ANENCEPHALY AND RESIDENCE NEAR TEXTILE INDUSTRIES: AN EPIDEMIOLOGICAL CASE-CONTROL STUDY IN SOUTH AMERICA

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ABSTRACT

Case reports on solvent exposure in humans and occupational as well as water contamination studies are the main source of information about the adverse effect of solvents on pregnancy. This matched case-control study evaluates the environmental exposure to organic solvents released by textile industries and the risk of anencephaly. The sample comprises 69 cases and 207 controls registered in the ECLAMC network in five counties from Argentina between 1982 and 1994. Statistically non-significant risk was observed for mothers living within a radius of 3 km from the textile industry (OR=1.09, 95% CI=0.60-2.02, p=0.774). A lineal risk trend could not be shown, although a slightly increased risk was observed for mothers living less than 2 km far from textile industries. After controlling for several possible confounding factors, the conditional logistic regression model showed an OR=0.72 95% CI=0.32-1.66, p=0.447. The principal confounder was low socioeconomic level which modified 2.9% the crude risk. The estimated risk is low and statistically non significant, however, further research is necessary to demonstrate a cause-effect relationship between organic solvents exposure and anencephaly. Regional surveillance programs and case-control studies are useful for public health to respond at population concerns about environmental agents that could cause adverse effects on human health.
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Introduction

Several experimental studies on animals have analysed the toxic effects of solvents on the reproductive functions and embryo development. Hydrocephaly and heart defects have been found to be associated with trichloroethylene (Dawson, et al., 1990); and cleft palate with toluene and benzene (Nawrot and Staples, 1979; Hardin, et al., 1984). Recent research (Chen, et al., 2005) in mouse embryo cultures showed the association of ethanol exposure with neural tube defects (NTD), consistent with total dysraphia and anencephaly.

Case reports on solvent abuse in humans, occupational as well as water contamination studies (EUROCAT, 2004; Shaw, et al., 1990) are the main source of information about the effect of occupational solvents exposure on pregnancy. Pregnant women working under occupational exposure to organic solvents (hydrocarbon, phenol, trichloroethylene, xylene, vinyl chloride, acetone, and related substances) have been reported to be at high risk for delivering children with anomalies (coronary disorders, congenital deafness, and central nervous system defects) (Khattak, et al., 1999). By means of a meta-analysis approach, McMartin, et al., (1998) reported an overall average value (OR=1.64 95% CI=1.16-2.30) for studies evaluating maternal occupational exposure to organic solvents and risk of major congenital malformations.

Environmental exposure to chemical contaminants has been linked to the occurrence of neural tube defects. High risk of NTDs and anencephaly or spina bifida subtypes was associated with maternal residential proximity of about 1 km (0.62 miles) to industries using chemical pesticides (amide, benzimidazole, methylcarbamate, or organic-phosphoric pesticides) (Rull, et al., 2006). The ecological study known as ECOTERAT (Castilla, et al., 2000) showed that anencephaly is more common in newborns from counties with textile industrial development than in those from other counties. These authors suggest that solvents released by these industries might be the cause of such increase. Following that hypothesis and sampling the same source data, a matched case-control study was carried out in order to assess the relationship between the risk for anencephaly and the maternal environmental exposure to organic solvents released by textile industries in five counties of Argentina. The hypothesis considers that the distance from the maternal place of residence to the source of contamination is shorter for cases of anencephaly than for their matched controls.

Materials and Methods

In this study 388,251 children born between 1982 and 1994 at 6 Argentine hospitals belonging to the ECLAMC network (Castilla and Orioli, 2004) were evaluated. Hospitals were selected among those included in the ecological study ECOTERAT (Castilla, et al., 2000), which associates the industrial activity in 21 counties with 34 congenital anomalies. The hospitals were selected for this study because they are located in counties of Argentina where the ECLAMC registered at least 20% of all births occurred during the study period.

The ECOTERAT study found 7 counties with significant association between anencephaly (ICD-8: 7400) and proximity to textile industries (ICIU-International Classificiation Industrial Uniform: 3211, spinning, dyeing and fabric final treatment). The sample selected for the present study comprises 69 cases of anencephaly and 207 controls matched by sex, hospital and time of birth (1:3 matching ratio) from 5 counties of Argentina (Paraná, Tucumán, Córdoba, Rosario, and Mar del Plata). Live births and stillbirths with anencephaly were included. For controls, only live births were included. Syndrome cases and those in which causes were known were excluded from the study. This sample allows 60% power of test (β=40%) to detect a double minimum risk for a population with 25% mothers living less than 3 kilometres (1.86 miles) far from textile industries. The level of significance selected was 5%.

The risk indicator was obtained by measuring the distance (kilometres = km) between the
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mother’s place of residence during pregnancy and the centroid of the textile industry area. Data about the maternal place of residence of cases with anencephaly and their controls were obtained from ECLAMC database. Details on textile industries location were taken from the National Economic Census of 1974 and 1984 carried out by the National Institute of Statistics and Census. We obtained the postal address of all industries, cases and controls, except for 44 controls and so not included in the analysis. Then, they were located in the city maps using a geographic coordinates system (latitude and longitude). The most polluted area (up to 3 km radius) was defined for each county (Dolk, et al., 1998). Since each county included more than one textile industry, the closest distance between the maternal place of residence and the textile industry was used as surrogate measurement of exposure to chemical contaminants.

The study was controlled for the following confounder variables: maternal age under 19 and over 30 years old, primiparity (only one gestation), and multiparity (4 gestations or more), maternal and paternal education, paternal occupation, health care system of the hospital, and socioeconomic level index. Four variables were considered when assigning the socioeconomic level index: maternal and paternal education (7 levels), paternal occupation (8 levels), and health care system of the hospital (2 levels). Levels considered for maternal and paternal education were: 1: illiterate, 2: less than 7-years education, 3: 7-years education, 4: less than 12-years education, 5: 12-years education, 6: less than 18-years education, and 7: 18-years education. Paternal occupation levels were: 1: housework, 2: unemployed, 3: unqualified worker, 4: qualified worker, 5: independent worker, 6: clerk, 7: boss, chief, owner, 8: professional, executive. Hospital health care systems considered were either public or private.

We compared the demographic characteristics of control mothers living less than 3 km far, with those living more than 3 km far from the textile industry and the linear trend of the log odd was estimated in order to assess the risk for anencephaly and the proximity to the textile industry. The modifier effects were evaluated for each variable using the Breslow test. Changes in the odds ratio higher than 10% were defined as confounding factor. A conditional logistic regression analysis was used to assess the proximity of the maternal place of residence to the textile industry and the adjusted risk for anencephaly.

Results

Low level of paternal education was higher among controls mothers living farther than 3 km. Any other variable showed significant difference. (Table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>≤3 km</th>
<th>&gt;3 km</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>25.0±6.1</td>
<td>25.5±7.1</td>
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</tr>
<tr>
<td>Birth weight</td>
<td>3214.0±548.9</td>
<td>3201.6±562.7</td>
<td>0.887</td>
</tr>
<tr>
<td>Gestational age</td>
<td>39.3±2.7</td>
<td>38.6±3.0</td>
<td>0.138</td>
</tr>
<tr>
<td>Paternal education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>28.6</td>
<td>24.1</td>
<td>0.736</td>
</tr>
<tr>
<td>Medium</td>
<td>26.4</td>
<td>29.2</td>
<td>0.427</td>
</tr>
<tr>
<td>High</td>
<td>45.0</td>
<td>46.7</td>
<td>0.779</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>20.2</td>
<td>20.9</td>
<td>0.951</td>
</tr>
<tr>
<td>Medium</td>
<td>20.8</td>
<td>24.4</td>
<td>0.587</td>
</tr>
<tr>
<td>High</td>
<td>59.0</td>
<td>54.7</td>
<td>0.047</td>
</tr>
<tr>
<td>Socioeconomic level</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Low</td>
<td>22.5</td>
<td>16.9</td>
<td>0.572</td>
</tr>
<tr>
<td>Medium</td>
<td>55.0</td>
<td>55.4</td>
<td>0.075</td>
</tr>
<tr>
<td>High</td>
<td>22.5</td>
<td>27.7</td>
<td>0.060</td>
</tr>
<tr>
<td>Acute illness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>11.4</td>
<td>12.2</td>
<td>0.675</td>
</tr>
<tr>
<td>Medium</td>
<td>6.4</td>
<td>8.5</td>
<td>0.307</td>
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<tr>
<td>Vaginal bleeding</td>
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<tr>
<td>Acute illness</td>
<td>6.3</td>
<td>2.4</td>
<td>0.226</td>
</tr>
<tr>
<td>Medicines use</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Acute illness</td>
<td>17.2</td>
<td>14.2</td>
<td>0.325</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>91.0</td>
<td>92.5</td>
<td>0.379</td>
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</tbody>
</table>

Table 1. Demographic characteristic between controls mothers living less than 3 km and more than 3 km far from source textile industry.

(a): during first trimester of pregnancy
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The mean for the distance from maternal place of residence to textile industry was 3.6 ± 0.3 km for cases and 3.8 ± 0.2 km for controls; the difference was not significant (t=1.04, p=0.149). The matched odds ratio for anencephaly associated with residence within 3 km from the textile industry was OR=1.09, 95% CI=0.60-2.02, p=0.774 (Table 2). The test for linear trend of the log odds showed a statistically non-significant relationship between the distance from the source of contamination and the risk of anencephaly: score test for trend of odds X²(1df)=0.26, p=0.612; homogeneity test of odds X²(3df)=2.52, p=0.472 (Table 2).

This case-control study showed a low and non-significant risk for anencephaly when the maternal place of residence is close (d<3km) to textile industries, (OR=1.09, 95% CI=0.60-2.02). The low risk observed in this study is an expected result for studies evaluating the source of environmental pollution and the risk for congenital malformations. This topic was approached by other authors (Vrijheid, 2000; Castilla, et al., 2001; Brent, 2004; Dolk, 2004) and all of them agree that finding a significant association between environmental exposure and risk for congenital malformation is quite difficult due to multiple confounders such as the use of the maternal place of residence, unspecific contaminants exposure, unspecific dose and time of exposure during pregnancy, nature and nurture of birth defects, incomplete ascertainment rate, and sample selection and size (Shepard, 2002). However, similar results were found in studies on congenital malformations using the maternal place of residence as proxy for exposure. After checking for confounding factors, Geschwing, et al., (1992) observed that maternal proximity to hazardous waste sites produces a slight increase in the risk of congenital malformations in the child (OR=1.12, 95% CI=1.06-1.18). The case-control study carried out in New York by Marshall, et al., (1997) found no association between CNS defects and drinking water contamination, but the authors observed a relationship between CNS defects and the proximity of the maternal residence during pregnancy to industries releasing solvents (OR=1.39, 95% CI=0.97-2.01).

The socioeconomic level is the main confounding factor for spatial analysis and risk for birth defects (Dolk, 2004; Dolk, et al., 1998; Sullivan, 1993). This variable is outstanding in South America because of the great variety of socioeconomic levels in this region. The positive correlation between proximity to textile industry and low socioeconomic level could not be demonstrated. After adjustment, the crude risk (OR=1.07) was similar to the adjusted risk by socioeconomic level (OR=1.10, modified 2.9% in

<table>
<thead>
<tr>
<th>Distance (km)</th>
<th>Cases</th>
<th>Controls</th>
<th>t-value</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 – 2.0</td>
<td>21</td>
<td>36</td>
<td>1.00</td>
<td>1.20</td>
<td>0.85</td>
</tr>
<tr>
<td>2.1 – 3.0</td>
<td>14</td>
<td>44</td>
<td>0.71</td>
<td>0.70</td>
<td>0.41</td>
</tr>
<tr>
<td>3.1 – 5.0</td>
<td>13</td>
<td>36</td>
<td>0.81</td>
<td>0.80</td>
<td>0.59</td>
</tr>
<tr>
<td>&gt; 5.0</td>
<td>21</td>
<td>47</td>
<td>1.00</td>
<td>1.00</td>
<td>--</td>
</tr>
<tr>
<td>(≤ 3 \text{ km} )</td>
<td>35</td>
<td>80</td>
<td>1.07</td>
<td>1.09</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Score test for trends of odds X²(df)=0.26, p=0.612
Homogeneity test of odds X²(df)=2.52, p=0.472

Table 2. Risk according to distance from textile industry.

The conditional logistic regression model showed OR=0.72, (95% CI=0.32-1.66, p=0.447) for mother living at less than 3 km from the textile industry. The principal confounder was low socioeconomic level. For mothers living less than 3 km far from the textile industry, a high risk was observed for those younger than 19 years old (OR=4.20, 95% CI=1.12-15.8, p=0.034), while for those older than 19 years old, risk showed to be lower (OR=0.80, 95% CI=0.35-1.82).

Discussion

This study complements research work by Castilla, et al., (2000) that showed higher frequency of anencephaly for those counties with textile industry development, suggesting a possible relationship with the environmental exposure to the organic solvents released. In the present study, a matched case-control approach was used to assess the risk for anencephaly after the maternal environmental exposure to organic solvents released by textile industries in five counties of Argentina.

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risk value), even when adjusted for overall confounders.

The high risk observed for mothers younger than 19 years living near textile industries was not an expected result. Social factors (not measured in this study) and other exposure such as life style or low prenatal care could reflect this unexpected result. A more detailed study on this risk population of mothers under 19 should be developed in the future. Although the risk trend could not be demonstrated, a slightly increased risk was observed for mothers living less than 2 km far from textile industries.

This study has focused only on one specific malformation, anencephaly, in only one country (Argentina), with demographic homogeneity and accurate information about the place of residence of mothers as well as of textile industries. Furthermore, studies of this sort have never been carried out before in South America using standardized forms for cases and controls from more than 300,000 births registered at ECLAMC hospitals. Since 20% overall births of each county selected are registered in hospitals included in this study, the sample is highly representative of the referred population. However, the sample size is rather small. This study has 60% statistical power to detect a two-fold risk ratio, which is quite significant for environmental pollution assessment. For anencephaly, with an incidence of 1 in 1,700 births, more than 3,000 case-controls pairs would be necessary in order to detect an OR=1.2 fold real increase of the risk (one tail hypothesis), with 80% statistical power for 5% level of significance. Scarce information about polluting agents and the combined exposure and possible fostering, make it necessary to find a formal mechanism for the vigilance of eventual risks before and after pollutants release into the environment (Monteleone-Neto and Castilla, 1994).

Conclusions

The estimated risk is low (OR= 1.09) and statistically non significant. These results agree with those from other authors (Marshall, et al., 1997; Geschwind, et al., 1992). Findings evidencing that organic solvents are a risk factor for anencephaly are limited, and results from this study are not enough to demonstrate a cause – effect relationship in anencephaly etiology.

Acknowledgments

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Abbreviations

ECLAMC: Latin-American Collaborative Study of Congenital Malformations
Km: kilometers (1 km = 0.62 mi)
CNS: central nervous system
NTD: neural tube defects

References

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