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# Birth defects in Brazil: Outcomes of a population-based study

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## Abstract

Birth defects (BDs) are functional and structural alterations in embryonic or fetal development. With an incidence of approximately 3-5%, BDs are a leading cause of infant mortality and lifelong disability. A population-based prospective case-control study was conducted for one year with 5204 infants, between March 1ˢᵗ, 2011 and February 29ᵗʰ, 2012 in the city of São José do Rio Preto, State of São Paulo, Brazil. The incidence of BDs was 3.2% [95% confidence interval (95%CI): 2.8-3.8%]. The most common congenital anomalies were heart diseases in isolation (11.2%; 95%CI: 7.3-16.9%) followed by Down syndrome (9.5%; 95%CI: 5.9-14.8%), neural tube defects (8.9%; 95%CI: 5.4-14.1), urinary tract anomalies (7.7%; 95%CI: 4.4-12.7%), and polydactyly (7.0%; 95%CI: 4.0-12.0%). The majority of mothers with Down syndrome babies had advanced age. Family members with the same BD, maternal alcohol consumption, gestational diabetes, and previous miscarriages were the most frequent risk factors. The results were similar to published data from other countries except for the incidence of Down syndrome, which was twice as high as reported by other authors and is probably due to the high sociocultural level of the region where the current study was performed, leading to pregnancies at older maternal age.

*Keywords*: Malformation, congenital anomaly, fetal development, genetic counseling, public health.

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## Introduction

Birth defects (BDs) are functional and structural alterations in embryonic or fetal development resulting from genetic, environmental, or unknown causes. BDs have a significant impact on the health and development of a child. They contribute to 50% of neonatal deaths, besides being a leading cause of infant mortality and lifelong disabilities (Gill *et al.*, 2012; Arioglu Aydin *et al.*, 2015). About eight million babies worldwide are born each year with significant BDs (Reece, 2012); the overall incidence is approximately 3-5% (Oliveira *et al.*, 2011; Gill *et al.*, 2012). Although there are well-established risk factors, the causes of most BDs remain unknown (Miller *et al.*, 2011; Kong *et al.*, 2012; Wiener-Megnazi *et al.*, 2012; Ooki, 2013).

While there are many published studies about BDs, few have been performed in underdeveloped and developing countries, with the majority being hospital-based and not population-based studies (Groisman *et al.*, 2013). This article describes data on the incidence and risk factors of BDs obtained in a population-based study performed over one year involving 5204 Brazilian infants.

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## Subjects and Methods

This study was approved by the Research Ethics Committee of the Medical School of Sao Jose do Rio Preto (FAMERP # 5838). The parents of all subjects were informed about the nature of the study and signed informed consent forms.

This population-based, prospective, case-control study collected data on all infants born in the city of São José do Rio Preto over one year, between March 1, 2011 and February 29, 2012. Located in the northwestern region of the state of São Paulo, Brazil, the city has a population of 408,258 and, according to the Instituto Brasileiro de Geografia e Estatística, it is the second most developed city in Brazil (IBGE, 2016).

The investigation was performed by a multidisciplinary team involving several kinds of health professionals, in particular neonatologists and geneticists, in all six hospitals of the city. In order to verify the populational character of the study, a partnership with the Health Department of São José do Rio Preto was made. Thus, births of children with BDs carried out in municipalities other than that of the mothers residing in the city could also be considered resident and characterized. However, during the study period, there was no birth of BD babies in a locality other than São José do Rio Preto, according to the official re-

cords. In addition, babies born in the city, whose families resided in other municipalities were excluded.

During the study period, 5204 children were born and all were investigated for the presence of major and minor defects. The data of children with BDs (BD Group) were compared with data of healthy infants matched for gender and born in the same hospital immediately after each study case (Control Group). This Group was used to compare maternal and paternal data and obstetric and perinatal variables. Deaths were considered stillbirths when they occurred after 20 weeks of gestation (O'Neill *et al.*, 2011). All cases of BDs were analyzed following the classification of Garne *et al.* (2011).

Trained researchers collected the data by face-to-face interviews with the parents and from medical records. Variables included sociodemographic data, obstetric history, family antecedents, previous pregnancies, periconceptional folate supplementation, gestational exposure to teratogenic agents, prenatal data, type of delivery, birth weight, birth stature, gestational age and results of exams (neonatal screening for metabolic diseases, radiographic evaluations, karyotype, etc.). Samples of peripheral or umbilical cord blood were collected for a karyotype study when indicated in order to confirm or investigate chromosomal abnormalities. Other genetic tests were performed depending on the needs of each individual.

Results were stratified according to BDs and epidemiological parameters. Statistical analysis was performed using the Minitab (version 16) and GraphPad statistical programs. Descriptive statistics using frequencies and proportions were employed to describe the demographic characteristics of subjects. The effects were evaluated by 95% confidence intervals (95%CIs). Statistical analyses included the paired t-test, and Mann-Whitney, chi-square, and Fischer's exact tests, adopting a level of significance of 5%.

## Results

One hundred and sixty-nine individuals were identified as having BDs revealing an incidence of 3.2% (95% CI: 2.8-3.8%). Table 1 shows the characteristics of subjects with birth defects.

The gestation age of babies with BDs ranged from 20 to 42 weeks [mean: 36.0 weeks; standard deviation (SD): 3 weeks and 6 days]. With respect to the gestational age,

**Table 1** - Characteristics of subjects with birth defects.

| Factors | Cases (%) | 95% CI |
|---|---|---|
| Live Births | 158 (93.5%) | 88.7-96.3% |
| Stillbirths | 11 (6.5%) | 3.7-11.3% |
| Male | 95 (56.2%) | 48.7-63.5% |
| Female | 66 (39.0%) | 32.0-46.6% |
| Undetermined | 8 (4.7%) | 2.4-9.0% |

CI = exact confidence interval.

41.2% (95%CI: 34.0-48.8%) were preterm (<37 weeks) and 58.2% (95%CI: 37.2-60.0%) were born at term (≥37 weeks). The majority of children (92.3%; 95%CI: 85.9-97.2%) were delivered by C-section and 42.0% (95%CI: 28.4-49.6%) had low birth weights (<2500 g).

For the Control Group, the period of gestation ranged from 33 to 41 weeks (mean: 38 weeks; SD: 1 week and 2 days), 16.6% (95%CI: 13.4-31.5%) were preterm and 83.4% (95%CI: 68.5-86.6%) were born at term. The majority (93.0%; 95%CI: 87.4-98.0%) were delivered by C-section and 14.7% (95%CI: 10.2-20.9%) had low birth weights (<2500 g). Differences between the groups were statistically significant in respect to the period of gestation (*p*-value = 0.0) and birth weight (p-value = 0.0). There was no significant difference observed in the frequencies of C-sections (*p*-value = 0.8).

Karyotype alterations were detected in 25 individuals; 0.48% (95%CI: 0.33-0.71%) of the total sample (5204 individuals) and 14.8% (95%CI: 10.2-20.9%) of the individuals with BDs (169 individuals). The most common finding was chromosome 21 trisomy (16 cases - 64.0%; 95%CI: 44.5-79.7%), followed by chromosome 13 trisomy (5 cases - 20.0%; 95%CI: 8.9-39.1%), chromosome 18 trisomy (2 cases - 8.0%; 95%CI: 2.2-25.0%), X chromosome monosomy (1 case - 4.0%; 95%CI: 0.7-19.5%) and del(8)(pter→q24:) (1 case - 4.0%; 95%CI: 0.7-19.5%).

The frequencies of BDs are listed in Table 2. Isolated heart diseases (11.2%; 95%CI: 7.3-16.9%) were the most common BDs followed by Down syndrome (9.5%; 95%CI: 5.9-14.8%), neural tube defects (8.9%; 95%CI: 5.4-14.1%), urinary tract anomalies (7.7%; 95%CI: 4.4-12.7%), and polydactyly (7.0%; 95%CI: 4.0-12.0%). According to the classification of Garne *et al.* (2011), isolated anomalies were more frequent, followed by chromosomal syndromes, monogenic diseases, multiple congenital anomalies, and environmental diseases.

Table 3 lists the frequencies of risk factors that were observed in controls and affected children. The frequencies of family members with the same BD (cleft lip/palate - 4 cases, polydactyly - 2 cases, and abnormality of the 3rd toe bilaterally - 1 case), cases of maternal alcohol consumption, gestational diabetes, and previous miscarriages were statistically different between the two groups. The intake of periconceptional folate by mothers of children with BDs and controls was 21.6% and 28.4%, respectively, which was not statistically different between the two groups.

The mean maternal age for mothers of babies with BDs was 28.0 years (95%CI: 26.9-29.2%; range: 14-45 years; SD: 7.3 years) and for control mothers was 26.0 years (95%CI: 25.0-26.9%; range: 14-41 years; SD: 6.2 years). Of the mothers of babies with BDs, 66.0% (95%CI: 58.6-72.8%) were aged from 20 to 34 years, 19.6% (95%CI: 14.3-26.3%) were 35 years old or more, and 14.3% (95%CI: 9.8-20.4%) were under 19 years old. Among the Control Group mothers, 74.0% (95%CI: 66.8-

**Table 2** - Test for independent interaction of SNPs with LOAD.

| Polymorphism | AD Patients N (%) | Controls N (%) | OR (95% IC) | $p$-value[a] | OR (95% IC) | $p$-value[b] |
|---|---|---|---|---|---|---|
| *ABCA7* (rs3764650) | | | | | | |
| T | 52 (68.4%) | 105 (75.5%) | 1 (Reference) | - | 1 (Reference) | - |
| G | 24 (31.6%) | 34 (24.5%) | 1.425 (0.767-2.648) | 0.262 | 1.552 (0.794-3.037) | 0.199 |
| *CLU* (rs11136000) | | | | | | |
| C | 89 (57.1%) | 170 (58.6%) | 1 (Reference) | - | 1 (Reference) | - |
| T | 67 (42.9%) | 120 (41.4%) | 0.938 (0.632-1.390) | 0.764 | 0.840 (0.537-1.314) | 0.445 |
| *BIN1* (rs744373) | | | | | | |
| T | 106 (67.1%) | 186 (65%) | 1 (Reference) | - | 1 (Reference) | - |
| C | 52 (32.9%) | 100 (35%) | 0.912 (0.605-1.377) | 0.662 | 0.960 (0.606-1.520) | 0.861 |
| *APOE* (rs429358 rs7412) | | | | | | |
| ε4 - | 103 (65.2%) | 245 (84.5%) | 1 (Reference) | - | 1 (Reference) | - |
| ε4 + | 55 (34.8%) | 45 (15.5%) | 2.907 (1.842-4.588) | <0.001 | 3.029 (1.873-4.898) | <0.001 [c] |

ε4 - = ε4 non-carriers; ε4+ = ε4 carriers; AD Patients = Alzheimer's disease patients; OR = odds ratio; CI = confidential interval; $p$-value considered ≤ 0.05; [a]crude $p$-value; [b]$p$-value adjusted by the variables age, gender, educational attainment, ethnic background and APOE ε4 status; [c] = $p$-value adjusted by the variables on [b] except for APOE ε4 status.

**Table 3** - Characteristics of subjects and their relationship with birth defects.

| Factors | Cases N (%) | Controls N (%) | p | OR | 95%CI |
|---|---|---|---|---|---|
| Parental consanguinity | N=167 | N=169 | | | |
| No | 164 (98.2) | 169 (100) | 0.210 | - | 0-2.38 |
| Yes | 3 (1.8) | 0 (0) | | | |
| Family history of the same birth defect | N=167 | N=169 | | | |
| No | 160 (95.8) | 169 (100) | 0.007* | - | 0-0.67 |
| Yes | 7 (4.2) | 0 (0) | | | |
| Maternal alcohol consumption | N=165 | N=169 | | | |
| No | 144 (87.3) | 162 (95.9) | 0.008* | 3.37 | 1.39-8.17 |
| Yes | 21 (12.7) | 7 (4.1) | | | |
| Gestational diabetes | N=167 | N=169 | | | |
| No | 158 (94.6) | 168 (99.4) | 0.023* | 9.56 | 1.19-76.4 |
| Yes | 9 (5.4) | 1 (0.6) | | | |
| Previous miscarriage | N=167; % | N=169; % | | | |
| No | 132 (79.0) | 155 (91.8) | 0.000* | 2.93 | 1.51-5.69 |
| Yes | 35 (21.0) | 14 (8.2) | | | |
| Twin pregnancy | N=169 | N=169 | | | |
| No | 158 (93.5) | 166 (98.2) | 0.056 | 3.85 | 1.05-14.0 |
| Yes | 11 (6.5) | 3 (1.8) | | | |

OR=odds ratio; CI = exact confidence interval; *statistically significant.

80.0%) were aged from 20 to 34 years, 17.7% (95%CI: 12.7-24.2%) were under 19 years old, and 8.3% (95% CI: 5.0-13.4%) were 35 years old or more. Significantly more mothers of affected children had advanced age (≥ 35) than in Control Group mothers ($p$-value = 0.008). Forty-six percent (95%CI: 27.9-64.9%) of the mothers of children with numerical chromosomal abnormalities were at least 35 years old.

The mean age of the fathers of babies with BDs was 31.5 years old (95%CI: 30.2-32.7%; range: 17-54 years; SD: 7.9 years) and for the Control Group fathers it was 29.6 years (95%CI: 28.6-30.6%; range: 17-49 years; SD: 6.5

years) Advanced age (≥ 40) was seen in 15% (95%CI: 9.8-21.0%) of the fathers of the BD Group and 6% (95%CI: 2.8-10.6%) of the Control Group (p-value = 0.016). None of the fathers of children with monogenic syndromes was over 40 years old.

## Discussion

Studies of BDs should address the collection, analysis, and dissemination of information and contribute to local interventions such as prevention, diagnosis, and treatment. However, in many low- and middle-income countries, BDs are not considered a public health priority and are perceived by the medical community as rare, unpreventable events. There are few studies performed in these countries and most are usually hospital-based (Groisman *et al.*, 2013). In Brazil, the situation is not different, and this population-based study can be considered an example of the BDs reality in a country that has a highly mixed population with broad cultural diversity (IBGE, 2016).

Although the incidence of BDs around the world is variable, most studies report 3-5% in different populations (Oliveira *et al.*, 2011). The incidence in this study (3.2%) corroborates previously described data despite the differences in diagnostic levels, sample sizes, and methodologies of other studies performed both in Brazil (1.4-5%) and other countries (Oliveira *et al.*, 2011; Gill *et al.*, 2012; Naim *et al.*, 2013). The incidence of BDs was slightly higher in males than in females as has previously been reported(Asindi *et al.*, 1997).

Many infants with BDs have low birth weights and are premature. Globally, an estimated 13 million babies are born annually before completing 37 weeks of gestation with the rates generally being the highest in low- and middle-income countries. Even so, preterm birth rates vary greatly within countries and are related to sociodemographic characteristics (Lawn *et al.*, 2010). In the current study population, the frequency of premature births and babies weighing less than 2500g was high compared to the world literature (Lawn *et al.*, 2010; Herbert *et al.*, 2012). Ordinarily, much higher incidences of congenital anomalies are observed among children who weigh 2500g or less at birth than among those who are heavier (Herbert *et al.*, 2012).

Generally, the rate of C-sections is related to prematurity and low weight as they are performed for convenience reasons. Elective preterm C-sections are still largely practiced in cases of prenatal diagnoses of major congenital anomalies (Calisti *et al.*, 2012). The C-section was the commonest mode of delivery in both the BD and Control Groups. This was expected because it is common for parents to opt for this kind of delivery in Brazil, regardless of the fetal status (Freitas *et al.*, 2015).

Most chromosomal defects are lethal and identified after miscarriages. They account for a high rate of congenital anomalies. For example, trisomies of chromosomes 13, 18, and 21 and X chromosome monosomy have an impact on births (~0.3% of all births; Wiener-Megnazi *et al.*, 2012), and their frequency was similar in the current study. However, the trisomy of chromosome 21 (the second most common BD observed here) affects approximately 1 in 660 births (Hwang and Jea, 2013) with the incidence in the current study being 2 in 660, twice as high as generally described. This could be explained by the significant advanced age observed among mothers; it should also be considered that abortion is illegal in Brazil.

Congenital heart diseases are the most common BDs in humans. They can be isolated or one of multiple defects (Weber, 2012; Zaidi *et al.*, 2013). In this study, heart diseases in isolation were the most common BD. The frequency of neural tube defects ranges from 0.2 to 10 per 1000 live births in specific geographical locations (Copp *et al.*, 2013). In this study, this was the third most common BD. Other BDs, such as congenital anomalies of the kidneys and urinary tract, and polydactyly, the fourth and fifth most common findings, respectively, are among the most common anomalies in newborn infants (Richter-Rodier *et al.*; 2012; Liu *et al.*, 2016).

The incidence of BDs not only reflects allelic frequencies of deleterious genes in a population but it is also affected by environmental factors (Alaani *et al.*, 2011; Naim *et al.*, 2012). Of the known risk factors for congenital abnormalities that were investigated in this study, the frequencies of familial recurrence, maternal alcohol consumption, gestational diabetes, previous miscarriages and advanced maternal age were significantly higher in the BD Group than the Control Group.

Similar to previous descriptions, certain BDs in this study recurred in families, such as non-syndromic oral cleft, polydactyly and abnormalities in the position of fingers (Jones, 2007; Grosen *et al.*, 2010; Ravichandran *et al.*, 2012).

Three times more mothers of the BD Group consumed alcohol during pregnancy. In Brazil, as in other countries, this is a health problem (Feldman*et al.*, 2012; Veloso and Souza Monteiro, 2013). In the United States, approximately 80,000 women annually consume alcoholic beverages through all three trimesters of pregnancy. Prenatal alcohol exposure is a risk factor for BDs and can lead to a wide range of adverse effects in a developing fetus. Fetal alcohol spectrum disorder is a developmental disorder that affects up to 0.2% of births(Bates, 2013). The risk of comorbid disorders is also increased for this population; this increases the phenotype severity and complexity of management (Paintner *et al.*, 2012; Viteri *et al.*, 2015).

The rate of gestational diabetes mellitus was significantly different between the groups. This is believed to be a risk factor as it has been correlated to limb and heart defects, as observed in this study. Epidemiologic studies have

shown that low glycemic dietary management can reduce the incidence of BDs (Reece, 2012; Glover *et al.*, 2016).

Recurrent pregnancy loss affects 2-5% of all couples with >50% being characterized as unexplained or idiopathic (Hodes-Wertz *et al.*, 2012). The results of this study showed that the rate of previous miscarriages in mothers of the BD Group was significantly higher. Indeed, previous miscarriages are considered to be a risk factor for future babies to have some type of BD(Lu *et al.*, 2011; Machado *et al.*, 2013).

More women are delaying child bearing, which results in an annual rate of 14.9% of live births to women aged 35 years or older (Hamilton*et al.*, 2010). Both younger and older maternal ages may pose increased risks for BDs (Miller *et al.*, 2011; Gill *et al.*, 2012). In this study, about 20% of mothers of babies with BDs were at least 35 years old. Thus, the effect of advanced maternal age was, as expected, greatly related to BDs, such as Down syndrome. Although advanced paternal age has been associated with an increased risk for congenital disorders (Kong *et al.*, 2012; Wiener-Megnazi *et al.*, 2012; Goriely and Wilkie, 2012), this was not observed in the current study.

There was no significant difference between the BD and Control Groups in relation to the rate of consanguineous marriages and twin pregnancies, considered major risk factors for congenital anomalies (Weller *et al.*, 2012; Boyle *et al.*, 2013; Sheridan *et al.*, 2013; Maghsoudlou *et al.*, 2015); however, one case of Smith-Lemli-Opitz syndrome, an autosomal recessive disorder (Quélin *et al.*, 2012), probably resulted from parental consanguinity.

Neural tube defects were one of the most common BDs observed in this study, as is reported in publications around the world, with a prevalence from 1-10% (Wang *et al.*, 2013). A prudent periconception supplementation with folic acid may decrease the risk, as well as the threat of heart defects and other BDs (Czeizel, 2012; Sotres-Alvarez *et al.*, 2013). In this study, the periconception supplementation did not differ between the groups and was low, below the expected, for a developed region.

Infant mortality is one of the most important conditions to be considered in relation to BDs because it is indicative of the health of a community or country. Early recognition of anomalies is important for planning and care (Calisti *et al.* (2012). For example, congenital disorders continue to be a leading cause of infant mortality and rank within the top 15 contributors to the global burden of disease, even though many congenital disorders are preventable (Shannon *et al.*, 2013). Thus, the identification of incidence, risk factors, and consequences of BDs are essential to plan preventive measures and effective treatment.

Findings involving BDs around the world vary due to the methods of investigation and differ because of the cultural, social, and geographic context of each population. No similar study for Brazil was found, i.e., involving birth data of all infants born in a municipality over a period of time.

The studies on BDs are usually performed with a hospital-based sample of births. Even the Latin-American collaborative study of congenital malformations (ECLAMC), a program for the clinical and epidemiological investigation of risk factors in the etiology of congenital anomalies in Latin-American hospitals (Castilla and Orioli, 2004), offers limited information, since the number of participant hospitals is still small (Guerra *et al.*, 2008).

Based on these preliminary findings, this population-based study performed in Brazil can collaborate in developing strategies for the healthcare and education needs of the population. The incidence of BDs reported was similar to published data from other countries, but the incidence of Down syndrome was twice as high as the rate reported in the literature. This can be the result of the reality in the region where the study was performed. The region is economically more advanced and many women delay child bearing, increasing the risk for congenital abnormalities. Family history of the same BDs, maternal alcohol consumption, gestational diabetes, and previous miscarriages were the more frequent risk factors. In this context, different strategies should be developed to reduce the occurrence of BDs depending on the current situation of congenital defects in different regions.

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## Conflict of interest

The authors declare no conflict of interest.

## Author contributions

CIFO-B carried out the data collection, karyotypic analysis and confection of the manuscript. VCCF carried out the karyotypic analysis. ARC participated in the investigation of the diagnoses. ACF-C designed the study, clinical assessment, oversaw the whole study and did the critically reviewing manuscript. All authors read, revised and approved the final manuscript.

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