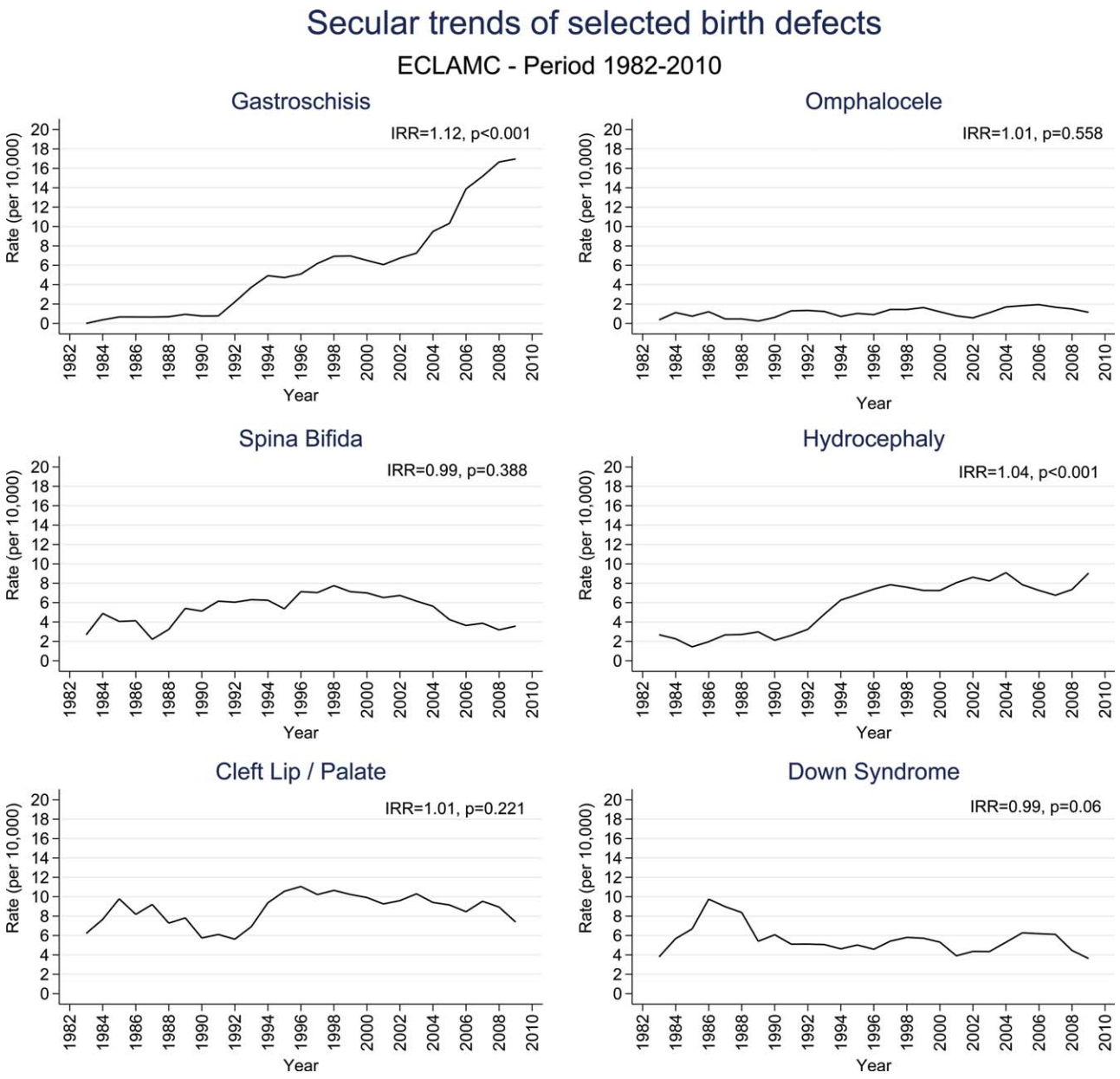

FIGURE 1. *Secular trends of selected birth defects.*

The higher frequency of young maternal age and the increasing secular trend of gastroschisis was confirmed, while previous pregnancy losses and the use of medication were identified as risk factors specific for gastroschisis.

SECULAR TREND

A secular trend increase of gastroschisis has been observed by many birth defects registries (Clearinghouse, 2012) and several operational (nonbiological) factors may have contributed, such as better diagnostic tools, greater access to health services, and an increased survival due to improvement of obstetrical, clinical, and surgical management (Murphy et al., 2007; Niramis et al., 2011), thereby reducing the proportion of possibly missed or not reported cases because of prenatal or early neonatal death. Furthermore, the use of prenatal ultrasound, starting in the 80s and rapidly expanding thereafter, has contributed to the improvement of differential diagnoses between gastroschisis and other abdominal wall defects.

Remarkably, in ECLAMC, which started operating in 1967, the first gastroschisis case was only reported in

TABLE 1. *Variables for Gastroschisis and for Five Other Selected Birth Defects (1995–2010)*[a]

	GS	Ompha	SB	Hydro	CL/CP	Down		
	N **= 472**	***N*** **= 65**	***N*** **= 275**	***N*** **= 390**	***N*** **= 469**	***N*** **= 245**		
Variables	**%**	**%**	**%**	**%**	**%**	**%**	X_2^5	***p***
Demographic								
Young paternal age	76.0	76.6	75.3	74.8	75.2	78.0	0.968	0.965
Low maternal education	26.1	20.6	22.2	32.0*	23.2	21.6	14.340	0.014
Low paternal education	20.5	25.0	27.7	28.5*	21.0	20.3	12.472	0.029
Low paternal occupation	53.8	60.7	61.5	56.9	58.9	55.8	4.983	0.418
Parental consanguinity	1.5	3.2	1.9	2.1	1.5	1.7	1.312	0.934
Native	56.6*	58.1	66.4	62.5	76.4*	75.1	52.562	<0.001
African	30.4*	24.2	21.0	27.7*	11.7*	16.0	59.431	<0.001
Latin European	10.0	11.3	9.2	6.1	7.5	6.8	6.385	0.271
Reproductive								
Previous pregnancy loss	38.2*	42.1	31.9	19.8	18.2	12.3*	25.757	<0.001
Short inter-birth interval	3.5	13.3	9.1	6.0	9.0	6.8	2.926	0.711
Change in paternity	24.0	18.8	22.6	17.9	14.6	25.5	4.670	0.457
Current pregnancy								
Primigravidity	78.0	74.2	75.5	74.3	72.4	77.4	4.602	0.466
Short time of cohabitation	28.7	21.1	24.2	25.5	28.5	31.8	5.207	0.391
Poor prenatal control	22.8*	34.0	18.8*	33.2	32.9	34.2	28.203	<0.001
Prenatal diagnosis	73.4*	37.5	59.4*	78.6*	12.4*	3.3*	714.448	<0.001
Medication	83.1*	72.3	75.3	75.1	70.6	68.2	28.454	<0.001
Maternal illness	49.7	42.2	43.4	44.4	46.4	45.0	4.157	0.527
Smoking	30.6	22.2	23.2	18.9	19.9	33.8	10.573	0.060
Alcohol	26.2	31.0	18.2	14.9	22.5	17.7	7.731	0.172
Illicit drugs	2.0	3.9	1.6	1.9	0.8	1.7	1.412	0.923

[a]X_2^5 = chi square, 5 degrees of freedom. *$p < 0.01$.

GS, gastroschisis; Ompha, omphalocele; SB, spina bifida; Hydro, hydrocephaly; CL/CP, cleft lip with or without cleft palate.

1982, while thereafter, and most notably since 1990, its birth prevalence has increased steadily. This was confirmed after reviewing all abdominal wall defect cases and correcting possible misdiagnoses (Castilla et al., 2008). In hospital-based programs, the secular trend increase of gastroschisis, among other defects, such as hydrocephaly, largely depends on prenatal ultrasound diagnosis and referral to tertiary centers. However, this factor can only explain part of the observed increasing trend. When cases with and without prenatal diagnosis were compared, a significantly larger 19% per year increase was observed for the former than the 4% of the latter. However, even for those without prenatal diagnosis, the 1.2/10,000 frequency in 1985 reached 4.9/10,000 in 2010, similar to values reported to the International Clearinghouse for Birth Defects Surveillance and Research (www. icbdsr.org) by some population-based registries, such as Canada and Norway, and to the significant 6% per 2-years increasing Pan-European trend, observed by Loane et al. (2011) with the EUROCAT statistical monitoring system. Therefore, some other factor/s must be involved, and some kind of interaction between operational and biological factors should be considered.

LIFESTYLE FACTORS

Undoubtedly, young maternal age is a significant risk factor for gastroschisis, and although some hypotheses have been brought up (Lubinsky, 2012), its meaning remains unclear. Some studies have found an association between gastroschisis and lifestyle or other age related factors, such as alcohol (Torfs et al., 1994; Richardson et al., 2011), smoking (Werler et al., 2003; Lam and Torfs, 2006; Feldkamp et al., 2008a), illicit drugs (Werler et al., 2003;

TABLE 2. *Risk Factors for Gastroschisis*

	GS vs. non-malformed			GS vs. other BDs		
Variables	**OR**	**CI**	**p**	**OR**	**CI**	**p**
Demographic						
Young paternal age	1.03	0.81-1.31	0.807	0.98	0.75-1.28	0.889
Low maternal education	0.95	0.62-1.45	0.802	1.06	0.70-1.59	0.786
Low paternal education	0.78	0.56-1.09	0.140	0.80	0.59-1.08	0.142
Low paternal occupation	1.07	0.57-2.00	0.828	0.83	0.66-1.04	0.105
Parental consanguinity	1.57	0.76-3.25	0.225	0.82	0.33-2.06	0.674
Native	0.70	0.39-1.26	0.237	0.57	0.33-0.99	0.046
African	1.41	0.67-2.70	0.372	1.85	0.94-3.63	0.076
Latin European	1.31	0.66-2.59	0.441	1.37	0.66-2.84	0.399
Reproductive [a]						
Previous pregnancy loss	2.71	1.63-4.52	0.000	2.20	1.35-3.58	0.002
Short inter-birth interval	0.54	0.13-2.34	0.412	0.40	0.09-1.72	0.218
Change in paternity	1.25	0.71-2.21	0.437	1.37	0.79-2.35	0.259
Current pregnancy						
Primigravidity	1.03	0.82-1.37	0.655	1.22	0.95-1.55	0.117
Short time of cohabitation	1.16	0.68-1.24	0.330	1.08	0.78-1.50	0.623
Poor prenatal control	0.90	0.68-1.17	0.420	0.67	0.51-0.89	0.006
Prenatal diagnosis	-	-	-	4.34	2.98-6.34	0.000
Medication	1.73	1.14-2.63	0.010	1.74	1.19-2.56	0.004
Maternal illness	1.53	1.25-1.87	0.000	1.21	0.96-1.53	0.104
Smoking	1.29	0.91-1.84	0.154	1.51	0.98-2.33	0.062
Alcohol	1.53	0.97-2.43	0.068	1.46	0.90-2.35	0.121
Illicit drugs	1.19	0.39-3.62	0.761	1.24	0.35-4.41	0.741

GS, gastroschisis; BD, birth defect; OR, Odds ratio; CI, confidence interval
[a]Only multigravidae

Draper et al., 2007), stress (Palmer et al., 2013), short interpregnancy intervals (Getz et al., 2012), change in paternity (Chambers et al., 2007), diet (Paranjothy et al., 2012), over the counter drugs, such as acetaminophen (Burdan et al., 2012) and aspirin (James et al., 2008). The present work, however, showed that none of these factors was stronger associated with mothers of infants with gastroschisis than with mothers of the same age but with different pregnancy outcomes.

BIOLOGICAL FACTORS

This work revealed previous pregnancy losses, predominantly miscarriages, as the main risk factor for gastroschisis and significantly more frequent in young gastroschisis mothers than in other mothers of the same age. Several studies have shown that primigravidae were at high risk for gastroschisis (Hougland et al., 2005; Vu et al., 2008; Benjamin et al., 2010; Duong et al., 2012). Here, however, it was demonstrated that the risk of young women with a previous miscarriage was even greater than that of primigravidae, while it was lowest for those who had had a normal previous pregnancy. The association between a previous miscarriage and an infant with gastroschisis in a

TABLE 3. *Risk Gradient for Previous Pregnancy Losses (PPL)*

	GS vs. non-malformed			GS vs. other BDs		
	OR	**CI**	***p***	**OR**	**CI**	***p***
Multigravidae with PPL	2.71	1.63-4.52	0.000	2.20	1.35-3.58	0.002
Primigravidae	1.43	0.99-2.07	0.057	1.56	1.12-2.20	0.009
Multigravidae without PPL	1.00			1.00		

GS, gastroschisis; BD, birth defect; OR, odds ratio; CI, confidence interval.

subsequent pregnancy suggests that the etiologic factor/s is related to both events.

To our knowledge, a relationship between gastroschisis and previous miscarriages has only been mentioned in one study (Getz et al., 2012), which, however, was limited to mothers with short interpregnancy intervals. The authors found that the risk of such a short interval was higher if the previous pregnancy had ended in miscarriage and they considered a secondary inflammatory effect as possibly responsible. This theory could also stand for our work, where, however, the identified risk factor was the miscarriage, regardless of the interpregnancy interval which is expected to be shorter after a miscarriage.

In our study, gastroschisis mothers had used more sex hormones than other birth defects mothers, perhaps because of their history of reproductive failures. The use of sex hormones was twice as high in mothers with previous miscarriages, but the sample size was probably too small to achieve statistical significance (data not shown). Similarly, in a case-control study, Waller et al. (2010a) found a significant association between oral contraceptives and two among 32 birth defects, namely, gastroschisis and hypoplastic left heart syndrome. Previous miscarriages were not analyzed.

In gastroschisis mothers, an excess of pregnancy losses and exposure to sex hormones can both be related to thrombosis, in agreement with Lubinsky (2012) who suggested a relationship between a hyperthrombotic status during pregnancy and gastroschisis. High estrogen levels are typical for young women at early gestational stages, and it could be hypothesized that the thrombophilic effect of estrogens causes gastroschisis through a disruptive mechanism. In addition, an association between abdominal wall defects and maternal exposure to atrazine, an endocrine disruptor with estrogenic effect, and commonly used as herbicide, has been demonstrated (Mattix et al., 2007; Waller et al., 2010b; Agopian et al., 2013).

Furthermore, we showed that maternal urinary tract infections, recognized as predisposing for venous thromboembolism (Lee, 2005), were significantly associated with gastroschisis, in accordance with other reports (Draper et al., 2007; Feldkamp et al. 2008b) and with Yazdy et al. (2014) who observed a synergistic effect between young maternal age and urinary tract infections. Thrombophilia is a recognized cause of reproductive failures, and could represent a common cause for both gastroschisis and the observed excess of miscarriages in gastroschisis mothers. Notably however, a literature search did not yield any significant association between thrombophilia and gastroschisis.

Cardonick et al. (2005) have analyzed the genetic predisposition to thromboembolism in infants with gastroschisis by testing them for three mutations related with thrombotic conditions (Factor V Leiden, prothrombin, and MTHFR). The results, which were only conclusive for the latter, led the authors to doubt about a role of MTHFR in gastroschisis, but perhaps other mutations predisposing to thrombosis might be involved.

STRENGTHS AND LIMITATIONS

The main strength of the study resided in the magnitude of ECLAMC series of infants with birth defects, allowing for a large enough sample of mothers younger than 20 years. Further strengths are the availability of verbatim descriptions, and that ascertainment and reporting are performed by pediatricians specially trained in diagnosing and describing birth defects, and who assure homogeneous data by following clearly defined rules. Furthermore, considering possible diagnostic mistakes, all cases with an abdominal wall defect of the ECLAMC database were reviewed and, if necessary, recoded, thereby increasing the diagnostic reliability of gastroschisis. The ECLAMC database provides information on more than 50 risk factors, including lifestyle issues, such as use of alcohol, illicit drugs, and smoking.

Recognized limitations are those related to hospital-based programs, such as uncertain prevalence values due to patients transfer to tertiary centers, and those related to retrospective case control studies, such as the memory bias for data obtained by interviewing the mothers. Terminations of pregnancy because of fetal anomalies are illegal in all South American countries. Therefore, information on spontaneous or induced abortions might be unreliable. To minimize some of these effects, both nonmalformed and malformed infants were taken as controls. Further limitations were unavailable data on some variables possibly relevant in gastroschisis, such as maternal body mass index or nutritional status, as well as the possible existence of unknown and therefore unconsidered confounders.

CONCLUSIONS

This work showed that neither primigravidity nor most of the lifestyle factors mentioned in the literature and common to teenagers are stronger associated with young mothers of infants with gastroschisis than with mothers of the same age but with different pregnancy outcomes.

Previous pregnancy losses were identified as the main risk factor for gastroschisis, while they were not associated with the other selected birth defects. We showed that young women with a previous miscarriage were at greater risk for gastroschisis than primigravidae, while the risk was lowest for those who had had a normal previous pregnancy.

We propose that a relationship exists among young maternal age, pregnancy losses, sex hormones, thrombosis, and gastroschisis. Although no evidence could be found for an association between thrombophilia and gastroschisis, some less frequent thrombotic conditions or a certain thrombophilic gene background cannot be ruled

out as predisposing factors and should be further analyzed.

Acknowledgments

The authors thank all the people working in collaboration in ECLAMC, a network that has been active for more than 40 years.

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APPENDIX

Young Mothers (< 20 Years) of Infants with Gastroschisis and of Malformed and Non-malformed Controls (1982–2010)

	Young mothers					
	N	**%**	**Expected**	**O/E**	**Z**	***p***
Gastroschisis	504	44.1	224	2.25	348.69	<0.01
Omphalocele	80	13.2	119	0.67	12.90	<0.01
Spina bifida	360	14.8	477	0.75	28.90	<0.01
Hydrocephaly	448	21.5	409	1.09	3.63	
CL/CP	589	13.3	870	0.68	90.67	<0.01
Down syndrome	342	5.4	1243	0.28	653.28	<0.01
Non-malformed	21992	19.6[a]	22004	1.00		

[a]Expected value.

CL/CP, cleft lip with or without cleft palate; %, young mothers/total mothers (3,390,212); O/E, Observed/Expected.