# Chapter 62

## Maternal exposure to pesticides and malformation by cleft cleft in a specialized service of the SUS: a population-based case-control study

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**ABSTRACT**
Introduction: Studies associate human exposure to pesticides with congenital malformations, including cleft lip and palate. Objectives: to estimate the association between maternal exposure to pesticides and cleft lip and palatein children aged 0 to 5 years living in the state capital of agribusiness from January to November 2019. Method: a control case study performed with the fathers of children with cleft lip and palate (cases) and fathers without children with malformations (controls). Information was obtained regarding the diagnosis of malformation from the records of the Rehabilitation Service of Labiopalatine Fissures of the General Hospital of Cuiabá. Socioeconomic information on environmental and occupational exposure was obtained through the application of a standardized questionnaire. The cases and controls were matched by age and gender. The 95% confidence interval was considered, estimated exposure frequency of the controls of 40%, a ratio of 1:4 controls and significant Odds Ratio of 2.4. The final sample resulted in 58 mothers of children with cleft lip and palate (case group) and 232 mothers of children without malformations (control group). Results: The variables associated with cleft lip and palate were: prematurity (OR= 6.05; CI95% = 1.24 - 29.53), mother's occupation when she became pregnant (OR= 1.90; CI95% = 1.02 - 3.52), previous home of the mother in rural areas (OR= 2.08; CI95% = 1.01 - 4.27). Conclusion: mothers who reported premature delivery, occupation not being from the home when pregnant and living in a rural area before becoming pregnant were conditions associated with the occurrence of cleft lip and palate in children up to 5 years of age in Greater Cuiabá.

**Keywords:** pesticides, cleft lip, cleft palate.

### 1 INTRODUCTION

Pesticides were introduced to Brazil in the 1960s, whose purpose was the modernization of agriculture(1). In recent decades, this country is one of the most used agrochemicals, reaching between 2001 and 2008 the position of the world's largest consumer of pesticides. In 2009, Brazil reached the mark of 5.2 kg of these agrochemicals per inhabitant(2), having, in 2010, used 828 million liters of the product formulated in the crops(3, 4).

According to the National Health Surveillance Agency (ANVISA), half of the most used pesticides in our country are banned in the European Union(1). In addition to the pesticides applied in Brazil being the most toxic, they also affect workers and residents in the surroundings of plantations(3, 4).

In this context, the state of Mato Grosso, which is located in the Midwest region of Brazil, is the largest pesticide consumer in the country(5). In addition, it is the largest producer of soybeans, corn, cotton and cattle in Brazil. In 2015 alone, the state consumed about 207 million liters of pesticides for the13.9 million hectare plan(6).

At this juncture , there is great concern about the use of pesticides in Brazil and worldwide,where they reveal positive associations between pesticides and the occurrence of various diseases and diseases, especially in populations proximally exposed to these poisons(5,7-8) .

Pesticides have different classifications and mechanisms of action, however, they cause numerous occurrences of human intoxication and other animal species. Among the population groups most vulnerable to these effects are children, women of reproductive age, pregnant and lactating women, as well as agricultural workers and the elderly(9-11).

Among the causes related to the environment, studies indicate an association between pregnant women or women of reproductive age in contact with pesticides with the risk of congenital malformations(10,12-13). Corroborating this, research conducted in the state of Mato Grosso demonstrated the increased occurrence of congenital anomalies in children of mothers living in regions of great use of pesticides(6).

These anomalies are morphological, structural or functional alterations that can be detected in intrauterine life or after the birth of children, including cardiac and neurological defects, chromosomal abnormalities and cleft lip and palate, among others(14). In developed countries, congenital malformations constitute approximately 20% of the main causes of neonatal deaths. In Brazil, the World Health Organization (WHO) estimated these deaths in about 7% of all newborns who diedin the first month of life(15).

Several pesticides used in Mato Grosso are reported in the literature as associated with the occurrence of malformations and cleft palate(16). Among the most cited, organochlorinated(17), whose use has been prohibited in Brazil since the end of the 1970s, but with intense bioaccumulation property in the food chain and in humans(16). Another pesticide is the herbicide glyphosate, of the organophosphate class, the most used in transgenic soybean in this region(18).

The most common craniofacial congenital malformations in live newborns are cleft lip and/or palate and have shown an increasing trend in rates both in Brazil and in other countries(19,20). Its etiology is unclear, however genetic and environmental factors, including pesticides, provide important clues for the explanation of the pathophysiological mechanisms of the disease(21).

Considering the importance of the theme for society, the magnitude of the use of large-scale pesticides in this region, the large direct or indirect exposure of this population to pesticides and a large number of occurrences of births with congenital anomalies in the region, the aim of this study was to evaluate the association between the use of pesticides and the occurrence of cleft lip and palate in a region of intense agribusiness activity in the State of Mato Grosso.

## 2 MATERIAL AND METHODS

A case-control study of hospital base was conducted in the greater Cuiabá, which consisted of the cities of Cuiabá and Várzea Grande, from January to November 2019. The study population consisted of mothers of children from 0 to 5 years of age. The research was carried out at the Craniofacial Anomalies Rehabilitation Service of the General Hospital of Cuiabá - Mato Grosso. This choice was made since the institution has a specialized service in the care of people with cleft lip and palate. The hospital meets the referenced demand of the Unified Health System - SUS of Cuiabá and all municipalities in the State of Mato Grosso. For the control group, we opted for the pediatric outpatient clinic of the University of Cuiabá - UNIC, which serve the children of Greater Cuiabá.

For the group of cases, mothers over 18 years of age were selected, who had children with cleft lip and palate and/or palatines - diagnosed by a physician through clinical and/or imaging tests and, classified in chapter XVII by ICD-10 - in the age group from 0 to 5 years in care at the Rehabilitation Service of Labiopalatine Fissures of the General Hospital of Cuiabá-MT. All mothers older than 18 years of age, with live births aged 0 to 5 years in treatment at the Rehabilitation Service of Labiopalatine Fissures of the General Hospital of Cuiabá-MT, were included. Mothers whose children had associated other malformations, twin, mothers of children belonging to the yellow and indigenous ethnicgroups, coming from other states, mothers under 18 years of age and mothers who did not provide information for any variable were excluded.

The parents, older than 18 years old, were selected from the pediatric outpatient clinic of the University of Cuiabá - UNIC, considering that their children were devoid of congenital malformations, metabolic syndromes and cancer diagnoses. Mothers over 18 years of age were included, in which their child was in pediatric outpatient clinic of the University of Cuiabá - UNIC during the period of data collection of the research. Mothers from other cities other than those born in Cuiabá or Várzea Grande (Greater Cuiabá), mothers under 18 years of age and mothers who did not provide information for any variable were excluded. The interviews of the controls were conducted after selection and use of pairing criteria, randomized through simple systematic sampling. Both for cases and for controls, mothers must reside in Cuiabá and Várzea Grande throughout the gestational period.

The cases and controls were matched by age and gender. The 95% confidence interval was considered, estimated exposure frequency of the controls of 40%, a ratio of 1:4 controls and significant

Odds Ratio of 2.4. The initial sample resulted in 58 mothers of children with cleft lip and palate (case group) and 232 mothers of children without malformations (control group).

The information was obtained through the application of a structured questionnaire adapted according to the methodology of the Latin American Collaborative Study of Congenital Malformations(22), a collaborating body of the World Health Organization (WHO) for the prevention of birth defects, plus questions related to maternal and paternal exposure to pesticides, heavy metals, ores, dust and smoke. Sociodemographic, socioeconomic, socio-environmental and morbidity information reported to the genitors was included in the questionnaire.

The interviews of the case group were conducted in the clinic of cleft lip and palate and, those of the control group, in the pediatric outpatient clinic of the University of Cuiabá - UNIC, all by students of scientific initiation of the same university duly trained, on the days of normal elective care of the participating mothers.

All mothers agreed to participate voluntarily in the study after explaining the objectives and signed the Free and Informed Consent Form (TCLE). The project was approved by the Research Ethics Committee of the University of Cuiabá- CEP/UNIC under the caae no.: 02403318.3.0000.5165.

Regarding maternal exposure, the period evaluated covered the mother's previous history before pregnancy and the first three gestational months, periods referred to as having a higher maternal risk associated with the occurrence of congenital malformation(23). In the evaluation of paternal exposure, the period considered as at risk was twelve months before the probable date of fertilization of the fetus(24).

For statistical analysis, the data were first categorized and descriptive exploratory analysis was performed using tables and frequency measurements. Subsequently, bivariate, stratified and logistic regression analyses were performed. In the stratified bivariate analyses, the crude associations between exposure and effect (cleft lip and palate) were identified using the chi-square method.

Finally, logistic regression was performed considering all variables when crude and stratified analyses presented p-value lower than 0.25, keeping in the final model the variables with significance level less than or equal to 0.05 or those considered of importance, a priori, according to the literature as adjustment variables. The analysis of the results was performed in the Epi-Info® 7.2 program, the final data were analyzed by the SPSS® version 18.0 program.

## 3 FINDINGS

We included 288 mothers of patients, of which 56 mothers of children with cleft lip and palate (case group) and 232 mothers of children without malformations (control group). Table 1 shows a higher proportion of black/brown children with cleft lip and palate. In relation to the cases, the left unilateral complete transforame fissures presented the highest frequency of occurrence with 25% among the cases, followed by incomplete post forame fissures, which had an occurrence of 20.83%.

Table 1. Distribution of socio-demographic characteristics of children from the cases and controls groups. Cuiabá, January/2019 to November/2019

| Variable | Cases | | Controls | |
|---|---|---|---|---|
| **Sex** | N | % | N | % |
| Male | 32 | 57 | 132 | 57 |
| Female | 24 | 43 | 100 | 43 |
| **Race/color** | | | | |
| White | 22 | 39,29 | 77 | 33,19 |
| Black/Brown | 34 | 60,71 | 155 | 66,81 |
| **Prematurity** | | | | |
| Yes | 4 | 7,14 | 3 | 1,29 |
| No | 52 | 92,86 | 229 | 98,71 |
| **Type of delivery** | | | | |
| Normal | 25 | 44,64 | 110 | 47,41 |
| Caesarean | 31 | 55,36 | 122 | 52,59 |
| **Fissure Type** | | | - | - |
| Complete forame post fissure | 4 | 8,33 | - | - |
| Incomplete forame post fissure | 10 | 20,83 | - | - |
| Left unilateral incomplete pre forame fissure | 1 | 2,08 | - | - |
| Bilateral complete pre forame fissure | 1 | 2,08 | - | - |
| Right unilateral complete forame pre fissure | 3 | 6,25 | - | - |
| Left unilateral complete pre forame fissure | 5 | 10,42 | - | - |
| Bilateral complete transforame fissure | 4 | 8,33 | - | - |
| Right unilateral complete transforame fissure | 7 | 14,58 | - | - |
| Left unilateral complete transforame fissure | 12 | 25 | - | - |
| Rare fissure of the face | 1 | 2,08 | - | - |

Regarding sociodemographic variables, considering that gender and age were used as pairing variables, only premature birth was associated with the occurrence of cleft lip and palate (OR = 5.2, 95% CI = 1.16 - 32.03). The variables marital status and level of education and race/skin color did not present statistically significant associations with the outcome variable (Table 2).

Table 2. Odds ratio and 95% confidence interval (CI) of maternal and child socio-demographic variables. Cuiabá, January/2019 to November/2019

| Variable | Case | | Control | | *OR* | . IC | | *p value* |
|---|---|---|---|---|---|---|---|---|
| **Sex** | n | % | n | % | | | | |
| **Male** | 32 | 57,00 | 132 | 57,00 | 1,00 | - | | - |
| **Female** | 24 | 43,00 | 100 | 43,00 | 1,00 | | | |
| **Age group** | | | | | | | | |
| **< 1 year** | 10 | 18,00 | 41 | 18,00 | 1,00 | - | | - |
| 1 to 5 years | 46 | 82,00 | 191 | 82,00 | 1,00 | | | |
| **Prematurity** | | | | | | | | |
| Yes | 4 | 7,14 | 3 | 1,29 | 5,82 | 1,16 | 32,03 | 0,028 |
| No | 52 | 92,86 | 229 | 98,71 | | | | |
| **Marital status** | | | | | | | | |
| Married/amasiada | 49 | 87,50 | 195 | 84,05 | 0,75 | 0,29 | 1,73 | 0,520 |
| Single/others | 7 | 12,50 | 37 | 15,95 | | | | |
| **Education level** | | | | | | | | |
| Fund, fund. incomplete to med. Complete | 42 | 75,00 | 172 | 74,14 | 1,04 | 0,53 | 2,10 | 0,894 |
| Incomplete superior and more | 14 | 25,00 | 60 | 25,86 | | | | |
| **Race/Mother Color** | | | | | | | | |
| White | 17 | 30,36 | 50 | 21,55 | 1,58 | 0,81 | 3,02 | 0,162 |
| Other | 39 | 69,64 | 182 | 78,45 | | | | |

Regarding the variables on gestational data and maternal lifestyle, no statistically significant associations of fissures and medication consumption (medicine) and reference to some disease in the first trimester of pregnancy were found, as well as exposure to smoking (Table 3).

Table 3. Odds ratio and confidence interval (95% CI) of gestational data and maternal lifestyle. Cuiabá, January/2019 to November/2019

| Variable | Case | | Control | | *OR* | *IC* | | *p value* |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | | | | |
| **Drug use (remedy) 1st trimester gestation** | | | | | | | | |
| Yes | 13 | 23,21 | 73 | 31,47 | 0,65 | 0,32 | 1,28 | 0,226 |
| No | 43 | 76,79 | 159 | 68,53 | | | | |
| **Disease 1st trimester gestation** | | | | | | | | |
| Yes | 10 | 17,86 | 65 | 28,02 | 0,55 | 0,25 | 1,15 | 0,120 |
| No | 46 | 82,14 | 167 | 71,98 | | | | |
| **Smoking near pregnant women** | | | | | | | | |
| Yes | 12 | 21,43 | 35 | 15,09 | 1,53 | 0,71 | 3,15 | 0,249 |
| No | 44 | 78,57 | 197 | | | | | |

Regarding the environmental and occupational exposure of parents, pregnant women who reported having an occupation other than that of the home were associated with a higher occurrence of those born with cleft palates (OR = 1.85, 95% CI = 1.02 - 3.33). The variables use of poison in the mother workplace, existence of an industry near the mother's workplace in the 1st trimester of pregnancy, use of poison in the father's work, industry close to paternal work and father having worked in rural areas in the past did not present statistically significant results in relation to the occurrence of the disease (Table 4).

Table 4. Odds ratio and confidence interval (95% CI) of mother environmental exposure 1st trimester gestational; mother occupational exposure 1st trimester gestational; previous data from the father. Cuiabá, January/2019 to November/2019

| Variable | Case | | Control | | *OR* | *IC* | | *p value* |
|---|---|---|---|---|---|---|---|---|
| **Mother occupation when she became pregnant** | N | % | | % | | | | |
| Other | 29 | 1,79 | | 5,38 | | 1,02 | ,33 | 2 |
| From home | 27 | 8,21 | | 3,62 | | | | |
| **Use of poison in the mother workplace** | | | | | | | | |
| Yes | 3 | ¡,36 | | 1,64 | | 0,10 | ,34 | 4 |
| | 53 | 4,64 | | 8,36 | | | | |
| **Industry next mother work 1st gestational quarter** | | | | | | | | |
| Yes | 4 | 7,14 | 7 | 3,02 | 2,46 | 0,61 | 8,82 | 0,233 |
| No | 52 | 92,86 | 225 | 96,98 | | | | |
| **Mother lived in the countryside before becoming pregnant** | | | | | | | | |
| Yes | 16 | 28,57 | 43 | 18,53 | 1,75 | 0,88 | 3,40 | 0,095 |
| No | 40 | 71,43 | 189 | 81,47 | | | | |
| **Use of poison in father's work** | | | | | | | | |
| Yes | 8 | 14,29 | 21 | 9,05 | 1,67 | 0,66 | 3,94 | 0,243 |
| No | 48 | 85,71 | 211 | 90,95 | | | | |
| **Industry next parent work** | | | | | | | | |
| Yes | 7 | 12,50 | 16 | 6,90 | 1,92 | 0,70 | 4,86 | 0,165 |
| No | 49 | 87,50 | 216 | 93,10 | | | | |
| **Workplace for father** | | | | | | | | |
| Urban | 54 | 96,43 | 210 | 90,52 | 2,82 | 0,74 | 18,27 | 0,185 |
| Rural | 2 | 3,57 | 22 | 9,48 | | | | |

In the final model, after logistic regression (Table 5), the variables associated with cleft lip and palate were: birth of premature children (OR= 6.05; CI95% = 1.24 - 29.53), mother's occupation not being from the home when in the 1st trimester of pregnancy (OR= 1.90; IC95% = 1.02 - 3.52). The fact of the mother's previous home in rural areas was also associated with the occurrence of children born with cleft palates (OR= 2.08; CI95% = 1.01 - 4.27), although this variable did not present a statistically significant association in the bivariate analysis.

Table 5. Crude and adjusted analysis (Logistic regression) - Odds Ratios and 95% CI of variables associated with cleft lip and palate, according to cases and controls, Cuiabá-MT- 2020

| Variables | OR Gross | IC | | *p value* | OR adjusted | IC | p value |
|---|---|---|---|---|---|---|---|
| **Prematurity** | | | | | | | |
| Yes | 5,83 | 1,16 | 32,03 | 0,028 | 6,05 | 1,24- 29,53 | 0,026 |
| No | 1,00 | | | | 1,0 | | |
| **Race/Mother Color** | | | | | | | |
| White | 1,58 | 0,33 | 0,81 | 3,02 | - | - | - |
| Other | 1,00 | | | | | | |
| **Disease 1st trimester gestation** | | | | | | | |
| Yes | 0,55 | 0,25 | 1,15 | 0,25 | - | - | - |
| No | 1,00 | | | | | | |
| **Mother occupation when she got pregnant** | | | | | | | |
| Other | 1,85 | 1,02 | 3,33 | 0,042 | 1,90 | 1,02 – 3,52 | 0,041 |
| From home | 1,00 | | | | 1,0 | | |
| **Previous House in the Rural Zone** | | | | | | | |
| Yes | 1,75 | 0,28 | 0,88 | 3,40 | 2,08 | 1,01 – 4,35 | 0,046 |
| No | 1,00 | | | | 1,00 | | |
| **Near by industry father work** | | | | | | | |
| Yes | 1,92 | 0,70 | 4,86 | 0,165 | - | - | - |
| No | 1,00 | | | | | | |
| **Workplace for father** | | | | | | | |
| Urban | 2,82 | 0,74 | 18,27 | 0,185 | - | - | - |
| Rural | 1,00 | | | | | | |

## 4 DISCUSSION

The most frequent occurrences of labial malformations among the cases attended in the reference service were the left unilateral complete transforame fissures, followed by incomplete post forame fissures. Cleft lip and palate were associated with cleft lip and palate, premature lyborn children, occupation of the mother not being from the home in the 1st trimester of pregnancy and previous housing of the mother in rural areas in the first trimester of pregnancy.

In line with the above, data from a research conducted throughout Brazil from 2009 to 2013, cleft palate was the most frequent type of fissure in all geographic regionsduring the study period(25).

Our study found that mothers who lived in the rural area before had a higher chance of birth of children with cleft lip and palate malformation. This association is important because it corroborates with some previous studies, such as two case-control studies that evaluated exposure sexhibits to pesticides in rural pregnant women in the periconceptional period in a region with one of the highest pesticide uses in

California, United States(12,26). The two studies found a higher occurrence of cleft lip and palate in children of women who lived, during the periconceptional period, in regions close to places where pesticide applications were available. Still in agreement with these results, a study conducted in the same region of the previous study found that exposure to agricultural pesticides increased between 5 and 9% the occurrence of gestational adverse outcomes, including malformation by cleft palates (13).

Also in the final model, our study showed an association with statistical significance between the occurrence of these malformations in mothers who, when they became pregnant, worked outside the home. Possibly, these women were exposed to higher gradients of occupational and environmental pollutants than women who stay at home. Considering that the great Cuiabá is the agribusiness capital of the state, possibly pregnant women who worked in extra-home activities, in addition to exposure to several other environmental risks, they also had a higher chance of exposure of coexistence in environments with greater pesticide dealing, therefore, with the possibility of higher gradients of exposure to these contaminants(27) . It is important to highlight that the state of Mato Grosso, regardless of the direct exposure of workers, is also the state with the highest environmental exposure of its population to pesticides, corresponding to 14 times more than the Brazilian average 28. It is not excluded the possibility that, during pregnancy, the exposure of pregnant women to chemical agents from other work activities such as work in industries andmineral exploration can also lead to increased malformations and other pregnancy outcomes (29).

Premature birth was a variable associated with the occurrence of cleft palate slits in the present study. It is known that weight reduced at birth is a risk factor for numerous effects adversos to the health of the newborn(30). It is important to highlight that a study that analyzed data from live births from the Live Birth Information System in the years 2005 to 2016 found that premature babies were, on average, twice as likely to be born with cleft lip and/or cleft palate(20). Still inthe same sense, a study conducted by Heeren et al (2003)(31) in a region of intense pesticide use in Africa also encountersor this same association. In fact, evaluating the biological plausibility of the object studied, the placenta is a temporary organ that presents a natural barrier between the mother and fetus throughout pregnancy. Although it has long been considered to be an impenetrable barrier by xenobiotics, it has been shown that several environmental pollutants can cross the placenta(32). Premature birth is considered to be one of the indirect causes of various pregnancy outcomes, including cleft lip. However, little is discussed about a possible reversal of causality or confusion between these two variables, since it is not clear the temporality between cause and effect, or even whether both are effects of a concomitant cause, possibly biological, for the occurrence of these outcomes at birth.

It is important to mention that some variables that did not present statistical association with the occurrence of fissures are reported in the literature, such as maternal sociodemographic variables (marital status, schooling, race/color, etc.)(19), life habits in the gestational period (medication use, smoking habit,

concomitant diseases during pregnancy, etc.)(33)(33), could be important, specifically in the adjustment of multiple analysis.

Some evides are passive to have occurred in the present study. Memory bias is a possible limitation inherent to case-control studies, especially in the case of differential errors, when the case group is more likely to recall about environmental and/or occupational exposure to teratogens(34), compared to the control control group. It is also not excluded the occurrence of observer bias because it was impossible to blind the interviewers. However, in their training, the importance of avoiding any prior evaluation of cases and controls was highlighted, regarding their partial judgments of values and rigorous release of responses, according to the answers of the journaled patients. It is also believedthat there is no minimum possibility of the occurrence of classification bias, since the cases were selected through rigorous diagnostic criteria in a pediatric hospital of state reference and the controls were selected through randomization in the pediatric outpatient clinic, at the time of the interview. Finally, it is expected that the eligibility and parament criteria may have minimised the possibility of these effects occurring.

The data of the present study indicate a potential teratogenic effect in the occurrence of cleft palates among women living in regions of intense pesticide use. The consistent findings of the association measures found, based on references from similar studies in the literature, reinforce our findings. It is important to highlight that this was one of the first studies conducted in agribusiness capital in the Brazilian Amazon conducted by specialist and experienced professionals of the service itself.

## 5 CONCLUSION

Maternal exposure to pesticides was associated with a higher occurrence of cleft lip and palate in the state capital with higher consumption of pesticides in the country. It is expected that the results of this study can support health prevention actions and support the actions of professionals offering integrated care to patients with cleft lip and palate and control of the use of pesticides in the work process of agricultural production.

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