

Pesticide exposure and poor pregnancy outcomes: weaknesses of the evidence

Exposição a agrotóxicos e resultados adversos da gravidez: a fragilidade da evidência

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Dear Sir,

An analytical observational study by Cremonese et al. ¹ recently suggested that prenatal exposure to pesticides is a risk factor for poor pregnancy outcomes such as pre-term births and lower Apgar scores. The authors used an ecological (correlational) study to investigate whether there was an association between exposure to pesticides (in general) and poor pregnancy outcomes in micro-regions of states in the South Region of Brazil. Making use of group-level variables and routinely collected data, ecological studies have the advantage of being relatively inexpensive and quick and easy to conduct. Nonetheless, owing to their inherent methodological limitations, correlational studies are generally regarded as one of the weakest approaches to analytic epidemiology. Ecological studies are even weaker strategies for testing associations between “exposure” and health outcomes, when group-level measures are used as surrogates for individual measures. The study by Cremonese et al. is a good example of this type of approach. The exposure status (exposure to pesticides in individual pregnant women) was estimated based on the group average (“per capita pesticide expenditure in the micro-region” referred to as per capita pesticide consumption) i.e., the group-level variable served as a proxy for individual values. Besides being imprecise, using group average data to represent individual exposure may lead to the erroneous inference (“ecologic fallacy”) that specific individuals in the local group share the characteristics of the group. Groups are far from being homogeneous in terms of

pesticide exposure and a subgroup may markedly differ from the group mean.

In addition to the common drawbacks of an ecological epidemiology approach, important flaws regarding hypothesis formulation and exposure assessment can be observed in the aforementioned study.

The authors' hypothesis was that exposure to pesticides (in general and not to a particular substance or group of related compounds) is associated with adverse pregnancy outcomes. Pesticides are a highly diverse range of substances with quite different toxicological and physical-chemical properties and actions on pests (insecticides, fungicides, herbicides, miticides or acaricides, nematocides, bactericides and so on) and non-target species. It seems, therefore, unreasonable to estimate collective exposure to these substances and investigate the association of this “general pesticide exposure” with a particular adverse health outcome without considering the dissimilarities. Per capita pesticide expenditure calculated from local sales (in the local currency, Real R\$) is a rather strange and unreliable, not to say meaningless, estimate of exposure. The authors make an uncritical assumption without demonstrating its validity. It should be borne in mind that the active ingredients used in pesticides (insecticides, fungicides and so on) and their sale price and volume of use (and also how they are used) depend on the crops (soybean, rice, beans, tobacco, maize, vegetables and so on) and prevailing agricultural practices in the micro-region. It is therefore likely that micro-regions are heterogeneous in terms of the type of pesticide used. For instance, in regions where soybean is a major crop it is likely that expenditure on pesticides will relate predominately to herbicides, whereas in regions with greater emphasis on vegetable crops insecticide and fungicide use is likely to be more dominant. Calculations of consumption based on local per capita pesticide expenditure are a quantitative estimate of qualitatively different types of pesticides. In other words, micro-regions may differ not only regarding the amount of pesticide use but also due to the type of active ingredients used (i.e., micro-regions may differ in terms of degree of exposure and type of exposure). The investigation of an association between exposure to different types of uncharacterized pesticides and the occurrence of adverse health outcomes seems meaningless.

In their conclusions, the authors are cautious and suggest that further prospective studies should be undertaken involving individuals as analytical units rather than populations to better evaluate their findings.

Ecological studies on adverse health effects of environmental exposure are increasingly common in the literature. Essentially negative studies are rarely found in the literature and most published ecological studies generally report findings suggestive of a positive correlation. A possible explanation for this apparent publication bias is the perception that although ecological studies are methodologically weak in dem-

onstrating associations, they are nevertheless a useful tool for generating hypotheses that should be further tested using rigorous analytical studies. A meaningful and original hypothesis and valid estimate of exposure are, however, minimum requirements for accomplishing this goal.

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The authors reply

Os autores respondem

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Pesticide exposure and poor pregnancy: weakness of the evidence?

According to their methodological design, ecologic studies are descriptive investigations – and not one of the approaches of the analytic epidemiology – that

have been largely used to explore hypothesis on possible epidemiological associations towards the use of aggregate variables. Using the MEDLINE databank, a search with the keywords “pesticide” and “pregnancy”, yields 4,122 publications, the first of which dates back to 1937. In this sense, although the interest on the effects of such chemicals during pregnancy is old, the establishment of an accurate exposure assessment presents several difficulties¹.

As an ecologic study, the paper by Cremonese et al.² has explored the available population-based data on pesticide exposure, i.e. data on the per capita pesticide expenditures in micro-regions in the South Region of Brazil. These data were related to available information on the recorded local pregnancy outcomes at that regional level. Because the former information is collected with socio-economical purposes rather than epidemiological ones, its use as a proxy of pesticide exposure is reasonably inaccurate.

Information on the use of specific classes of pesticides (e.g. herbicides, insecticides, fungicides), rather than overall pesticide use, would be preferable, but this information is unavailable at the micro-region level. Nevertheless, in relation to the observed results, the use of the variable per-capita pesticide expenditure would only be methodologically misleading if one/some of the pesticide classes showed a protective effect on the studied outcomes (prematurity and low Apgar score), which does not occur.

Therefore, with these limitations, how important was the authors' decision to use such inaccurate exposure indicator in this ecologic study?

The answer arises from the results of the present analysis exploring more than 2 million childbirths in the South of Brazil. A statistically significant monotonic increase in the prevalence ratio of newborns with Apgar score 6-7 in the first minute was observed across to quartiles of per capita pesticide expenditures in the study region. The prevalence ratio of such outcome among girls born in micro-regions in the 4th quartile compared to those in the 1st quartile was 1.71 (95%CI: 1.68-1.73). Among boys, prevalence ratios of low Apgar score were very similar to girls, while a non-monotonic trend was observed for pregnancies lasting less than 22 weeks.

The strength of the evidence emerges from single questions about the present results: considering the current knowledge on the effects of pesticides exposure during pregnancy, is it reasonable that the opposite scenario would occur, i.e., that children born in micro-regions in the 1st quartile of per capita pesticide expenditures presented a statistically significant 70% higher prevalence of low Apgar score (6-7) compared to those born in micro-regions in the 4th quartile? Additionally, is it probable that a statistically significant inverse trend between per capita pesticide expenditures in the study areas and low Apgar scores occur?

As a whole, what these results seem to suggest is that despite inaccurate, the exposure indicator based

on aggregate information on per capita pesticide expenditure, as well as others such as the amount of pesticide sales, are indeed able to discriminate regional differences in terms of pesticide exposure and subsequent health effects. In fact, they present the necessary requirements to be used in ecological studies, since a regression to the mean seems not to have been introduced in the studied outcome distributions.

What is the biological plausibility that this broad measure of exposure may be efficient to characterize the exposure variability at an aggregate level?

Pesticide exposure is pervasive and prone to trigger many different human and animal health effects. They are able to disturb various crucial biological mechanisms, such as fetal programming and endocrine homeostasis, as well as produce genotoxic effects and epigenetic changes, among others. Hence, despite limitations regarding exposure assessment, ecologic studies can be successfully used to point towards the potential association between exposure and health outcomes.

Some studies have been performed in the country using this approach, and they have added to the evidence on the link between pesticide exposure and several health effects. They include the role of pesticide sales in the decline of the proportion of male births in the agricultural areas of the State of Paraná, a state also in southern Brazil ³; the correlation between pesticide sales in Brazilian states and the distribution of performed seminal quality exams, which are indeed the first laboratory exam usually made to couples investigating infertility ⁴; the thirteen-fold higher risk estimate of hospitalizations due to suicide attempts among all male agricultural workers in the largest area of fruit and vegetables production (Serana Region) in the State of Rio de Janeiro, compared to its capital city ⁵; the higher cancer mortality for selected anatomic sites among agricultural workers in the country ⁶, among others.

From a public health perspective, what is the importance of using of such indicators to evaluate the wide range of effects related to pesticide exposure?

Exposure to pesticide is very disperse, both in the agricultural occupational set – in which Brazil has become the largest consumer of pesticides worldwide –, and in non-occupational environments (through intake of fruits, vegetables, and other food items contaminated with pesticide residues), that the attributable risk related to pesticide exposure is very high. As evidenced in the literature, a large number of illnesses (e.g. spontaneous abortion, premature birth, low Apgar score, birth defects, neurobehavioral disorders in children, precocious puberty, poor seminal quality, infertility, testis and other hormonal cancers, depression and mood disorders, Parkinson disease, among others) can be expected to occur as a consequence of human exposure to these substances.

Considering such a high attributable risk by pesticide exposure in Brazil, one of the main roles of

scientists is to provide data analyses to the society with the aim of expand its consciousness about the environmental hazards, and the need of collectively pressuring for pesticide control. The paper by Cremonese et al. ² will surely contribute to accomplish such endeavor.

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