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Journal of Community Genetics

ISSN 1868-310X

J Community Genet
DOI 10.1007/s12687-015-0249-x

J Community Genet
DOI 10.1007/s12687-015-0249-x

COUNTRY REPORT

Primary prevention of neural tube defects in Brazil: insights into anencephaly

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Received: 2 January 2015 / Accepted: 2 August 2015

Introduction

Anencephaly is a lethal malformation characterized by the absence of the skull and both cerebral hemispheres caused by deficiency of closure of the neural tube at rostral level between 23 and 25 days of gestation (Bronberg et al. 2011). The occurrence of anencephaly and other neural tube defects (NTDs) such as meningocele and spina bifida are between 50 and 70 % preventable by periconceptional folic acid (FA) administration to reduce their prevalence across populations (Blencowe et al. 2010). The percentage decrease is dependent upon the background prevalence. The percentage of NTDs that are preventable by periconceptional folic acid intake is dependent on the prevalence of folate-sensitive NTDs in the population (Robbins et al. 2006; Bronberg et al. 2011).

To prevent anemia due to iron deficiency and the occurrence of NTD, the Brazilian Ministry of Health approved the resolution RDC No. 344 on December 13, 2002, whereby the flour fortification of wheat and maize was regulated. This resolution determined that as of June 2004, wheat and corn flours be supplemented with at least 4.2 mg iron and 150 mcg of FA/100 g flour (ANVISA 2002).

As in many South American countries, there are only two exceptions to penalized abortion in Brazil: in case of rape or to save the woman's life. The Brazilian Criminal Code does not include fetal malformations as a cause of penalized abortion. This limitation was partially overcome in 2004, when the Brazilian Supreme Court of Justice authorized abortion in cases of anencephalic fetuses (Diniz 2007). Termination of pregnancy (TOP) with an anencephalic baby was made legal in 2012, without need of a special judicial authorization (Carvalho 2011). Until 2012, TOP had been legal in Brazil in cases of anencephaly only after special authorization from a judge. A survey performed with Brazilian obstetricians showed that 37 % of women with a pregnancy of anencephalic fetus had successfully obtained authorization for legal abortion (Diniz et al. 2009).

About ten South American countries, in most of which abortion for congenital malformations is not authorized by law, primary prevention of anencephaly and other NTDs is managed through mandatory fortification of flour with FA (PAHO 2003). In some of these countries, fortification has proven to be an effective strategy for the primary prevention of anencephaly and NTDs. In particular, Argentina (Bronberg et al. 2011) and Chile (Cortes et al. 2012) have reduced the number of deaths by anencephaly by about 50 % in the post-fortification period compared to the pre-fortification stage.

There are dissimilar records in Brazil in terms of fortification results according to NTDs, the type of data used (infant deaths or born alive), and level of spatial and temporal coverage these results are based on (Orioli et al. 2011; Pacheco et al. 2009; Fujimori et al. 2013; Schuler-Faccini et al. 2014).

For its lethality, since 99 % of those born with anencephaly die within the first month of life and because the phenotype is well identified, even by non-specialists, anencephaly is a malformation whose epidemiological behavior can be analyzed with some confidence and provide an accurate and precise

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picture of the effect of flour fortification with FA and other preventive measures. Given the socioeconomic, geographical, ecological, and cultural diversity of Brazil, it is estimated that spatial and temporal variations of infant deaths from this NTD may be present. In this paper, the temporal variation and spatial distribution at different levels of the state organization in Brazil, infant and fetal deaths by anencephaly were analyzed in relation to the different phases that occurred in the process of fortification with FA.

Materials and methods

This is an ecological and population study gathering information from databases of births, infant, and fetal deaths occurred in Brazil collected by the Information Department of the Sistema Único de Saúde (Unified Health System), Ministério de Saúde of Brazil (Datasus) (http://www2.datasus.gov.br/DATASUS/index.php?area=01) between 1998 and 2011. Information on infant and fetal deaths due to anencephaly specifically came from the Sistema de Informações sobre Mortalidade (SIM) (Mortality Information System, MIS).

Data were analyzed with reference to the maternal place of residence. The variables used were (a) number of live births (NLB), (b) number of infant deaths (<1 year old) and fetal deaths (>28 weeks gestation) by anencephaly coded by ICD-X (Q000 Code), and (c) total number of infant and fetal deaths classified by ICD code Q (all congenital malformations, CM).

Based on these figures and regardless of sex, descriptive statistics were calculated for (1) infant mortality rate by anencephaly (IMR-A) (infant deaths by anencephaly / 10000 LB), (2) percent of child deaths by anencephaly (ID%-A) (infant deaths by anencephaly / CM infant deaths *100), (3) fetal mortality rate by anencephaly (FMR-A) (fetal deaths by anencephaly / 10000 LB), (4) percentage of fetal deaths by anencephaly (FD%-A) (fetal deaths by anencephaly / CM fetal deaths * 100), (5) rate of infant mortality + fetal by anencephaly (IMR + FMR-A) (infant deaths + fetal deaths by anencephaly / 10000 LB), and (6) percentage of infant deaths + fetal anencephaly ((ID + FD%-A) (infant deaths + fetal deaths by anencephaly) / (CM infant deaths + CM fetal deaths) * 100).

These indicators were calculated on a temporal and spatial basis. Depending on the year of commencement of FA flour fortification (ANVISA 2002), the total period of analysis was divided into two sub-periods: (a) pre-fortification (1998–2004) (PRF) and (b) post-fortification (2005–2011) (POF). At space level, calculations were performed for the whole country, 5 geographic regions (North, Northeast, Southeast, South, and Central West), 27 States (Rondonia, Acre, Amazonas, Roraima, Pará, Amapá, Tocantins, Maranhão, Piauí, Ceará, Rio Grande do Norte, Paraíba, Pernambuco, Alagoas, Sergipe, Bahia, Minas Gerais, Espirito Santo, Rio de Janeiro, Sao Paulo, Paraná, Santa Catarina, Rio Grande do Sul, Mato Grosso do Sul, Mato Grosso, Goiás, Distrito Federal), and 5600 municipalities (IBGE 2012).

The risk between periods for the entire country, at regional and state levels, calculated using a Poisson regression model was evaluated. The independent variables in this model correspond to the newborn's year of birth.

Statistical calculations were performed using STATA 12 statistical package.

Result

When infant deaths for all Brazil were considered, in the POF there were only 338 infant anencephalic deaths less than in the PRF. However, when the number of fetal deaths compared with anencephaly death was observed for all Brazil, 2273 less anencephalic cases were recorded in the POF. This trend continued in all regions and states (Table 1).

The difference between periods of IMR-A throughout Brazil was slightly lower and not statistically significant in the POF. At the regional level, it only dropped significantly in the South and Southeast regions and significantly increased in the Northeast region. The only states that showed a significant drop in IMR-A were Rio de Janeiro, Sao Paulo, and Santa Catarina (Table 2). Roraima, Maranhao, Piaui, Paraiba, Sergipe, Bahia, and Espiritu Santo presented significantly increased IMR-A records (Table 2).

The ID%-A decline between periods for all Brazil was very small (10 %) but statistically significant. At the regional level, this percentage dropped significantly in the Northeast, South, and Southeast and in the following states: RG do Norte, Pernambuco, Rio de Janeiro, Sao Paulo, and Santa Catarina (Table 2). Instead, the FD%-A decreased across the country and in all regions and states, becoming statistically significant at the national, regional, and state level in the following states: Rondonia, Amazonas, Para, Rio Grande do Norte, Bahia, Minas Gerais, Rio de Janeiro, Sao Paulo, Parana, Santa Catarina, Rio Grande do Sul, and Goiás (Table 3). The FMR-A also showed a modest (33 %) but significant decrease for the whole of Brazil and all regions except the northeast region (Table 3). At the state level, on the contrary, this indicator showed a not significant increase in some states (Tocantins, Maranhao, and Bahia) (Table 3).

The IMR + FD-A significantly decreased only 15 % between periods for all Brazil. At the regional level, it also decreased but significantly only in the northeast, southeast, and south regions. At state level, the decline was significant only in Rio Grande do Norte, Rio de Janeiro, Sao Paulo, Parana, Santa Catarina, and Rio Grande do Sul. In the remaining states, the IMR + FD-A remained stable or either not significantly increased or significantly increased (Maranhao and Bahia) (Table 4).

Table 1 Number of live born, infant deaths, and fetal deaths (due to anencephaly, congenital malformation, and all causes) throughout Brazil in the pre-fortification (PRF) and post-fortification (POF) periods

Period	Year	Live borns	Infant deaths			Fetal deaths		
			Anencephaly	Congenital malformation	All causes	Anencephaly	Congenital malformation	All causes
PRF	1998	3,148,037	541	7401	71,690	441	1676	40,321
	1999	3,256,433	651	7564	69,345	584	1977	40,824
	2000	3,206,761	595	7798	68,199	477	1761	39,429
	2001	3,115,474	637	7537	61,943	490	1798	38,759
	2002	3,059,402	626	7683	58,916	480	1704	37,417
	2003	3,038,251	640	7934	57,540	454	1663	37,103
	2004	3,026,548	623	8080	54,183	533	1791	36,214
	1998–2004	21,850,906	4313	53,997	441,816	3459	12,370	270,067
POF	2005	3,035,096	539	7830	51,544	346	1531	34,233
	2006	2,944,928	591	7910	48,332	320	1576	33,434
	2007	2,891,328	566	7795	45,370	293	1525	32,165
	2008	2,934,828	590	8034	44,100	323	1560	32,065
	2009	2,881,581	578	7832	42,687	278	1581	32,147
	2010	2,861,868	543	7709	39,870	317	1645	30,929
	2011	2,913,160	568	7906	39,369	309	1605	31,613
	2005–2011	20,462,789	3975	55,016	311,272	2186	11,023	226,586

The IM + FD%-A for all Brazil presented a decline of 21 % between periods. It decreased significantly in all regions except the Central West and in the following states: Amazonas, Para, Ceara, RG do Norte, Paraiba, Pernambuco, Alagoas, and in all states of the South and Southeast Region, except Espirito Santo. In the states of Roraima, Tocantins, Mato Grosso, and Distrito Federal, it had not significantly increased (Table 4).

Discussion

The results obtained provided basic epidemiological information on the prevalence of anencephaly by fetal and infant deaths in Brazil between 1998 and 2011, a critical period of transition in the process of mandatory FA fortification of flour (ANVISA 2002) and the Brazil Supreme Court endorsement of discretionary termination of pregnancies diagnosed with anencephaly (Diniz 2007).

While the validity of death certificates is in question due to deficiencies in the competence and quality of diagnosis, it is the only information available in Brazil at the population level on the epidemiological behavior of this lethal malformation (Rosano et al. 2000; Copeland and Russell 2007; Northam and Knapp 2006; Bronberg et al. 2009). Data from the SIM had an average quality with completeness of 84 % and 79 % coverage. However, specifically for anencephaly, death certificates would have a predictive value of 100 % (Lydon-Rochelle et al. 2005) and a sensitivity of 86 % (Honein et al. 2001), a reason by which anencephaly could be considered as a sentinel deficiency of the effect of flour fortification with FA and other actions to reduce the prevalence of NTDs.

The indices commonly used to report at health status anencephaly deaths before the first year of life are the IMR-A and ID%-A, which provide complementary but not superimposable information, since the IMR-A expresses the proportion of children who died with anencephaly out of the total number of living children while ID%-A relates it to dead children. Therefore, the ID%-A may provide a more accurate epidemiological picture. The identification of fetal deaths is rare in the death records of Latin American countries. In this respect, Brazil data provide valuable information for analyzing the behavior of anencephaly deaths at this stage of ontogenesis. This analysis is particularly relevant in the legal context of the country allowing abortion for this reason.

Considering infant deaths by anencephaly, both IMR-A and FD%-A would indicate that preventive actions handled by fortification with FA in Brazil were not effective or at least not as effective as in other Latin American countries (Bronberg et al. 2009). The greatest achievements were restricted to the more developed and in better economic condition regions and states in the south of the country.

Since anencephaly is a malformation of multifactorial etiology, spatial IMR-A differences in Brazil could also be explained by genetic and environmental variation in populations and risk factors. MTHFR (methylenetetra-hydrofolate reductase) polymorphism 677C→T is associated with a

Table 2 Infant mortality rate by anencephaly (IMR-A) and percent of child deaths by anencephaly (ID%-A) throughout Brazil, regions, and states in the pre-fortification (PRF) and post-fortification (POF) periods and risk for POF compared to PRF period

Region/states	IMR-A				ID%-A			
	PRF	POF	Risk	95 % CI	PRF	POF	Risk	95 % CI
Brazil	1.98	1.94	0.98	0.94–1.03	7.99	7.22	0.90*	0.87–0.94
North	1.96	2.15	1.09	0.96–1.25	9.16	8.37	0.91	0.80–1.04
Rondônia	2.86	3.71	1.30	0.91–1.84	11.31	11.68	0.99	0.70–1.42
Acre	2.42	2.69	1.10	0.65–1.85	9.78	10.22	1.06	0.63–1.78
Amazonas	2.19	2.19	1.02	0.78–1.33	8.71	7.05	0.82	0.63–1.07
Roraima	1.37	3.38	2.47*	1.14–5.34	7.07	14.10	2.88*	1.33–6.21
Pará	1.70	1.81	1.06	0.85–1.31	9.60	8.14	0.85	0.69–1.05
Amapá	2.50	2.23	0.89	0.51–1.57	11.63	10.19	0.79	0.45–1.39
Tocantins	1.48	1.59	1.07	0.63–1.82	6.67	6.47	0.97	0.57–1.64
Northeast	1.80	2.14	1.18*	1.10–1.28	9.60	8.09	0.84*	0.78–0.91
Maranhão	1.02	1.62	1.56*	1.18 - 2.06	7.06	6.83	1.04	0.79–1.37
Piauí	1.48	2.14	1.43*	1.02–2.02	9.09	6.69	0.82	0.58–1.15
Ceará	2.18	2.28	1.05	0.87–1.27	10.11	8.92	0.87	0.72–1.05
R G do Norte	3.53	2.75	0.77	0.60–1.01	15.21	10.91	0.71*	0.54–0.92
Paraíba	2.08	2.84	1.35*	1.03–1.78	14.96	10.57	0.80	0.61–1.05
Pernambuco	2.27	2.07	0.91	0.76–1.10	9.64	6.99	0.73*	0.60–0.87
Alagoas	1.67	1.89	1.13	0.82–1.56	10.58	7.59	0.70*	0.51–0.96
Sergipe	2.11	2.94	1.41*	1.00–2.00	10.14	10.43	1.09	0.77–1.53
Bahia	1.22	2.01	1.64*	1.38–1.96	7.53	7.89	1.04	0.87–1.24
Southeast	2.07	1.79	0.87 *	0.81–0.93	7.73	6.86	0.89*	0.83–0.95
Minas Gerais	1.66	1.83	1.11	0.95–1.29	7.57	7.15	0.95	0.81–1.10
Espírito Santo	1.93	2.65	1.38 *	1.02–1.86	7.27	8.83	1.18	0.87–1.59
Rio de Janeiro	2.36	1.83	0.78 *	0.68–0.91	8.26	6.64	0.81*	0.69–0.94
São Paulo	2.17	1.69	0.78 *	0.71–0.86	7.61	6.62	0.87*	0.79–0.96
South	2.18	1.76	0.81*	0.72–0.91	7.21	6.08	0.84*	0.75–0.95
Paraná	2.18	1.91	0.87	0.72–1.04	6.94	6.28	0.90	0.75–1.08
S. Catarina	2.92	1.88	0.64 *	0.51–0.81	10.70	6.97	0.66*	0.52–0.83
RG do Sul	1.78	1.52	0.86	0.70 - 1.07	5.82	5.31	0.91	0.74–1.13
Central West	1.73	1.94	1.22	0.95–1.32	5.69	6.37	1.12	0.96–1.32
MG do Sul	2.28	1.66	0.73	0.50–1.06	7.40	5.16	0.70	0.48–1.01
Mato Grosso	1.78	2.21	1.24	0.89–1.74	5.99	7.22	1.22	0.87–1.71
Goiás	1.57	1.98	1.27	0.97–1.64	5.49	6.94	1.26	0.97–1.64
D Federal	1.54	1.83	1.19	0.81–1.73	4.41	5.66	1.27	0.87–1.86

*$p \leq 0.05$, significant level

roughly 1.4 times higher risk of NTDs, although this association is detectable only in non Latin-European populations. Other folates and NTD-related genes, such as methylenetetra-hydrofolate dehydrogenase (MTHFD), have not been evaluated in Brazilian population yet. Brazilian antecedents on the prevalence of the 677C>T mutation came from different populations and ethnic groups and in general, they indicated a prevalence below 10 % of TT homozygous individuals and higher prevalence of the mutation in individuals with European than African or Amerindian ancestry (Ferreira-Fernandes et al. 2013; Franco et al. 1998; Brandalize et al. 2007; Arruda et al. 1998). In Brazil, populations of higher Amerindian or African ancestry are concentrated in the North and Northeast regions with major risk of death for anencephaly (Parra et al. 2003) (Tables 2 and 3).

Food habits of the Brazilian population related to folate intake are an important factor in the epidemiology of deaths from NTD in general and anencephaly in particular. The Brazilian Institute of Geography and Statistics (IBGE 2012) conducted a National Food Survey (Inquérito Nacional de Alimentação, INA) between 2008 and 2009 developed in the context of the Household Budget Survey by which consumption for two nonconsecutive days of 34,003 individuals

Table 3 Fetal mortality rate by anencephaly (FMR-A) and percentage of fetal deaths by anencephaly (FD%-A) throughout Brazil, regions, and states in the pre-fortification (PRF) and post-fortification (POF) periods and risk for POF compared to PRF period

Region/states	FMR-A				FD%-A			
	PRF	POF	Risk	95 % CI	PRF	POF	Risk	95 % CI
Brazil	1.58	1.07	0.67*	0.64–0.71	27.9	19.8	0.71*	0.67–0.75
North	1.33	0.98	0.74*	0.62–0.88	31.7	22.3	0.69*	0.58–0.83
Rondônia	1.57	0.83	0.52*	0.28–0.96	33.9	15.5	0.49*	0.27–0.91
Acre	1.22	1.01	0.83	0.38–1.81	41.0	34.6	0.90	0.41–1.97
Amazonas	1.40	0.86	0.62*	0.42–0.91	32.3	17.3	0.51*	0.35–0.74
Roraima	1.16	0.14	0.12*	0.02–0.98	18.4	3.6	–	–
Pará	1.38	1.08	0.78	0.61–1.01	33.7	25.7	0.75*	0.58–0.96
Amapá	1.40	1.07	0.76	0.35–1.68	35.8	28.6	0.65	0.29–1.43
Tocantins	0.71	1.19	1.67	0.84–3.33	15.6	22.5	1.55	0.77–3.09
Northeast	1.39	1.27	0.92	0.83–1.01	30.8	24.9	0.81*	0.74–0.89
Maranhão	1.04	1.03	1.01	0.74–1.38	34.5	29.0	0.87	0.64–1.18
Piauí	0.79	0.83	1.03	0.62–1.71	22.0	16.2	0.76	0.46–1.26
Ceará	1.88	1.57	0.83	0.67–1.04	33.4	29.5	0.89	0.72–1.11
R G do Norte	2.45	1.12	0.45*	0.31–0.66	41.2	23.2	0.58*	0.40–0.85
Paraíba	1.79	1.32	0.74	0.52–1.05	40.8	31.3	0.74	0.52–1.04
Pernambuco	1.56	1.53	0.99	0.79–1.23	27.1	22.7	0.84	0.68–1.05
Alagoas	0.81	1.13	1.42	0.92–2.20	27.1	26.9	0.98	0.63–1.52
Sergipe	1.49	1.32	0.88	0.55–1.38	27.3	22.6	0.91	0.58–1.44
Bahia	1.08	1.23	1.14	0.93–1.40	29.0	22.7	0.81*	0.66–0.99
Southeast	1.83	1.01	0.55*	0.51–0.60	27.9	17.8	0.64*	0.58–0.69
Minas Gerais	1.44	1.13	0.79*	0.66–0.94	25.3	17.4	0.69*	0.58–0.83
Espírito Santo	1.62	1.13	0.70	0.47–1.04	27.4	20.5	0.78	0.53–1.15
Rio de Janeiro	1.88	1.09	0.58*	0.48–0.70	35.5	20.0	0.56*	0.46–0.67
São Paulo	2.01	0.91	0.45*	0.40–0.51	26.9	16.8	0.63*	0.56–0.71
South	1.65	0.94	0.56*	0.48–0.66	24.3	16.1	0.66*	0.56–0.76
Paraná	1.87	0.91	0.49*	0.39–0.62	26.3	15.7	0.59*	0.47–0.75
S. Catarina	1.56	0.83	0.52*	0.37–0.73	25.4	16.2	0.62*	0.44–0.88
RG do Sul	1.48	1.03	0.70*	0.54–0.89	21.5	16.6	0.76*	0.59–0.97
Central West	1.21	0.91	0.75*	0.61–0.93	22.6	16.4	0.71*	0.58–0.89
MG do Sul	1.30	1.10	0.84	0.52–1.36	20.9	13.8	0.67	0.41–1.08
Mato Grosso	1.61	1.30	0.81	0.54–1.19	22.0	20.8	0.95	0.64–1.41
Goiás	1.22	0.73	0.60*	0.42–0.87	25.9	16.8	0.65*	0.45–0.94
D Federal	0.72	0.67	0.93	0.52–1.67	20.1	13.2	0.67	0.37–1.20

*$p \leq 0.05$, significant level

living in 13,569 households distributed throughout Brazil were recorded. The average per capita consumption (g/day) in rural areas was higher for traditional Brazilian food with low folate content, such as rice, beans, sweet potatoes, cassava flour, fresh and salted fish, and cured meats. Instead, in the urban area prevailed the consumption of ready-to-eat foods and some of them processed with fortified flour, such as salt bread, stuffed cookies, sandwiches, fried and baked snacks, pizzas, sodas, juices, and beers. Table 5 shows the prevalence of food consumption rate and the average per capita food consumption (g/day) of the main FA fortification or folate containing foods. As can be seen in the North and Northeast regions, the percentage of consumption of cassava flour (unfortified) was very high; the opposite occurred with the consumption of bread or other foods processed with fortified flour (macaroons, cakes, sweet biscuits), which was higher in the South and Southeast regions, the same as eating vegetables with green leaves rich in folate. Both indicators of food consumption, percentage and g/day, varied with income level of respondents and the financial situation of the family, so that the consumption of bread and fortified flour processed foods and green leave vegetable consumption increased with higher income and household wealth, while the opposite occurred with cassava flour. Likewise, the INA (IBGE 2012) provided

Table 4 Rate of infant mortality + fetal by anencephaly (IMR + FMR-A) and percentage of infant deaths + fetal anencephaly (ID + FD%-A) throughout Brazil, regions, and states in the pre-fortification (PRF) and post-fortification (POF) periods and risk for POF compared to PRF period

Region/states	IMR + FD-A				ID + FD%-A			
	PRF	POF	Risk	95 % CI	PRF	POF	Risk	95 % CI
Brazil	3.56	3.01	0.85*	0.82–0.88	11.71	9.33	0.79*	0.77–0.82
North	3.29	3.14	0.95	0.85–1.06	12.85	10.4	0.81*	0.73–0.90
Rondônia	4.43	4.54	1.02	0.76–1.37	15.18	12.41	0.81	0.60–1.09
Acre	3.64	3.70	1.01	0.66–1.55	13.31	12.90	0.99	0.64–1.52
Amazonas	3.59	3.06	0.86	0.70–1.07	12.17	8.43	0.69*	0.56–0.86
Roraima	2.53	3.52	1.37	0.73–2.54	6.90	12.89	1.69	0.91–3.15
Pará	3.07	2.89	0.93	0.79–1.10	14.18	10.96	0.77*	0.66–0.91
Amapá	3.90	3.30	0.85	0.53–1.34	15.25	12.47	0.74	0.46–1.18
Tocantins	2.18	2.77	1.27	0.83–1.92	8.13	9.26	1.15	0.76–1.74
Northeast	3.19	3.42	1.07*	1.01–1.14	13.73	10.82	0.79*	0.74–0.84
Maranhão	2.06	2.64	1.29*	1.05–1.58	11.82	9.75	0.89	0.73–1.09
Piauí	2.27	2.96	1.29	0.97–1.72	11.35	7.96	0.77	0.59–1.02
Ceará	4.07	3.86	0.95	0.82–1.10	14.94	12.44	0.83*	0.72–0.95
R G do Norte	5.98	3.86	0.64*	0.52–0.79	20.50	12.94	0.62*	0.50–0.77
Paraíba	3.87	4.17	1.07	0.86–1.32	20.95	13.48	0.69*	0.56–0.86
Pernambuco	3.83	3.59	0.94	0.82–1.09	13.06	9.91	0.76*	0.66–0.87
Alagoas	2.49	3.02	1.23	0.95–1.59	13.04	10.32	0.77*	0.59–0.99
Sergipe	3.60	4.26	1.19	0.90–1.56	13.81	12.54	0.97	0.74–1.27
Bahia	2.30	3.25	1.41*	1.23–1.61	11.50	10.47	0.91	0.79–1.04
Southeast	3.90	2.80	0.72*	0.68–0.76	11.69	8.80	0.75*	0.71–0.79
Minas Gerais	3.09	2.96	0.96	0.85–1.07	10.23	9.23	0.82*	0.73–0.92
Espírito Santo	3.55	3.78	1.07	0.84–1.35	10.88	10.72	0.95	0.75–1.21
Rio de Janeiro	4.24	2.92	0.69*	0.61–0.78	12.52	8.83	0.71*	0.63–0.80
São Paulo	4.17	2.60	0.62*	0.58–0.67	11.61	8.40	0.72*	0.67–0.78
South	3.83	2.70	0.70*	0.64–0.77	10.35	7.75	0.75*	0.68–0.82
Paraná	4.05	2.82	0.69*	0.60–0.80	10.51	7.82	0.74*	0.64–0.85
S. Catarina	4.48	2.71	0.60*	0.49–0.73	13.34	8.46	0.63*	0.62–0.77
RG do Sul	3.26	2.55	0.79*	0.67–0.92	8.70	7.33	0.84*	0.71–0.98
Central West	2.95	2.86	0.97	0.85–1.10	8.23	7.92	0.96	0.85–1.10
MG do Sul	3.58	2.75	0.77	0.57–1.03	9.59	6.79	0.71*	0.53–0.96
Mato Grosso	3.39	3.51	1.04	0.80–1.34	9.30	9.54	1.06	0.82–1.37
Goiás	2.79	2.71	0.97	0.79–1.20	8.34	8.23	0.98	0.80–1.21
D Federal	2.26	2.51	1.10	0.80–1.52	5.82	6.67	1.13	0.82–1.55

*$p \leq 0.05$, significant level

information on the average folate intake in mg, where a large interregional variation with the highest value can also be observed in the South (394.2 mg), followed by the Southeast (384.4 mg), Northwestern (36.8 mg), Central West (362.7 mg), and North (324.1 mg) regions. The regional variation pattern of folate intake of Brazilian population revealed by these studies keep a close relationship with the regional variation of risk of death by anencephaly (Tables 2 and 3). These facts reinforce the need for nutritional reeducation of Brazilian population in order to increase consumption of folic acid food sources and reduce the incidence of NTDs (Uehara and Rosa 2010). However, it would seem that another option would be to change or increase the number of food types that are fortified.

So far, evaluation of FA fortification of wheat and corn flour in Brazil is insufficient. A study on a total of 70 samples of flour from supermarkets in the cities of Campinas and São Paulo State, one of the states with significantly reduced risk of anencephaly (Table 2), showed that the concentration of folic acid ranged between 96 and 558 mg per 100 g (in corn) and 73–233 mg per 100 g (in wheat). These results showed a great variation in FA concentration, and that the Brazilian population would seem to be most likely exposed to inadequate concentrations of FA (Rezende Boen et al. 2008) particularly in

Table 5 Percentage and per capita food consumption of various foods by region of Brazil

Foods	Prevalence of food intake (%)					Food intake per capita (g/day)				
	North	Northeast	Southeast	South	Central West	North	Northeast	Southeast	South	Central West
Mandioca flour	45.3	18.2	1.8	0.7	1.3	46.2	11.5	0.8	0.2	0.5
Bread	53.4	55	66.9	73.6	58.8	44.7	56.1	52.1	59.2	43.1
Bowls	11.9	11.1	13.5	16	17.7	11.2	10.5	14.6	17.3	18.6
Sweet cookie	6.8	9	9.1	10.1	8.9	3.9	4.6	3.9	3.1	3.6
Macarones	16.7	22.7	14.8	25.6	15.8	29.9	33.4	33.8	56.5	28.6
Lettuce	2.7	2.4	11.8	18.4	11.6	1.1	0.6	3.8	9.2	4.6
Salad	10.2	10.6	17.8	18.2	27.4	9.6	8.8	16.8	17	26.6
Other vegetables	1.1	0.6	3.5	3.5	3	0.8	0.4	1.9	2.5	1.6

Source: The Brazilian Institute of Geography and Statistics (IBGE 2012)

Brazilian states with the highest risk of anencephaly (Tables 2 and 3). In this study, on the one hand, the concentrations were very close or lower than the issued value (wheat flours). On the other hand, corn flours presented extremely high values of FA. Another study carried out by Soeiro et al. (2010) would indicate that flour packed in plastic containers showed lower amount of folic acid (152 g μg, 100-1 on average) when compared to samples stored in paper cartons (259 μg, 100 g-1 on average).

The regional variation to the risk of anencephaly is also related to the measures of prevention by folic acid supplementation. From the central level in Brazil, there are clear provisions in force since 2005 about the primary prevention of NTDs. Indeed, a technical manual from the Brazilian Ministry of Health indicates that "prophylaxis of open neural tube defects should be made by administering folic acid. The required oral daily dose is 0.4 mg, for 60 to 90 days before conception and up to 3 months after it" (Brazil Ministry of Health 2005). However, several studies made in the most developed regions of the country and with lower risk of death due anencephaly indicate that supplementation with FA is used only between 20 and 32 % of pregnancies, and that this percentage is not affected by per capita income, ethnicity, education, and age of pregnant women (de Antunes et al. 2012; Mezzomo et al. 2007; Matos Fonseca et al. 2003; Fujimori et al. 2013). Family planning, another opportunity for primary prevention of NTDs, emerged in Brazil in 1983 with the Program for Integral Assistance to Women's Health (Ministry of Health 1984) mainly oriented to date to the control of fertility and not perinatal health (Dos Santos and Martins de Freitas 2011). At Ribeirão Preto, 62.7 % of puerperal women are unaware of the family planning service offered by the National Health System, and 60 % of pregnant women have an unplanned pregnancy (Pereira Machado et al. 2013).

SIM data since 2004 would theoretically include among fetal deaths anencephaly cases interrupted by selective termination of pregnancies. However, this confusing factor could not be objectively evaluated because the information withheld by the SIM did not allow separating spontaneous fetal deaths from those resulting from elective anencephaly pregnancy termination. However, in the POF period throughout Brazil, and in general for all regions and states, a significant decrease in anencephaly fetal deaths was observed (n). This pattern could be indirectly related to the regional risk variation of induced abortion observed in Brazil. In 2005, there was an important regional difference in the risk of induced abortions per 100 women aged 15 to 49 years which was higher in the North (2.81) followed by the Northeast (2.73), Central West (2.01), Southeast (1.82), and South (1.29) regions (Monteiro and Adessel 2006). According to these authors, these differences could be attributed to a greater and more effective use of contraception by women in the South, which reduced the occurrence of unwanted pregnancies and therefore the need to resort to induced abortion.

Among the environmental risk factors associated with anencephaly, local socioeconomic conditions (neighborhood, education, poverty, overcrowding, and occupational level) are to be highlighted (Shaw et al. 1997). These risks increase because the most disadvantaged populations tend to be located near hazardous sites being more exposed to emissions (WHO 2010). There is a clear socioeconomic differentiation among the poorest populations in the north compared to southern Brazil.

Since Brazil is a heterogeneous country in terms of private versus public delivery practice and social economic status throughout the different regions, it seems that many confounding factors would play a role influencing indirectly through the study period. In the same sense, judicialization of pregnancy termination in the period analyzed, as much as the prohibition that followed during the same period, could masquerade the folic acid benefits as well.

Conclusions

Compared to other Latin American countries and according to the indicators used in this paper, Brazil has experienced a moderate and in some cases zero anencephaly infant and fetal deaths decrease between 1997–2004 and 2005–2011. Large spatial disparities persist between regions and states attributable to dietary habits, genetic, socioeconomic, and health history of Brazilian populations. Exploratory and descriptive knowledge of the geographical distribution of deaths from anencephaly achieved in this work would guide the search for environmental or genetic risk factors and contribute to define and/or strengthen strategies for primary prevention, not only by mandatory fortification but also by folate intake and supplementation.

Ethical standards This study comply with the current laws of the country in which they were performed.

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