Prevalence of oral clefts in the State of Rio Grande do Norte, Brazil, between 2000-2005

Prevalência de fissuras orais no Estado do Rio Grande do Norte, Brasil, entre 2000 e 2005

Prevalencia de fisuras orales en el estado de Rio Grande do Norte, Brasil, entre 2000 y 2005

Cristina Jordão R. Figueirêdo[1], Willyanne Kathia S. Vasconcelos[1], Shirley Suely S. V. Maciel[2], Wamberto Vieira Maciel[3],

Líbia Augusta M. Gondim[4], Rafael Miranda Tassitano[5]

ABSTRACT

Objective: To analyze the epidemiological aspects of oral clefts in children born alive between 2000 and 2005 in the State of Rio Grande do Norte, Brazil.

Methods: Cross-sectional study with data obtained from Live Births System Data provided by the Department of Health Surveillance of the Ministry of Health. Data regarding mother's age, type of cleft, type of delivery, birth weight, gender, race and place of birth were analyzed.

Results: During the studied period, the number of live births in the state was 318,667, of which 155 had some kind of lip and/or palate cleft, with a prevalence of 0.49 cases/1,000 live births. When assessing the prevalence in the eight health regions, the metropolitan region of Natal (0.51), João Câmara (0.81) and Santa Cruz (0.67) presented ratios slightly above the average for the State. Some cities, however, presented very high prevalence of oral clefts such as Maxaranguape and Serra do Mel, with 3.52 and 2.52 cases/1,000 live births, respectively. The most prevalent type was cleft lip with involvement of the palate and males were most affected.

Conclusions: The prevalence of oral cleft was low in the State, but some cities deserve attention due to the high prevalence of malformations. Further studies are needed in order to understand potential teratogenic risks to which the pregnant women may be exposed in such places, predisposing them to fetal congenital anomalies such as cleft lip and palate.

RESUMO

Objetivo: Analisar os aspectos epidemiológicos das fissuras orais em crianças nascidas entre 2000 e 2005 no Estado do Rio Grande do Norte, Brasil.

Métodos: Realizou-se um estudo transversal com dados obtidos do Sistema de Informações sobre Nascidos Vivos (Sinasc) disponibilizados pela Secretaria de Vigilância em Saúde do Ministério da Saúde. Descreveu-se a faixa etária da mãe, o tipo de fissura, o tipo de parto, o peso ao nascer, o sexo, a etnia da criança e as regionais de saúde.

Resultados: Nesse período, o número de nascidos vivos no Estado foi de 318.667, dos quais 155 possuíam algum tipo de fissura de lábio e/ou palato, representando uma prevalência de 0,49 casos/1.000 nascidos vivos. Ao se avaliar a prevalência nas oito regionais de saúde, Grande Natal (0,51), João Câmara (0,81) e Santa Cruz (0,67) ficaram um pouco acima da média do Estado. Entretanto, existiram municípios com valores discrepantes dessa frequência, como o de Maxaranguape, com uma prevalência de 3,52 casos/1.000 nascidos vivos e Serra do Mel, com 2,52 casos/1.000 nascidos vivos. O tipo mais frequente foi fenda labial com envolvimento palatino, e o sexo masculino foi o mais atingido.

Conclusões: A prevalência das fissuras orofaciais foi baixa para o Estado. Destaca-se que alguns municípios merecem atenção devido à alta prevalência da malformação, havendo necessidade

Instituição: Associação Caruaruense de Ensino Superior (ASCES), Caruaru, PE, Brasil

[1]Especialista em Saúde Pública pela ASCES; Cirurgiã-dentista da Secretaria de Saúde de Caruaru, PE, Brasil

[2]Doutora em Saúde Coletiva pela Universidade de Pernambuco (UPE); Docente da Faculdade do Vale do Ipojuca (Favip), Caruaru, PE, Brasil

[3]Mestre em Dentística pela UPE; Docente da ASCES, Caruaru, PE, Brasil

[4]Mestre em Odontologia Preventiva e Social pela Universidade Federal do Rio Grande do Norte (UFRN); Docente da Associação Brasileira de Odontologia – Regional Caruaru, Caruaru, PE, Brasil

[5]Mestre em Hebiatria pela UPE; Docente da ASCES, Caruaru, PE, Brasil

Endereço para correspondência:
Shirley Suely S. V. Maciel
Avenida Londres, 110, apto 002 – Bairro Universitário
CEP 55016-370 – Caruaru/PE
E-mail: shirleyverasmaciel@gmail.com

de estudos para compreender os potenciais riscos teratogênicos aos quais a mulher grávida pode estar exposta e que propiciam anomalias congênitas, tais como as fissuras labiopalatais.

Palavras-chave: fenda labial; fissura palatina; recém-nascido.

RESUMEN

Objetivo: Analizar los aspectos epidemiológicos de las fisuras orales en niños nacidos entre 2000 y 2005 en el estado de Rio Grande do Norte, Brasil.

Métodos: Se realizó un estudio transversal con datos obtenidos del Sistema de Informaciones sobre Nacidos Vivos (SINASC) puesto a la disposición por la Secretaría de Vigilancia en Salud del Ministerio de Salud. Se describió la franja de edad de la madre, el tipo de fisura, el tipo de parto, el peso al nacer, el sexo, la etnia del niño y las regionales de salud.

Resultados: En este periodo, el número de nacidos vivos en el Estado fue de 318.667, de los que 155 poseían algún tipo de fisura de labio y/o paladar, representando una prevalencia de 0,49 casos por 1000 nacidos vivos. Al evaluar la prevalencia en las ocho regionales de salud, Grande Natal (0,51), João Câmara (0,81) y Santa Cruz (0,67) quedaron un poco por encima del promedio del Estado. Sin embargo, hubo municipios con valores discrepantes de esta frecuencia, como el municipio de Maxaranguape, con una prevalencia de 3,52 casos/1000 NV y Serra do Mel, con 2,52 casos/1000 NV. El tipo más frecuente fue la hendidura labial con implicación palatina y el sexo masculino fue el más afectado.

Conclusiones: la prevalencia de las fisuras orofaciales fue baja para el Estado. Se destaca que algunos municipios merecen atención debido a la alta prevalencia de la malformación, habiendo la necesidad de estudios para comprender los potenciales riesgos teratogénicos a los que la mujer embarazada puede estar expuesta, propiciando anomalías congénitas, tales como las fisuras labiopalatales.

Palabras-clave: hendidura labial; hendidura palatina; epidemiología.

Introduction

Cleft lip and palate is a congenital deformity of still-unclear etiology, characterized by the presence of fissures or gaps[1], which arises during the first stages of embryonic development (between the fourth and eighth week of intrauterine life) from the branchial or pharyngeal arches and their derivatives[2]. In addition to the lip and palate, clefts affect facial structures such as the maxilla, bones and cartilage, and may occur as isolated malformations or as features of congenital syndromes[1,3].

In the United States, the highest incidence of oral clefts is among Native Americans (approximately 1/278 live births)[4]. Approximately 1 out of every 750 European-American liveborn infants have cleft lip and/or palate[4]; African-Americans are less affected, with one case per 3300 births[4]. In Brazil, the overall prevalence of oral clefts is 1/650, that is, 1.53 cases per 1000 live births[4,5]. Cleft lip and palate is predominant in males[6-10], and involvement is more often unilateral than bilateral[10], with left-sided clefts the most common of all[5,7].

In addition to major cosmetic issues, patients with cleft lip and palate present with severe functional impairment[11], which may include phonation disorders, dental arch changes, abnormal maxillary development, and fluid buildup in the middle ear[1]. Infants with cleft lip are usually diagnosed immediately at birth, but cleft palate may go unnoticed for hours or even weeks[12, 13].

Data on the prevalence of congenital anomalies are usually obtained through direct searches of hospital records. In Brazil, however, an important source of information makes collection of such data substantially easier: the Statement of Live Birth. The Statement of Live Birth is an official document and the basic instrument of the Live Births Information System (*Sistema de Informações sobre Nascidos Vivos*), a system implemented in Brazil in 1990 and managed by the Brazilian Ministry of Health. Ever since, use of the Statement has become mandatory in maternity hospitals, and, since 2001, one of the items on the Statement form has concerned the presence of congenital malformations and/or chromosomal abnormalities, with information on the type of abnormality and its corresponding code in Chapter XVII of the International Statistical Classification of Diseases (ICD-10)[14].

The incidence of orofacial clefts appears to be increasing slowly. This trend may, in part, be due to improved notification and record-keeping. However, a real increase—perhaps due to greater exposure to environmental teratogens and lower neonatal mortality—is likely[15]. Although studies have assessed congenital abnormalities in other Brazilian states, there is no published literature on their occurrence in the state of Rio Grande do Norte. In this context, the present study sought to estimate the prevalence of cleft lip and/or palate in children born between 2000 and 2005 in the state of Rio Grande do Norte, Brazil, using data obtained from the Live Births Information System (SINASC), made available by the Secretary of Health Surveillance of the Brazilian Ministry of Health.

Methods

This was a cross-sectional study, conducted using secondary data collected from records of infants born with oral clefts (stratified by the mother's place of residence) in the state of Rio Grande do Norte, Brazil, between 2000 and 2005. Data were obtained through the SINASC, made available by the Secretary of Health Surveillance of the Brazilian Ministry of Health. The state of Rio Grande do Norte comprises 167 municipalities and is home to a population of approximately 3 million[16].

The dependent variable was presence of cleft lip and/or palate, as reported on Statements of Live Birth by ICD-10 codes Q35 (cleft palate), Q36 (cleft lip), and Q37 (cleft palate with cleft lip). However, for comparison purposes, some nomenclature alternatives used elsewhere in the literature were also considered: "*fissuras lábio-palatais*" (FLP) "*fendas lábio-palatinas*" (FLP ± P) (both meaning "labiopalatal cleft")[2,7], "*fissura labial*" (FL, "labial cleft") "*fissuras palatinas*" (FP, "palatal clefts") or "*fendas palatinas isoladas*" (FP, "cleft palate alone")[17,18].

Independent variables were classified as maternal or neonatal. Maternal variables were age (years), educational attainment (years of formal schooling), and number of prenatal visits. Neonatal variables were birth weight (kg), mode of delivery, duration of pregnancy (gestational weeks), gender, and skin color.

Maternal age was estimated as a quantitative variable according to the presence or absence of oral clefts, and was then divided into three ranges: 10–19 years (teen mothers), 20–34 years, and 35 years or older. Educational attainment was also classified into ranges: 0 (illiterate) to 3 years of schooling, 4–7 years of schooling, and 8 or more years of schooling. The number of prenatal appointments was divided into "six or fewer" and "seven or more".

Birth weight (grams) was analyzed as a quantitative variable and classified into low birth weight (<2,500 g) or normal birth weight (≥2,500 g). As for duration of pregnancy, birth at < 37 weeks was considered preterm and birth at 37 weeks or more considered full-term. Mode of delivery was defined as vaginal or Cesarean. Gender was defined as male or female, and skin color, as white or brown, as there were no records of oral clefts occurring in children of other ethnicities (skin color "yellow" or "black") in the study sample.

The prevalence of oral clefts in each of the state's health regions was calculated by dividing the number of cleft cases (study endpoint) by the number of live births in each region and multiplying the quotient by 1000.

Data were initially analyzed by means of descriptive statistics. Qualitative variables were expressed as frequency distributions and quantitative variables, as means and standard deviations.

The Student t test was used for comparison of means between the "oral clefts present" and "oral clefts absent" groups. Fisher's exact test or the chi-square test were used for categorical variables as appropriate, and a chi-square test for linear trend was used for analysis of ordinal variables.

As orofacial clefts are rare events, risk was estimated by odds ratios (OR), with presence of a cleft as the study endpoint. The level of significance was set at p<0.05 for all analyses. The Tabwin 2.0 for Windows software, developed by the Brazilian Unified Health System Department of Information Technology (DATASUS), was used to tabulate data obtained from the Ministry of Health system. Data were processed and analyzed in the Statistical Package for the Social Sciences (SPSS) v. 13 environment.

It bears noting that, as this study was conducted solely on the basis of official, secondary, government data, no institutional review board approval was required. As no identifying variables or data were available at any point, a reference to the original government source suffices.

Results

A total of 318,667 live births were recorded in Rio Grande do Norte during the study period. Of these, 155 had some sort of cleft lip and/or palate (prevalence, 0.49 per 1000 live births). In this population, there were 32 cases of cleft lip (0.10/1000 live births), 19 of cleft palate (0.06/1000 live births) and 104 of cleft lip and palate (0.33/1000 live births).

The incidence rates of oral fissure in Rio Grande do Norte fluctuated over the study period, reaching their lowest levels in 2000 and 2001 (0.39 and 0.40/1000 live births respectively) and peaking in 2002 (0.55/1000 live births), 2003 and 2005 (0.54/1000 live births).

Oral clefts were most prevalent in males than in females (57.5 vs. 42.5%). Presence of clefts was significantly associated with gender, mode of delivery, and skin color (Table 1).

The mean age of mothers of infants with cleft palate was 24.4±7.6 years; the youngest and oldest mothers were 13 and 47 years old respectively. Table 2 shows that the risk of oral clefts was highest in infants whose mothers were 35 years old or older at the time of delivery.

Assessment of the prevalence of cleft lip and palate in the eight health regions of the state revealed rates above the state average of 0.49/1000 live births in the Greater Natal, João Câmara, and Santa Cruz regions (0.51, 0.81, and 0.67/1000 live births respectively). Some municipalities, however, had prevalence rates markedly higher than the state average, such as Maxaranguape

Table 1 – Distribution of neonatal variables according to presence of oral clefts, Rio Grande do Norte, Brazil, 2000-2005.

Neonatal variables	Cleft		p	OR (95%CI)
	Present	**Absent**		
Birth weight				
Low	34	23,467	0.001	3.54 (1.71 – 4.92)
Normal	120	293,999		1
Duration of pregnancy				
Preterm	26	17,480	0.001	3.48 (1.45 – 4.88)
Full-term	128	299,881		1
Mode of delivery				
Vaginal	95	220,229	0.04	1.41 (1.07-2.14)
Cesarean section	60	98,046		1
Gender				
Male	89	163,098	0.14	1
Female	66	154,985		0.78 (0.45 – 1.21)
Skin color				
White	56	135,695	0.06	1
Brown	97	171,036		1.37 (0.82 -1.91)

Table 2 – Distribution of maternal variables according to presence of oral clefts, Rio Grande do Norte, Brazil, 2000-2005.

Maternal variables	Cleft		p	OR (95%CI)
	Present	**Absent**		
Age range (years)				
10–19	46	79,441	0.08	1,38 (0,89-2,10)
20–34	88	210,900		1
>34	21	27,360	0.01	1,83 (1,26-2,42)
Educational achievement (years)				
0–3	37	74,756	0.75	0,91 (0,23-1,19)
4–7	55	126,839	0.27	0,80 (0,14-1,23)
≥7	60	111,054		1
No. of prenatal visits				
≤6	105	199,703	0.19	1,27 (0,73-1,81)
>6	47	114,046		1

Table 3 – Prevalence of oral clefts in the eight health regions of the state of Rio Grande do Norte, Brazil, 2000-2005.

Health region	Live births	Cases of oral cleft	Prevalence / 1000 live births
Greater Natal	111,416	61	0.51
São José de Mipibu	38,673	19	0.49
Mossoró	41,765	17	0.41
João Câmara	30,683	25	0.81
Caicó	27,977	11	0.39
Santa Cruz	19,331	13	0.67
Pau dos Ferros	23,791	1	0.04
Açu	18,002	7	0.39

Table 4 – Prevalence of oral clefts by municipality, state of Rio Grande do Norte, Brazil, 2000-2005.

Municipality	Live births	Cases of oral cleft	Prevalence / 1000 live births
Areia Branca	2,410	3	1.24
Ceará-Mirim	8,010	11	1.37
Currais Novos	4,157	3	0.72
Maxaranguape	853	3	3.52
Mossoró	24,014	3	0.25
Natal	84,077	49	0.58
Nova Cruz	3,891	3	0.77
Parnamirim	16,921	7	0.41
Santa Cruz	3,888	3	0.77
São José de Mipibu	4,666	3	0.64
Serra do Mel	1,190	3	2.52

(3.52 cases/1000 live births) and Serra do Mel (2.52/1000 live births) (Table 4).

Discussion

The first, landmark study of cleft lip and palate prevalence in Brazil was conducted by Nagem Filho *et al.* in 1968, on a sample of 13,429 schoolchildren from the municipality of Bauru, state of São Paulo. Twenty cases of oral cleft were detected, for a prevalence of 1.54 per 1000 schoolchildren[20]. In this seminal study, cleft lip and palate was most prevalent, followed by cleft lip and cleft palate alone. These findings are consistent with most published prevalence data[15, 21, 22].

In the present study, the prevalence of oral clefts was lower than that reported for other places in Brazil[4,5], such as Porto Alegre, Rio Grande do Sul (1.32/1000 live births)[6] and Joinville, Santa Catarina (1.24/1000 live births)[7]. However, broad variations were found when municipalities were assessed individually. One notable outlier was Maxaranguape, where the prevalence of cleft lip and palate was six times higher than the state average; other municipalities also had high prevalence rates, such as Serra do Mel, Ceará-Mirim, and Areia Branca. These findings may be explained by a variety of factors, from common etiological and risk factors for oral cleft to difficulties in record-keeping or undernotification of congenital abnormalities in some municipalities. These results reinforce the need for better analysis of the distribution of cleft lip and palate in the state of Rio Grande do Norte, producing data that can serve as inputs for further studies on the theme—such as investigations of risk factors prevalent in these municipalities, including environmental teratogens. Oral clefts are an etiologically complex condition, and may be associated with genetic factors, environmental factors, or a combination of both. The highest prevalence rates were found in the municipalities with the lowest birth rates, deep within the state, which serves as a warning regarding current health care policies.

Overall, there was no association between maternal age, educational attainment, or number of prenatal appointments and presence of malformations. However, corroborating the findings of prior studies[6,18], risk of oral clefts was significantly increased in infants born to mothers aged 35 years or older. Interestingly, oral clefts were most common among children born to more educated mothers.

It has been established that the presence or absence of oral clefts is not significantly associated with the number of prenatal care appointments attended by the mother. Nonetheless, a striking finding in this study was the nearly twofold risk of orofacial clefts in infants whose mothers attended few prenatal visits (six or fewer). During prenatal care, health professionals provide dietary guidance and prescribe vitamin supplements, which may corroborate the research finding that diets rich in fruit, vegetables, and other folate-containing foods are associated with reduced risk of cleft lip and palate[23-25]. However, this finding should be viewed cautiously, as information on the number of prenatal visits is only available for mothers seen within the Unified Health System. One must bear in mind that some mothers may have received neonatal care in the private sector, and that, despite adherence to dietary guidance, environmental teratogens may interfere with the pathophysiology of oral clefts.

Since 2004, pursuant to Pan American Health Organization/World Health Organization (PAHO/WHO) recommendations, the Brazilian Health Surveillance Agency (ANVISA) has made it mandatory for all wheat and corn flour to be fortified with iron and folic acid[26], which may provide an added measure of protection against development of congenital anomalies, including orofacial clefts.

These abnormalities were associated with certain neonatal features, such as gender, mode of delivery, and skin color. Oral clefts were most prevalent in male infants, as previously mentioned in the literature[8-10]. Regarding ethnicity or skin color, congenital lip and palate malformations were most common in brown-skinned infants in this study, contradicting the findings of a study conducted in Minas Gerais, which found higher rates among white (termed Caucasian in the study) versus nonwhite patients[10]. However, there is ample disagreement in the literature concerning any association between maternal ethnicity and clefting; some authors have suggested that the children of black and Asian mothers are less likely to develop orofacial clefts[27], whereas others believe that ethnicity is in no way associated with the presence of this congenital anomaly.

However, we must stress the role of the high level of miscegenation found in Brazil, and note the fact that ethnicity/skin color is not a standardized field in the Statement of Live Birth used by the Brazilian Ministry of Health.

In conclusion, we suggest that further studies on the theme be conducted elsewhere in Brazil, using secondary data made available by all State Secretaries of Health across the country. Furthermore, we recommend that dentists be included in the diagnostic process of orofacial clefts, in order to improve reporting to the Live Births Information System. We conclude that the present study provides valuable inputs for the implementation of health policies meant to prevent congenital malformations of the lip and palate, particularly in municipalities where these abnormalities were most prevalent.

References

1. Veronez FS, Tavano LD. Modificações psicossociais observadas pós-cirurgia ortognática em pacientes com e sem fissuras labiopalatinas. Arq Cienc Saude 2005;12:133-7.

2. Borges-Osório MR, Robinson WM. Genética Humana. 2ª ed. Porto Alegre: Artmed; 2001.

3. Gorlin RJ, Cohen Jr MM, Hennekam RC. Syndromes of the head and neck. 4th ed. New York: Oxford University Press; 2001.

4. Mazzotini R, Freitas JA, Silva Filho OG. Cirurgia ortognática no protocolo do tratamento das fissuras lábio-palatais. In: Araújo A, editor. Cirurgia Ortognática. São Paulo: Santos; 1999.

5. Armada L, Armada-Dias L, Tato NA, Alves MU. Prevalence of oral alterations in cleft lip and palate children from the Hospital Municipal Nossa Senhora do Loreto – RJ. Pesq Bras Odontoped Clin Integr João Pessoa 2005;5:165-70.

6. Collares MV, Westphalen AC, Costa TC, Goldim JR. Fissuras lábio-palatinas: incidência e prevalência da patologia no Hospital das Clínicas de Porto Alegre: um estudo de 10 anos. Rev AMRIGS 1995;39:183-8.

7. França CMC, Locks A. Incidência das fissuras lábio-palatinas de crianças nascidas na cidade de Joinville (SC) no período de 1994 a 2000. J Bras Ortodon Ortop Facial 2003;8:429-36.

8. Furlaneto EC, Pretto SM. Estudo epidemiológico dos pacientes atendidos no serviço de defeitos de face da PUCRS. Rev Odonto Cienc 2000;15:39-56.

9. Baroneza JE, Faria MJ, Kuasne H, Carneiro JL, Oliveira JC. Dados epidemiológicos de portadores de fissuras labiopalatinas de uma instituição especializada de Londrina, Estado do Paraná. Acta Sci Health Sci 2005;27:31-5.

10. Martelli-Júnior H, Porto LV, Martelli DR, Bonan PR, Freitas AB, Della Coletta R. Prevalence of nonsyndromic oral clefts in a reference hospital in the state of Minas Gerais, Brazil, between 2000-2005. Braz Oral Res 2007;21:314-7.

11. Rezende JR. Fundamentos da prótese buco-maxilo-facial. São Paulo: Sarvier; 1997.

12. Murray JC. Gene/environment causes of cleft lip and/or palate. Clin Genet 2002;61:248-56.

13. Habel A. Tratamento do lactente e da criança pequena com fissura labial e/ou fenda palatina. In: Watson AC, Sell DA, Grunwell P. Tratamento de fissura labial e fenda palatina. São Paulo: Santos; 2005. p.123-36.

14. Nascimento LF, Pinto CO, Proença FP, Gotlieb SL. Prevalence of congenital abnormalities in São José dos Campos, São Paulo, Brazil, in 2001. Rev Paul Pediatr 2006;24:47-51.

15. Watson AC. A natureza da fissura labial e da fenda palatina: embriologia, etiologia e incidência. In: Watson AC, Sell DA, Grunwell P. Tratamento de fissura labial e fenda palatina. São Paulo: Santos; 2005. p. 5-15.

16. IBGE - Instituto Brasileiro de Geografia e Estatística [homepage on the Internet]. Censos Demográficos [cited 2009 Aug 8]. Available from: http://www.ibge.gov.br/home/estatistica/populacao/default_censo_2000.shtm

17. Menegotto B. Epidemiologia e interação herança-ambiente nas fissuras labiopalatinas [tese de mestrado]. Porto Alegre (RS): UFRS; 1989.

18. Araújo Júnior E, Guimarães Filho HA, Pires CR, Zanforlin Filho SM, Santana RM, Moron AF. Fendas fetais labiais e palatinas detectadas pela ultra-sonografia tridimensional. Rev Imagem 2005;27:263-8.

19. Nagem Filho H, Moraes N, Rocha RG. Contribuição para o estudo da prevalência das más formações congênitas lábio-palatais na população escolar de Bauru. Rev Fac Odont S Paulo 1968;6:111-28.

20. Rezende JRV, Maringoni Filho N. Relacionamento entre os fatores presentes no nascimento de malformados do lábio e do palato: tipo e lado da lesão. Rev Paul Odontol. 1982;3:32-8.

21. Loffredo LC, Freitas JA, Grigolli AA. Prevalence of oral clefts from 1975 to 1994, Brazil. Rev Saude Publica 2001;35:571-5.

22. Loffredo LC, Souza JM, Yunes J, Freitas JA, Spiri WA. Fissuras lábio-palatais: estudo caso-controle. Rev Saude Publica 1994;28:213-7.

23. Wilcox AJ, Lie RT, Solvoll K, Taylor J, McConnaughey DR, Abyholm F *et al*. Folic acid supplements and risk of facial clefts: national population based case-control study. BMJ 2007;334:464.

24. Boyles AL, Wilcox AJ, Taylor JA, Shi M, Weinberg CR, Meyer K *et al*. Oral facial clefts and gene polymorphisms in metabolism of folate/one-carbon and vitamin A: a pathway-wide association study. Genetic Epidemiol 2009;33:247-55.

25. Anvisa - Agência Nacional de Vigilância Sanitária [homepage on the Internet]. Fortificação de Farinhas [cited 2010 Jan 10]. Available from: http://www.anvisa.gov.br/alimentos/farinha.htm

26. Williams LJ, Rasmussen SA, Flores A, Kirby RS, Edmonds LD. Decline in the prevalence of spina bifida and anencephaly by race/ethnicity: 1995-2002. Pediatrics 2005;116:580-6.