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ORIGINAL ARTICLE

Respiratory function in children of asthmatic mothers☆

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KEYWORDS
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Abstract
Objective: To evaluate lung function and clinical manifestations suggestive of asthma in children of mothers with a reported medical diagnosis of asthma.
Methods: An observational cross-sectional analytical study nested in a cohort of 4,757 pregnant women. A total of 86 six-year-old children were evaluated, born to mothers with a medical diagnosis of asthma before pregnancy. Information was collected regarding clinical symptoms of atopy and respiratory diseases, as well as socioeconomic and exposure variables; the children were submitted to spirometry.
Results: Spirometric alterations were observed in 30.3% of cases, with a prevalence of asthma in those who had an obstructive pattern. 9.3% of the children had a previous medical diagnosis of asthma; however, the established diagnosis based on the presence and frequency of asthma symptoms was 18.6%. Of the 86 participating children, 37.2% had a score of five or more points in the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, which was associated with spirometry alterations (p = 0.002). After multiple logistic regression analysis, higher paternal education, higher

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number of bedrooms in the family's home, and mother who did not have "wheezing" episodes during pregnancy were statistically significant as protective factors for the presence of respiratory disorder detected by spirometry.
Conclusions: The frequency of spirometry alterations in children of asthmatic mothers was high; the restrictive pattern was more often observed that the obstructive. There was a higher incidence of obstructive test results in those who presented clinical symptoms of asthma, with a higher frequency of clinical diagnosis of asthma than that found in the literature.
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PALAVRAS-CHAVE
Asma;
Criança;
Espirometria

Função respiratória em filhos de mães asmáticas

Resumo
Objetivo: Objetivo: Avaliar a função pulmonar e as manifestações clínicas sugestivas de asma em filhos de mães com diagnóstico médico referido de asma.
Métodos: Estudo observacional transversal analítico aninhado a uma coorte de 4.757 parturientes. Foram avaliadas 86 crianças aos seis anos de idade, filhas de mães com diagnóstico médico de asma antes da gestação. Foram coletadas informações referentes a sintomatologias clínicas de atopias e doenças respiratórias, variáveis socioeconômicas e de exposição; tendo sido as crianças submetidas à espirometria.
Resultados: Foram encontrados 30,3% de alterações espirométricas, havendo predomínio do diagnóstico de asma nos que apresentaram padrão obstrutivo. Diagnóstico médico pregresso de asma ocorreu em 9,3% das crianças; contudo, o diagnóstico estabelecido a partir da presença e frequência dos sintomas de asma representou 18,6%. Das 86 crianças participantes, 37,2% tiveram um escore de cinco ou mais pontos no questionário ISAAC, estando isso associado à alteração do padrão espirométrico (p = 0,002). Após a regressão logística múltipla, maior escolaridade paterna, maior número de quartos no domicílio e o fato de a mãe não ter apresentado "chiado" durante a gestação foram estatisticamente significantes como fatores protetores para a presença de distúrbio ventilatório à espirometria.
Conclusões: A frequência de alterações do teste espirométrico em filhos de mães asmáticas foi alta, com o padrão restritivo ocorrendo mais vezes que o obstrutivo. Houve uma maior ocorrência de exames obstrutivos naqueles que apresentavam sintomatologia clínica de asma, com uma frequência de diagnóstico clínico de asma superior à encontrada na literatura.
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Introduction

Asthma is considered the third leading cause of hospitalization among children and young adults in Brazil. There is evidence that its prevalence and mortality are increasing worldwide.[1,2]

Over the last 30 years, the world's population has experienced an era of technological evolution, which resulted in profound changes in lifestyle and eating habits. Concomitantly, there has been improvement in sanitary conditions and reduction of infectious diseases. Nevertheless, asthma continues to have a high impact on the morbidity and mortality of several age groups and all segments of society.[3,4]

Spirometry has an important role in the respiratory evaluation of children older than 6 years, as well as that of adults, due to its simplicity and low cost, combined with good reproducibility. Spirometry is also extensively used in research; it is the most common laboratory outcome in respiratory disease studies.[5]

The existence of family history of asthma is widely accepted by many authors as a risk factor for the onset of respiratory symptoms in children, as demonstrated in the study by Gray et al.[6] Nevertheless, as stated by Gaspar et al., studies are needed in order to identify the influence of family history on the severity and clinical course of bronchial asthma in children, as well as factors associated with symptom severity and persistence, in order to define strategies aimed at minimizing risks and reducing the growing morbidity of this disease.[7] Priority should be given to studies that more objectively associate prior family diagnosis, presence of symptoms,

and exposure variables with alterations in ventilatory function tests. Accordingly, the present study aimed to analyze such associations.

Patients and method

This was an observational cross-sectional analytical study nested in a cohort. In the original cohort, a questionnaire was applied to 4,757 women after an informed consent was obtained. This survey identified 135 pregnant women who reported medical diagnosis of asthma before pregnancy. The diagnosis method and specific therapeutic approach were not investigated. Patients included in the study were the children participating in the aforementioned cohort who were born to mothers with asthma, after the parents or legal guardians agreed to participate in the study and signed an informed consent.

A total of 86 children from the group of 135 mothers with a previous diagnosis of asthma were identified and evaluated. This number is consistent with that provided by the sample size calculation, which estimated a minimum number of 82. The assumptions adopted for this calculation were: frequency of obstructive respiratory pattern for the study group of 15% (ranging from 7% to 23%), a level of significance of 0.05, and test power of 0.80. The statistical test used was a two-tailed binomial proportion test; a sample loss of 10% was considered. This was a non-randomized sample and the children were selected consecutively. There were no losses due to exclusion criteria.

Age was considered in full months, as all subjects included in the study were born within the four-month interval of the initial data collection from the original cohort. Regarding the parents, age, years of education, type of occupation (skilled or not, as defined by the Brazilian Institute of Geography and Statistics [Instituto Brasileiro de Geografia e Estatística – IBGE]), and family income (stratified by up to or greater than three minimum wages) were analyzed.

Home location, presence of internal wall lining, type of street pavement, number of residents, number of rooms, number of rooms used as bedrooms, and number of individuals who slept in the same room as the child were the variables related to the family home.

The maternal-child history consisted of the number of maternal pregnancies, child's position among siblings, type of delivery, birth weight, birth length, appropriateness of birth weight, APGAR, smoking during pregnancy, reports of "wheezing" episodes by the mother during pregnancy, other atopic diseases of the mother and child, consumption of milk during pregnancy and lactation, and consumption of non-breast milk during the first four months of the child's life.

The anthropometric evaluation included the calculation of body mass index (BMI), using the z-score. Clinical severity criteria were used for the clinical assessment (Global Initiative for Asthma – GINA, 2002), which include evaluating the presence of symptoms and their frequency, in addition to the measurement of peak expiratory flow (PEF).[8] The asthma module of the International Study of Asthma and Allergies in Childhood (ISAAC, 1998)[9] questionnaire, which consists of eight questions, and environmental exposure assessment through the Environmental Assessment Guide for the Allergic Individual (CORA-USP)[10] were also employed; an *in loco* assessment was performed to identify the presence of "inadequate" accessories in the room where the child was sleeping and other rooms. Finally, lung function was evaluated by basal spirometry in all participating children.

The comparison of quantitative variables was performed using Student's *t*-test or Mann-Whitney's test, while the association of categorical variables was assessed using the chi-squared test or Fisher's exact test, when appropriate. Analysis of variance (ANOVA) was used for comparison of quantitative variables among the groups with normal, restrictive, and obstructive spirometry patterns with Tukey's post-test or the Kruskal-Wallis test, as appropriate. The assumptions of normality were assessed using the Kolmogorov-Smirnov test. The level of significance was set at 0.05, and two-tailed hypothesis testing was used.

Logistic regression (univariate and multivariate) was used to estimate the odds ratios related to the outcome event (ventilatory disorder at the spirometry), considering as independent variables: gender, birth weight, maternal level of education, paternal level of education, number of rooms in the house, number of bedrooms in the house, maternal pregnancies, family income, history of "wheezing" episodes during pregnancy, and presence of internal wall lining.

The study was approved by the Ethics Committee for Research in Humans of the Universidade Federal de Sergipe (UFS-CEP), with Certificate of Presentation to Ethical Consideration (CAAE) No. 0104.0.107.000-11. The parents of all children included in the study signed an informed consent authorizing their participation in the study.

Results

The distribution by gender showed 55.8% males and 44.2% females, comprising a sample of 86 children with a mean age of 79.8±1.1 months. Maternal education was reported as an average of 9 years of completed education, while paternal education was 8.6 years, on average. A total of 14% of the mothers and 26.7% of the fathers declared they had a skilled profession. Family income was reported as up to three minimum wages by 76.7% of respondents. It was observed that maternal and paternal education was significantly lower in children with the obstructive pattern. Family income was found to be markedly lower in the group with the obstructive pattern.

Of the households visited, 81.4% were located on streets with cobblestone or asphalt pavement. The predominant material of the housing structure was coated masonry (90.7%). The mean number of people in the household was five, with a mean of six rooms; the mean number of people (in addition to the child) who slept in the same room as the child was two, the mean number of rooms used as bedrooms was also two. The number of rooms of the home was also significantly lower in families of children with obstructive spirometric pattern. There was a predominance of households with no wall lining in the obstructive group.

Of the mothers included in the study, 90.7% reported not

smoking during the pregnancy of the child participating in the study, with no statistical significance in the association between maternal smoking and the child's spirometric pattern. During the systematic questioning, 69.8% of the mothers reported at least one episode of "wheezing" during the child's pregnancy. Of the participating mothers, 62.8% reported having at least one other type of atopy (allergic rhinitis; contact eczema; food allergy). Regarding the number of maternal pregnancies, there was a significant association between a smaller number of pregnancies and children with normal spirometry. The birth weight was significantly higher in those with restrictive pattern. The report of "wheezing" during pregnancy showed a clear association with the ventilatory pattern (children with a restrictive pattern were associated with a lower frequency of the event in comparison to those with normal or obstructive patterns).

The mean BMI was 14.3±2.7. 14.0% (n = 12) of the children were classified as underweight; 69.7% (n = 60), as normal weight; 9.3% (n = 8), as overweight; and 7.0% (n = 6), as obese. No association was observed with the spirometry pattern.

Clinical evaluation

When questioned about the existence of a medical diagnosis of asthma for their child, 9.3% of mothers answered affirmatively. Furthermore, when answering questions regarding the child's symptoms, there was a percentage of 18.6% indicating asthma.

The ISAAC questionnaire (eight questions) showed 2.4 mean positive answers (ranging from zero to eight). Of the 86 children participating in the study, 32 (37.2%) had a global score of positive answers at the ISAAC questionnaire of five or more.

When associating, through the receiver operating characteristic (ROC) curve, the clinical diagnosis of asthma (established at the survey during the home visit) with an ISAAC positive score equal to or greater than five, there was an area under the curve of 0.918±0.036 (95%CI: 0.847 to 0.988, p < 0.0001), which demonstrates a clear association between positive responses to the ISAAC questionnaire and a medical diagnosis of asthma in this sample (Fig. 1).

Environmental assessment

The CORA-USP[10] was used to evaluate the environment. Of the possible 25 points for the bedroom analysis, the mean was 7.6, whereas the score observed for the other rooms had a mean of 10.7. As defined by the guide, a score for the bedroom and/or total score for the other rooms above 15 is considered a risky environment for asthmatic individuals. No association was demonstrated between the home environment assessment and spirometry pattern.

Lung function assessment by spirometry

Regarding the ventilatory pattern, the distribution showed a predominance of normal, followed by restrictive pattern,

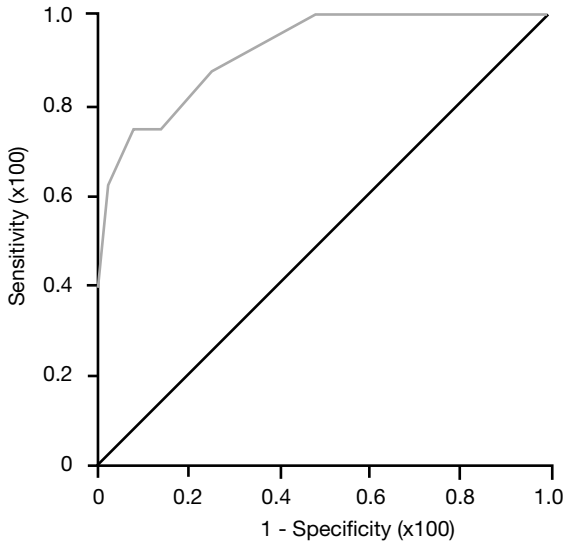

Figure 1 ROC curve of the ISAAC score to identify patients with asthma. Area under the ROC curve: 0.918±0.036. 95% CI: 0.847-0.988. ROC, receiver operating characteristic.

Table 1 Frequency of children according to the ventilatory pattern observed in basal spirometry.

	Frequency	Percentage	95% CI
Normal	60	69.7	60.5-79.1
Restrictive	14	16.3	9.3-23.3
Obstructive	12	14.0	7.0-22.1

95% CI, 95% confidence interval.
Classification according to the reference values by Polgar and Promadhat, modified by Pereira, 1992. Confidence interval obtained through simulation with 1,000 samples.

as shown in Table 1. Ten children with the obstructive pattern were characterized as mild intensity, as well as 11 with the restrictive pattern; there were no severe cases.

Univariate and multivariate analysis

The participants were grouped as normal (n = 70) or abnormal respiratory pattern (n= 26); the latter group comprised both obstructive and restrictive patterns. When associating the presence of spirometric alteration with the several variables (categorical or not) for which statistical significance had been observed, and after performing the univariate analysis, the data shown in Table 2 were obtained.

For the multivariate analysis, the multiple logistic regression technique was used, considering the outcome variable as the presence of spirometric alterations and the following as independent variables: gender of child, maternal and paternal level of education, number of rooms and bedrooms in the house, number of maternal pregnancies, family income, and report of "wheezing" episodes during pregnancy.

Table 2 Representation of non-adjusted odds ratio (of presenting spirometric alterations) of representative variables.

Variables	Odds ratio	95% CI	p
Male child	3.81	1.34-10.8	0.010
Birth weight	1.001	1.000-1.002	0.030
Mother's years of education	0.782	0.675-0.906	0.001
Father's years of education	0.681	0.560-0.827	< 0.001
Number of rooms in the house	0.688	0.493-0.961	0.030
Number of bedrooms in the house	0.281	0.130-0.604	0.001
Maternal pregnancies	1.38	1.06-1.80	0.020
Lower family income	5.14	1.10-24.1	0.040
No "wheezing" during pregnancy	2.82	1.06-7.47	0.040
Unlined walls	8.70	1.62-46.6	0.012

95% CI, 95% confidence interval.
Univariate logistic regression.

Table 3 Demonstration of the adjusted odds ratio (of presenting spirometric alterations) of representative variables.

Variables	Odds ratio	95% CI	p
Father's years of education	0.605	0.458-0.800	0.0004
Number of bedrooms in the house	0.174	0.0480-0.628	0.008
No "wheezing" during pregnancy	5.99	1.21-29.6	0.03

95% CI, 95% confidence interval.
Multiple logistic regression using the "forward stepwise" and "backward stepwise" methods after six interactions.

At the end of the multiple logistic regression analysis, it was observed that the variables paternal education, number of bedrooms in the house, and absence of "wheezing" during pregnancy were independently associated with the presence of spirometric pattern alteration (Table 3).

Discussion

There was a 30.3% frequency of abnormal respiratory pattern in this sample, with a slight predominance of the restrictive pattern. Veras and Pinto found 21.6% of obstructive pattern in a descriptive study conducted with preschool children, in whom the main indication for the examination had been a diagnosis of asthma (95.6%).[10] In the present study, the basal obstructive spirometric pattern was present in 14.0% (95% CI: 7.0% to 22.1%), which is a considerable percentage, considering that the study population did not necessarily have obstructive disease symptoms. The restrictive pattern was present in 16.3% (95% CI: 9.3% to 23.3%) of the study sample.

Constant et al.,[11] in a study that screened children aged 5 to 13 years from four schools in Lisbon for lung disease, found only 4% of a previous diagnosis of asthma, although there were reports of at least one episode of wheezing in about 35% of the same population. The present study showed that 18.6% of the children had the criteria for asthma diagnosis, while only half (9.3%) had received this diagnosis from a physician. Of the children included in the present study, 46.4% had at least one episode of wheezing reported by their caregivers. Both studies show the possibility of underdiagnosis in the studied populations.

Of the 12 children with the obstructive pattern, eight (66.7%) had clinical criteria for the diagnosis of asthma. The respective percentages for the restrictive and the normal group were 0% and 13.3%. This is consistent with the classical concept of spirometry as the gold standard in the complementary diagnosis of asthma, although normal results during the periods between crises do not rule out this diagnosis.[12]

Although ISAAC is a study population and thus does not constitute diagnostic criteria for asthma, the ROC curve for the population showed there was considerable agreement between the clinical diagnosis of asthma established during the interview and an ISAAC score ≥ 5 in the same population.

The home environment was very important. The number of bedrooms, the number of rooms in the house, and presence of internal wall lining were the most relevant factors observed; especially the number of bedrooms. All this clearly shows that environmental hygiene is a protective factor, which has been demonstrated in other studies, such as that by Han et al., who demonstrated several allergens as risk factors for the development of asthma in children.[13] In the last two decades, it has been demonstrated that mites are the main risk factors for the development of asthma, as seen in the work by Celedon et al.,[14] which showed that early exposure to high concentrations of house dust was associated with an increased risk of asthma at age 7 (OR = 3.0).

Regarding the level of education, a significantly higher number of completed years of study was observed in mothers

and fathers of children that showed normal spirometric pattern, when compared to those that had the obstructive pattern. These findings emphasize the importance of the educational level for disease control, especially when there is a known multifactorial environmental component. Räsänen et al.[15] concluded that low levels of education and poor socioeconomic status of the parents are risk factors associated with asthma.

Family income had an impact on the child's ventilatory function; 100% of children with obstructive pattern came from families whose monthly income was reported as lower than three minimum wages. Jentzsch et al.,[16] in a study on adherence to environmental control measures in asthmatic children, assessed a population with an average monthly income of 2.5 minimum wages and observed low rates of adherence to these measures.

The fact that the mother had "wheezing" episodes during pregnancy of the child involved in the study was higher in the group of patients with obstructive pattern when compared to restrictive. However, the frequency of this report was even greater in the group whose spirometry pattern was normal. This can be justified by some considerations. The first one concerns the mother's subjectivity when reporting the "wheezing" episode. Moreover, it must be considered that intrauterine sensitization via passage of IgE through the umbilical cord from mother to child, although recognized, has not been well-established to date with regard to timing, so that the gestational age at which the atopic manifestation occurred in the pregnant woman can indeed be a determining factor. There is evidence that this sensitization can occur more significantly after the sixth month of pregnancy, a period during which there would be a greater shift in Th-2 response.[17]

Birth weight was significantly higher in children with spirometric alterations; the mean in the restrictive group was higher than in the obstructive group. Chatkin et al.[18] evaluated lung function in a cohort from Southern Brazil aged 6 to 7 years, and showed no increased frequency of spirometric alterations related to birth weight.

The major limitation of the present study is the subjectivity of the information provided by the child's caregiver, which is inherent to all clinical research involving household surveys. Moreover, the high rate of restrictive pattern may be associated with difficulty in performing the spirometric test in the age range studied.

Endorsing the idea of asthma as a multifactorial disease, in which genetic and environmental factors intertwine as in perhaps no other human disease, it was observed a diversity of variables known to be involved with a clinical entity for which potential morbimortality should always be considered. A broader concept of health should be sought when considering the human-environment interaction and, thus, governmental actions must be taken aiming at asthma control, without overlooking any of the disease aspects.

Conflicts of interest

The authors have no conflicts of interest to declare.

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