Major birth defects in the Brazilian side of the triple border: a population-based cross-sectional study

Suzana de Souza 1,2,3*, Fernando Kenji Nampo 1,2 and Cezar Rangel Pestana 1,3

Abstract

Background: Major birth defects increase the risk of fetal death and pediatric hospitalization, which also impact on healthcare costs. Sociodemographic factors can drastically affect reproductive health and be used to discriminate the exposure to hidden risk factors. Foz do Iguassu is a Brazilian city located in the triple-border region of Brazil / Paraguay / Argentina with high rates of birth defects. However, no study aimed to verify factors associated with this incidence or preventive care is reported. The current work investigated the prevalence of major birth defects and its association with maternal sociodemographic factors in Foz do Iguassu.

Methods: In this population-based cross-sectional study, we used data of all live births occurred in Foz do Iguassu from 2012 to 2017. The associated sociodemographic variables such as maternal age, maternal education, maternal race, country of residence, maternal parity and onset of prenatal care were analyzed. Each major birth defect was described according to absolute and relative frequencies, Kruskal-Wallis and logistic regression models were used to evaluate variables associated with selected birth defects.

Results: The most prevalent major birth defects were Cleft Lip and/or Palate (9.5/10,000), gastroschisis (6.93/10,000), spina bifida (5.53/10,000), hydrocephalus (5.53/10,000), hypospadias (4.55/10,000), Down syndrome (4.23/10,000), anencephaly (2.93/10,000), anorectal atresia / stenosis (1.95/10,000), undetermined sex (1.95/10,000), esophageal atresia / stenosis with or without fistula (1.63/10,000) and limb reduction defects (1.30/10,000). Maternal age was associated with gastroschisis and Down syndrome. Only maternal education up to 7 years was statistically associated with major birth defects considering all other sociodemographic variables.

Conclusion: Cleft Lip and/or Palate and Gastroschisis prevalence were higher than those found in the literature. This finding may suggest a distinct epidemiological behavior regarding major birth defects in the region. The work opens new perspectives for birth defects risk factors in the triple-border.

Keywords: Major birth defect, Prevalence, Risk factors, Border region

* Correspondence: suzanasesouza@gmail.com
1 Latin-American Institute of Life and Natural Sciences, Federal University of Latin-American Integration, Foz do Iguaçu, Parana, Brazil
2 Evidence-Based Public Health Research Group, Foz do Iguaçu, Brazil

Full list of author information is available at the end of the article

© The Author(s). 2020 Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.
Background
Birth defects are structural, functional, or metabolic disorders diagnosed at birth or in the course of life [1]. They are classified as major or minor depending on severity and represent a challenge for clinical and a public health [1–3]. The most common major birth defects involves cardiovascular and nervous systems [4, 5]. Birth defects are multifactorial and related to genetics and environmental factors, which also may vary according to sociodemographic, cultural and economic condition [6]. Sociodemographic factors may affect reproductive health by distinct exposure to risk factors as access to health services and nutrition. Identifying these factors is important to address proper preventive care [7].

In Brazil, the staff from the hospital where the delivery occurred collects data regarding pregnancy care, and maternal and newborn characteristics using a paper-based form (Declaration of Live Birth). Then, this form is sent to the Municipal Health Department, which inputs the data from all births into the web-based Information System on Live Births (SINASC). If a neonate presents a birth defect, this information is recorded into the Declaration of Live Birth and the birth defect is coded according to Chapter XVII of the International Classification of Diseases Review 10 (ICD-10). The aggregated data is available on the Brazilian government website for epidemiological assessment. Foz do Iguassu is a Brazilian city located in the triple-border region of Brazil / Paraguay / Argentina, according to government records, in the period from 2012 to 2017, Foz do Iguassu presented a birth defect rate of 11.78 / 1000 live births, roughly 50% more than that observed in the state of Paraná and Brazil (7 / 1000 live births and 8.07 / 1000 live births respectively) [8]. In addition, while about 6% of all neonatal deaths worldwide are attributed to birth defects [4], birth defects are the main cause of neonatal mortality in Foz do Iguassu, accounting for 28% of the deaths occurred within the first 28 days of life [8, 9].

Despite the high rates of birth defects in this region, the risk factors associated with its occurrence have not been studied yet. The present work aims to describe the prevalence of major birth defects and its association with maternal sociodemographic factors in Foz do Iguassu. The results may contribute to the understanding of how sociodemographic factor influence the occurrence of major birth defects in Brazil’s borderlines.

Methods
Study design
This is a population-based cross-sectional study.

Settings and participants
Data regarding births in Foz do Iguassu between 2012 and 2017 was obtained from the Municipal Health Department. All live births in this period were eligible. Declaration of Live Birth forms lacking birth defect identification field were excluded.

Data sources and variables
The 25 most severe major birth defects were selected to the study [10, 11]. The classification according to the affected system is presented in Table 1. The dependent variable was the presence of major birth defects and independent variables were maternal age (years); maternal education (up to 7 years of study vs more than 7 years of study); maternal race (white vs black, brown, yellow, or indigenous); country of residence (Brazil vs Paraguay or Argentina); maternal parity (primiparous vs multiparous); onset of prenatal care (first trimester vs after the first trimester).

Statistical methods
Birth defects was expressed as both absolute and relative frequency (per 10,000 live births). The association

| System             | Birth defect                                         |
|--------------------|------------------------------------------------------|
| Central nervous system | Anencephalus                                           |
|                    | Hydrocephalus                                          |
|                    | Holoprosencephaly                                      |
|                    | Spina bifida                                           |
| Ear                | Anophthalmia                                           |
|                    | Anotia/microtia                                        |
| Cardiovascular     | Transposition of the great arteries                    |
|                    | Tetralogy of Fallot                                    |
|                    | Left heart hypoplasia                                  |
|                    | Coarctation of the aorta                               |
| Cleft Lip and/or Palate (CLP) | Cleft lip/palate/lip and/or palate                      |
| Gastrointestinal   | Esophageal atresia/stenosis with or without fistula    |
|                    | Small intestine atresia/stenosis                       |
|                    | Anorectal atresia/stenosis                             |
| Genitourinary      | Hypospadias                                            |
|                    | Undetermined sex                                       |
|                    | Renal agenesis                                         |
|                    | Cystic kidney                                          |
| Musculoskeletal systems | Limb reduction defects                           |
|                    | Diaphragmatic hernia                                    |
|                    | Omphalocele                                            |
|                    | Gastrochisis                                           |
| Chromosomal anomalies | Patau syndrome                                     |
|                    | Edwards syndrome                                       |
|                    | Down syndrome                                          |
between maternal age and birth defect was analyzed for each of the most prevalent major birth defects (anencephaly, spina bifida, hydrocephalus, CLP, esophageal atresia/stenosis with or without fistula, anorectal atresia/stenosis, undetermined sex, limb reduction defects, hypospadias, gastroschisis, and Down syndrome). We also pooled all birth defects to analyze the association between the other independent variables and the occurrence of birth defect.

Shapiro-Wilk test was applied to verify data distribution in each birth defect and Kruskal-Wallis test was used to verify differences between the mean maternal age of newborns with and without major defects.

Maternal education, maternal race, country of residence, maternal parity and the onset of prenatal care were described according to absolute and relative frequencies considering the distribution of newborns with and without major birth defects. To investigate the maternal sociodemographic factors associated with birth defects, a logistic regression models were proposed. Unadjusted and adjusted models were performed. The strength of association between dependent and independent variables was estimated by the Odds Ratio (OR) with 95% Confidence Interval (95% CI). Statistical analyses were conducted in Epi Info 7® and BioEstat 5.3®.

**Results**

A total 30,761 births were registered in Foz do Iguassu from 2012 to 2017. 32 (0.001%) cases were excluded due to no filled birth defect identification field. Among 305 (0.99%) cases of birth defects, 140 (46%) corresponded to selected major birth defects included in this study.

CLP was the most prevalent birth defect with 9.5 /10,000 live births (lip (N = 3), palate (N = 15), lip and palate (N = 11)) with mean maternal age of 26.4 ± 6.8 years. Among CLP cases, 41% (N = 12) presented more than one birth defect. Gastroschisis was the second most prevalent birth defect with 6.83 /10,000 live births (N = 21) and a mean maternal age of 21.5 ± 4.4 years. Birth defects of nervous system (anencephaly, spina bifida, and hydrocephalus) accounted for 43 cases with a mean maternal age of 25.6 ± 9.2 years, 25.2 ± 6.5 and 24.5 ± 5.1 years, respectively. Down syndrome had 4.23 /10,000 live births (N = 13) and the highest mean maternal age of 33.5 ± 7.3 years; including 3 cases with cardiovascular defect as well. Holoprosencephaly, Transposition of the great arteries, Tetralogy of Fallot, Coarctation of the aorta, Omphalocele, Patau syndrome, and Edwards syndrome 10 of the 140 included neonates presented more than one major birth defect at first trimester (20% vs 16%). In the logistic regression analysis, maternal education up to 7 years was the only variable associated with the major birth defects in both unadjusted and the adjusted analyzes (Unadjusted: OR = 2.33; CI 95% = 1.07 – 5.33; p = 0.0213) (Table 3). Regarding maternal age, gastroschisis was statistically associated with younger mothers (21.5 ± 4.4 years) whereas Down syndrome was associated with older maternal age (33.5 ± 7.3 years) when compared to no birth defects (26.6 ± 6.5 years) (Table 4).

**Table 2** Description of the major birth defects according to the rate per 10,000 live births

| Major birth defect | N  | Rate/10,000 |
|--------------------|----|-------------|
| Cleft lip and/or palate | 29 | 9.5 |
| Gastroschisis | 21 | 6.83 |
| Spina bifida | 17 | 5.53 |
| Hydrocephalus | 17 | 5.53 |
| Hypospadias | 14 | 4.55 |
| Down syndrome | 13 | 4.23 |
| Anencephalus | 9 | 2.93 |
| Anorectal atresia/stenosis | 6 | 1.95 |
| Undetermined sex | 6 | 1.95 |
| Esophageal atresia/stenosis with or without fistula | 5 | 1.63 |
| Limb reduction defects | 4 | 1.30 |
| Left heart hypoplasia | 2 | 0.65 |
| Small intestine atresia/stenosis | 2 | 0.65 |
| Diaphragmatic hernia | 2 | 0.65 |
| Anophthalmia | 1 | 0.33 |
| Anotia/microtia | 1 | 0.33 |
| Renal agenesia | 1 | 0.33 |
| Cystic kidney | 1 | 0.33 |

**Discussion**

This is the first study aimed to investigate the association between sociodemographic factors and major birth defects in Brazil triple side border. The most prevalent major birth defects were CLP, gastroschisis, spina bifida, hydrocephalus, hypospadias, Down syndrome, anencephaly, anorectal atresia/stenosis, undetermined sex, esophageal atresia/stenosis with or without fistula and limb reduction defects. Maternal age was statistically positive associated with only gastroschisis and Down syndrome. Regarding other maternal sociodemographic factors, only maternal education up to 7 years was statistically associated with major birth defects.
Despite not being a major cause of mortality, CLP causes considerable morbidity and imposes a substantial financial cost for families and health system. In Brazil, 2794 surgical procedures were performed for CLP repair between 2009 and 2013, with costs above 1.507 million dollars [12]. The prevalence of CLP observed was 9.5/10,000 live births, higher than 8.23/10,000 live births found in the south Brazil. Other regions such as the northeast and southeast reported rates of 4.55/10,000 live births and 6.18/10,000 live births, respectively [13, 12]. Besides, the percentage of 41% were syndromic and associated with other cognitive or structural defects, a higher prevalence compared to approximately 30% describe in the literature [14].

Central nervous system defects accounted for 43 (31%) of total cases and have been reported as the most common outcome. This fact may reflect the complex interactions between genes and poorly understood environmental factors [15]. Literature has also shown that prenatal vitamin supplements reduce the incidence of neural tube defects [16], which emphasizes the relevance of early prenatal care particularly in the first

### Table 3 Factors associated with major birth defects: unadjusted and adjusted odds ratio

| Variável               | With major birth defect | Without major birth defect | Unadjusted | Adjusteda | p value | Adjusteda | p value |
|------------------------|-------------------------|-----------------------------|------------|-----------|---------|-----------|---------|
| Maternal education     |                         |                             |            |           |         |           |         |
| Up to 7 years of study | 41 (30)                 | 6.739 (22)                  | 1.46b      | 1.01–2.10 | 0.0414  | 1.58b     | 1.07–2.33 | 0.0213  |
| More than 7 years of study | 99 (70)              | 23.792 (78)                 | 1.00       | –         | –       | –         | –       |
| Maternal race          |                         |                             |            |           |         |           |         |
| White                  | 92 (65.7)               | 19.118 (62.9)               | 1.00       | –         | –       | –         | –       |
| Other                  | 48 (34.3)               | 11.297 (37.1)               | 0.88       | 0.62–1.25 | 0.4854  | 0.82      | 0.57–1.19 | 0.3078  |
| Country of residence   |                         |                             |            |           |         |           |         |
| Brazil                 | 129 (92.1)              | 28.894 (94.5)               | 1.00       | –         | –       | –         | –       |
| Others                 | 11 (7.9)                | 1.695 (5.5)                 | 1.45       | 0.78–2.69 | 0.2392  | 1.11      | 0.54–2.29 | 0.7611  |
| Maternal parity        |                         |                             |            |           |         |           |         |
| Primiparous            | 59 (42)                 | 11.862 (39)                 | 1.00       | –         | –       | –         | –       |
| Multiparous            | 81 (58)                 | 18.596 (61)                 | 0.87       | 0.62–1.22 | 0.4392  | 0.82      | 0.58–1.18 | 0.2981  |
| Onset of prenatal care |                         |                             |            |           |         |           |         |
| First trimester        | 104 (80)                | 24.974 (84)                 | 1.00       | –         | –       | –         | –       |
| After the first trimester | 27 (20)              | 4.782 (16)                  | 1.35       | 0.88–2.07 | 0.1590  | 1.29      | 0.83–1.99 | 0.2450  |

aEstimates adjusted for all variables in the table
bStatistically significant association

### Table 4 Association between major birth defects and maternal age

| Maternal agea | p valueb |
|---------------|----------|
| Born without birth defect | 26.6 (6.5) | > 0.9999 |
| Anencephalus    | 25.6 (9.2) | > 0.9999 |
| Spina bifida    | 25.2 (6.5) | > 0.9999 |
| Hydrocephalus   | 24.5 (5.1) | > 0.9999 |
| Cleft lip and/or palate | 26.4 (6.8) | > 0.9999 |
| Esophageal atresia/stenosis with or without fistula | 20.4 (5.5) | 0.2730 |
| Anorectal atresia/stenosis | 27 (5.1) | > 0.9999 |
| Hypospadias     | 26.7 (5.4) | > 0.9999 |
| Undetermined sex | 25.7 (5.1) | > 0.9999 |
| Limb reduction defects | 30.3 (7.9) | > 0.9999 |
| Gastroschisis   | 21.5 (4.4) | 0.0022c |
| Down syndrome   | 33.5 (7.3) | 0.0073c |

aMean and standard deviation
bKruskal-Wallis test
cStatistically significant association
trimester of pregnancy. Moreover, families should receive a comprehensive assistance after the diagnosis of birth defect, including better explanation about physical or mental disabilities and proper care. Besides, intrauterine surgical interventions may also be necessary after pregnancy [17].

Compared to other studies, a low number of cardiovascular birth defects (i.e. transposition of the great arteries, tetralogy of Fallot, left heart hypoplasia, or coarctation of the aorta) were observed in the present study [10, 18, 19]. These defects may not be diagnosed right after birth when data in SINASC is collected.

The association between Down syndrome and advanced maternal age is well described in the literature [20–22]. However, its prevalence was lower than reported in other studies, likely as a result of the high prevalence of young pregnant in the region. Developed countries have shown late pregnancy in women older than 35-years old increases the prevalence of Down syndrome [23].

Gastroschisis is a full-thickness defect in the abdominal wall, usually in the right side of normal umbilical cord insertion [24]. The prevalence observed in the present study was 6.83 / 10,000 live births, higher than 3.8 per 10,000 live births found in the literature [25, 26] [10, 27]. In addition, significant differences between the mean maternal age of mothers with and without gastrochisis were observed. Previous studies support the increased risks for gastroschisis with younger maternal age [28, 29]. The etiology of gastrochisis is still unclear; however, the increased risk observed among younger women suggests it may be associated with low body mass index, tobacco or drug abuse, genitourinary infections and sexually transmitted diseases [30–35].

About 60% of birth defects have unknown etiology. Genetic defects such as chromosomal disorders are more often investigated when compared to environmental factors [18]. The exposure to potential teratogens is crucial to estimate the risk associated with the social context [36, 37]. In fact, the etiological complexity of birth defects, maternal sociodemographic factors may influence adverse outcomes in embryonic development [36]. In the present study, maternal education up to 7 years was associated with major birth defects. Low maternal education may also impact on health and nutritional care with early pregnancy and exposure to teratogenic agents [37]. Another relevant social variable is access to early prenatal care including vaccination and vitamin supplementation would reduce the risk in some cases.

We also hypothesized the high incidence of some major birth defects may be related to the indiscriminated use of pesticides in the region with mutagenic and endocrine disruption properties [38]. The exposure of pregnancies to pesticides is associated with a higher chance of CLP, neural tube defects, congenital heart disease [39]. Foz do Iguassu is predominantly urban but surrounded by agricultural regions in both Brazil and Paraguay sides.

Another potential risk factor considered is the residence proximity to the Electromagnetic Fields (EMF) from one of the world largest producers of energy power lines in this area. Studies have suggested an association between exposure to EMF and leukemia, abortion, and birth defects [40–44]. We emphasize the need for additional research concerning chronic pesticides and EMFs exposure as potential harmful environmental factors.

In our study, we analyzed only records of live births based on data collected at delivery. Considering that birth defects are an important cause of abortion, the prevalence of birth defects presented in our study may be underestimated, so comparisons with other settings should be done with caution. It is important to note that the Brazilian Mortality Information System (SIM) only records fetal death that occurred after 19 weeks of gestation; thus, severe congenital defects associated with abortions within the first 19 weeks of gestation would never get registered. Also, some defects are not easily diagnosed on a physical examination of the newborn, such as cardiovascular defects, which may be underreported.

**Conclusion**

The most prevalent cases of birth defects in Foz do Iguassu were CLP and gastroschisis. Moreover, the prevalence of birth defects in the region is higher than other regions. Regarding sociodemographic factors, maternal age is associated with gastrochisis and Down syndrome and education up to 7 years is determinant to the occurrence of major birth defects. Health information systems are important tools for epidemiology and data acquisition procedure should be better addressed to assure accurate diagnosis since the early stages of life.

**Abbreviations**

SINASC: Information System on Live Births (Sistema de Informação de Nascidos Vivos); ICD-10: International Classification of Diseases Rev. 10; CLP: Cleft Lip and/or Palate; EMF: Electromagnetic Fields; CNS: Central nervous system

**Acknowledgments**

Not applicable.

**Declarations**

This research was approved by the Ethics Review Board of the Universidade Dinâmica das Cataratas; evaluation number: 2,856,426; Certified Ethical Presentation number: 92477918.0.0000.8527.

**Authors’ contributions**

SS contributed to the conception and design, acquisition and interpretation of data and drafting of the manuscript. FKN contributed to the design, data interpretation, and revising the manuscript. CRP contributed to the conception, design, data interpretation, and revising the manuscript. All authors read and approved the final version of the manuscript.
Funding
This research was not funded.

Availability of data and materials
The datasets analyzed during the current study are not publicly available due to the privacy policy imposed by the Brazilian government but may be available from the corresponding author on reasonable request.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1Latin-American Institute of Life and Natural Sciences, Federal University of Latin-American Integration, Foz do Iguassu, Parana, Brazil. 2Evidence-Based Public Health Research Group, Foz do Iguassu, Brazil. 3Biochemistry, Toxicology and Molecular Pharmacology Research Group, Foz do Iguassu, Brazil.

Received: 14 January 2020 Accepted: 23 June 2020
Published online: 30 June 2020

References
1. Pei L, Kang Y, Cheng Y, Yan H. The association of maternal lifestyle with birth defects in Shaanxi Province, Northwest China. PLoS ONE. 2015;10(1):1–13.
2. César G, CM R, Avó D, LR S, Melo G. Maternal and perinatal aspects of birth defects: a case-control study, 2014.
3. Feldkamp ML, Carey JC, Byrne JLB, Kriskov S, Botto LD. Ectoderm and clinical presentation of birth defects: population based study. BMJ. 2017;357:1–8.
4. OMS. World health statistics 2018: monitoring health for the SDGs, sustainable development goals. Geneva: World Health Organization. 2018; 1–85. http://www.who.int/gho/publications/world_health_statistics/2018/en/. Accessed 15 Oct 2019.
5. Eure EN, Kalu N, Sokumbi OJ, Krukska P, Olusugnon-Joseph AD, Ilebudu D, et al. Clinical epidemiology of congenital heart disease in Nigerian children, 2012-2017. Birth Defects Research. 2018;110:1233–40.
6. Oliveira CI, Fett-contre AC. Birth defects : risk factors and consequences. J Pediatr Genet. 2013;2:85–90.
7. Reis RN. O EFEITO DA EDUCAÇÃO SOBRE O STATUS DE SAÚDE E OCORRÊNCIA DE DOENÇAS CRÔNICAS NA POPULAÇÃO DO ESTADO DA BAHIA. 2013. http://www.evb.seib.gov.br/pdf/2013/eb_o_efetdo_da_educacao.pdf.
8. Brazilian Ministry of Health. Health information. 2019. http://www2.datasus.gov.br/DATASUS/index.php?area=02. Accessed 15 Mar 2019.
9. De Souza S, Duim E, Nampo FK. Determinants of neonatal mortality in the largest international border of Brazil - a case-control study, BMC Public Health. 2019;19:1–9.
10. St. Louis AM, Kim K, Browne ML, Liu G, Liberman RF, Nembhard WN, et al. Prevalence trends of selected major birth defects: A multi-state population-based retrospective study, United States, 1999 to 2007. Birth Defects Res. 2017;109:1442–50.
11. OMS. WORLD ATLAS OF BIRTH. 2003. https://apps.who.int/iris/handle/10665/42630.
12. de Souza GFT, Roncalli AG. Orofacial clefts in Brazil and surgical rehabilitation under the Brazilian national health system. Braz Oral Res. 2017; 31:1–10.
13. Figueredo CJR, Vasconcelos WKS, Maciel SSV, Maciel WLV, Gondim LAM, Taristano RM. Prevalence of oral clefts in the State of Rio Grande do Norte, Brazil , between 2000–2005. Revista Paulista de Pediatria. 2011;29:29–34.
14. Dixon M, Marazita MJ, Beatty ML, Terri H, Murray CJ. Cleft lip and palate: understanding genetic and environmental influences. Nat Rev Genet. 2011; 12:167–78.
15. Hadzige-Catibusic F, Makis H, Ulicanin S, Heljic S, Zubcevic S, Merhemic Z, et al. Congenital malformations of the central nervous system: clinical approach, Bosnian J Basic Med Sci. 2008;8:356–60.
16. Ryan-Harshman M, Aldoori W. Folic acid and prevention of neural tube defects. Can Fam Physician. 2008;54:36–8.
17. Wilson RD, SOCG CG. Prenatal screening, diagnosis, and pregnancy Management of Fetal Neural Tube Defects. J Obstet Gynaecol Can. 2014;36:927–39.
43. Mjøen G, Sætre DO, Lie RT, Tynes T, Blaasaas KG, Hannevik M, et al. Paternal occupational exposure to radiofrequency electromagnetic fields and risk of adverse pregnancy outcome. Eur J Epidemiol. 2006; 21:529–35.

44. Brent RL. The cause and prevention of human birth defects: what have we learned in the past 50 years? Congenital Anomalies. 2001;41:3–21.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.