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Exposure to Pesticides in Pregnant Women: An Integrative Review

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Abstract: *Background:* Considering the development model adopted in Brazilian agriculture, which is based on the increasing demand for chemicals, studies that analyze the impact of pesticide use are relevant to measure the developments in affected populations. *Objective:* The aim of this study was to conduct a literature review using the digital platform, searching for scientific publications from 2009–2019 on exposure of pregnant women to pesticides. *Methods:* We used PubMed to search for scientific articles published between January 1, 2009, and December 31, 2019, and related to exposure of pregnant women to pesticides in rural areas. *Results:* Initially, 207 publications were selected considering the titles and abstracts. Literature works that did not meet the inclusion criteria were excluded. After selection, 15 studies remained. According to the publications on the exposure of pregnant women to pesticides in rural areas from 2009 to 2019, it was found that the damage caused by pesticide exposure to the health of pregnant women and their babies includes problems in gestational weight gain, premature birth, low birth weight, presence of pesticides in blood of both mother and newborn, presence of agricultural pesticides in the cerebral cortex of fetus, and miscarriages. *Conclusion:* Future prospective studies at individual level are needed to better assess the potential impact of pesticide exposure on the health of pregnant women and newborns.

Keywords: Agrochemicals; Pregnant women; Maternal and child health

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1. Introduction

The Green Revolution in the 1950s brought about the emergence of new technologies and the modernization of agricultural processes. These technologies include pesticides, chemicals intended to control diseases, and vectors to increase productivity [1]. Brazil began using the nomenclature "agrotoxic," instead of "defensive pesticide," to designate agricultural poisons, after a great mobilization of civil society to underline the toxicity of these products to the environment and human health [2].

Pesticides are used for crop production and to control vector-borne diseases in urban areas. They are potentially toxic to other organisms, including humans [3]. Human exposure to pesticides can occur environmentally, through air and consumption of food and water, as well as occupationally, during or after

indoor/outdoor application [2].

Research on the impact of pesticide use on human health is still lacking considering the extent of chemical load of occupational exposure and the extent of damage to health, resulting from the extensive use of these chemical compounds, and due to the lack of information on consumption of pesticides and insufficient data on poisoning by these products [4].

In Brazil, men are generally responsible for the application of pesticides; they tend to perform this activity in the company of their family and often without the use of personal protective equipment (PPE) [5].

Since women believe they are only helping around, they are more exposed to the risks of activities that promote handling and/or exposure to chemical agents without proper protection [6]. Therefore, more attention must be paid to pregnant women, who are characterized as a risk population. Research focuses on the complications in pregnancy, constituting an emerging concern in healthcare and highlighting the risks that vulnerable populations, such as pregnant women, are exposed to [7].

Undesirable outcomes of pregnancy, such as low birth weight, prematurity, and congenital malformations, are risk factors of infant mortality. In turn, such adverse outcomes may be influenced by various other factors during pregnancy, such as malnutrition, stress, smoking, use of illicit drugs, and exposure to chemical substances. Among the chemical substances that may cause these adverse outcomes, pesticides stand out. Studies in humans remain contradictory, but they indicate a higher risk of these outcomes in newborns whose mothers were exposed to pesticides during pregnancy [8].

Studies have shown that a number of pesticides can affect the reproductive system of animals and embryo-fetal development after intrauterine exposure, among which congenital malformations (CM) are highlighted [9]. When considering the development model adopted in Brazilian agriculture, which is based on the growing demand for chemicals, studies that analyze the impact of pesticide use are relevant to measure the developments in affected populations. Thus, the aim of this study was to conduct a literature review using the digital platform, searching for scientific publications concerning the exposure of pregnant women to pesticides in the period 2009–2019.

2. Methodology

This study used PubMed to search for scientific articles published between January 1, 2009, and December 31, 2019, and related to the exposure of pregnant women to pesticides in rural areas.

Studies were selected by searching PubMed (https://www.ncbi.nlm.nih. gov/pubmed/advanced) using the following keywords in English, Portuguese, and Spanish: (pesticide OR herbicide OR insecticide OR fungicide OR organophosphate OR carbamate) AND (rural population OR non-urban OR rural areas OR rural area OR rural) AND (women OR woman OR wife OR pregnancy OR prenatal OR gestation).

Inclusion criteria: original articles that presented the relationship of pesticides and pregnant women in rural settings published between 2009 and 2019. Exclusion criteria: (i) studies related to pregnant women in urban areas; (ii) studies that did not analyze the relationship between pesticides and pregnant women; (iii) review articles; (iv) studies that analyzed the intake of pesticides through food; (v) genetic studies; (vi) non-English, Portuguese, or Spanish articles; (vii) studies that were not fully available.

3. Results and discussion

Initially, the selection of publications was performed considering the titles and abstracts to exclude publications that did not fit the inclusion criteria. Of the 207 articles found, 167 were excluded, as they were unrelated to pregnant women and pesticides, written in languages besides English, Portuguese, or Spanish, focused on the use of pesticides in residences to combat malaria and/or vectors in combating possible diseases, and not fully available. Twenty-five articles were further excluded, as they were unrelated

to exposure of pregnant women to pesticides in rural areas and dealt specifically and only with exposure of children. After the screening, 15 studies remained. **Figure 1** illustrates the article selection process.

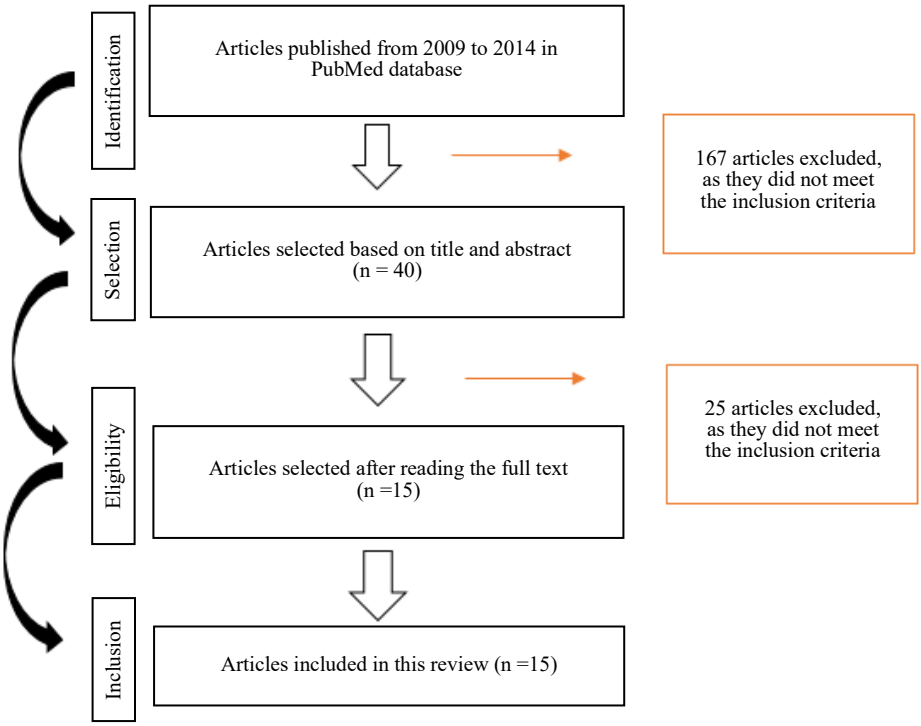

Figure 1. Article selection process

Of the 15 articles selected, only one was carried out in Brazil, being retrospective, exploratory, and descriptive in nature. In the study, Motta *et al*. [10] evaluated the rate of metal and pesticide contamination in pregnant women, relating it to perinatal outcomes, in the rural area of Botucatu, São Paulo, Brazil; they analyzed blood samples from 40 mothers and their newborns; the results indicated that there was no statistically positive correlation ($P > 0.05$) between maternal contamination index and clinical parameters of newborns as well as the contamination index of newborns and their clinical parameters.

Although the exposure to pesticides, involved in the different stages of agricultural production, among the rural population is through direct contact with products, understanding the full exposure scenario aids in identifying other important routes of exposure and populations at risk [11]. In addition to health risk factors to which pregnant farmers are subjected during the management and application of pesticides, there is risk to their relatives and other people living around agricultural areas as well as people who consume food and water with high concentrations of these chemicals. Certain groups of people, such as children, pregnant women, women of childbearing age, the elderly, and sick individuals, are more vulnerable to pesticide exposure and have a higher probability of developing adverse health effects; therefore, these groups deserve special attention [12].

Kongtip [13] carried out a study on prenatal exposure to organophosphorus pesticides, which may lead to developmental neurotoxicity. Organophosphate metabolites in maternal urine were measured at 28 weeks of pregnancy (n = 86), delivery (n = 67), and 2 months after delivery (n = 51). Labor, household, and behavioral factors that were potentially associated with pesticide exposure were investigated by a questionnaire survey. Samples of urine were collected and analyzed for dimethyl phosphate (DMP), diethyl phosphate (DEP), diethylthiophosphate (DETP), and diethyldithiophosphate (DEDTP) using gas chromatography mass spectrometry. Urinary DMP concentrations at 28 weeks of pregnancy and delivery were not significantly different, but DMP concentrations at 28 weeks of pregnancy and DAP concentrations

at delivery were significantly different from those at 2 months after delivery. Factors influencing urinary concentrations of DMP at 28 weeks of pregnancy included insecticide use at home, proximity to agricultural land, frequency of visits to agricultural fields during the first and second trimester of pregnancy, occupational activity of the participants, pesticide use, and other agricultural activities. When genetic and geographic variables (residence near pesticide application) were analyzed, the highest risks were among newborns with exposures to both, indicating a 2-to-4-times higher chance of developing hypospadias, a congenital malformation of the male external urogenital tract.

According to Ding *et al*. [14], pyrethroid insecticides are widely used, and little is known about the possible adverse effects on fetal growth. The study was on 454 mother-infant pairs in the northern region of China between September 2010 and 2012. Five non-specific metabolites of pyrethroids were measured in maternal urine at the time of delivery and examined for association with birth outcomes, including weight, length, head circumference, and gestation length. No association was found between individual or total levels of metabolites and infant length, head circumference, or gestational length, although an inverse association of prenatal exposure to pyrethroids, as measured by urinary metabolites, with birth weight was reported.

Elserougy [15] detected the transfer of organochlorine pesticides (OCPs) through placenta and breast milk in healthy lactating mothers in urban/rural areas. The study involved 38 healthy participants undergoing caesarean delivery. Sociodemographic data, maternal serum, and umbilical and adipose tissue samples were collected. The samples were analyzed for OCP residues. Olindane, p'-dichlorodiphenyldichloroethane (DDD) in maternal serum, dichlorodiphenyltrichloroethane (DDT) and p'-dichlorodiphenyldichloroethylene in umbilical serum were the only residues detected at significantly higher frequencies and/or averages in primigravidae.

The total amount of DDT residues in umbilical cord serum was significantly higher in rural mothers. The detection of OCPs in mothers suggests the possible placental transfer to the child during pregnancy and lactation and may reflect the persistence or recent use of these pesticides in the environment.

Sharma *et al*. [16] studied pesticide residues in the breast milk of nursing mothers living in Punjab. A total of 127 samples of breast milk were analyzed, and pesticide residues were detected in 25% of the samples. About 10 mL of milk was collected in a sterile glass bottle prewashed with acetone and taken to the laboratory under refrigerated conditions. The residue levels were observed to decrease with increasing age of the mother, and the residue levels were higher in rural population than in urban population, although no statistically significant difference was found between the two. The low levels of organochlorines indicated the effectiveness of the ban on their use as well as the increased demand for synthetic organophosphates and pyrethroids. The presence of organophosphates requires additional monitoring in future studies.

The overall exposure process in the agricultural environment fluctuates with periods of higher and lower exposure but is continuous. The exposure of children starts in intrauterine life, when most of these compounds pass through the placenta and, after birth, through mother's milk during breastfeeding. The excretion of organochlorines in milk is an important means of reducing maternal body burden, and there is a transfer of these compounds to the infant during breastfeeding. The contamination of breast milk attracts certain attention as milk is the only source of food for newborn infants, who consume proportionally large amounts of it [17].

OCPs persist for long periods, but little is known about plasma OCP levels in pregnant women. Therefore, a study was carried out to determine the exposure concentrations in a sample of pregnant women in Western Australia and the environmental factors, lifestyle, and activities that contribute to maternal exposure to OCPs as well as to compare maternal exposure concentrations with those measured in other countries. In this cross-sectional study on 167 pregnant women, located in rural and urban Western

Australia, their blood plasma was collected, and they were required to complete a questionnaire on lifestyle, demographics, and determinants of exposure to OCPs [18].

Organophosphate pesticides are widely used. Recent studies have suggested associations of exposure to these compounds *in utero* with adverse birth and neurodevelopmental outcomes. Few studies have characterized organophosphorus pesticides in human plasma and established how these levels correlate with urinary measurements. We measured organophosphate pesticide metabolites in urine as well as chlorpyrifos and diazine in maternal plasma and bone marrow of individuals living in agricultural areas to compare the levels of two different biological matrices. We also determined paraoxonase 1 genotypes (PON1-192 and PON1-108) and specific PON1 substrate activities in mothers and newborns to examine how PON1 can affect the measurements of organophosphorus pesticides in blood and urine [19].

The levels of chlorpyrifos in plasma ranged from 0 to 1,726 ng/mL, since non-zero levels were measured in 70.5% and 87.5% of maternal and cord samples, respectively. Diazine levels were lowest (0–0.5 ng/mL) in 33.3% of maternal plasma and 47.3% of umbilical cord plasma.

Logistic regression was used to analyze the relationship between atrazine exposure and preterm birth, which was controlled for maternal age, race/ethnicity, education, smoking, and prenatal care. An increase in the odds of preterm birth was found in women living in counties included in the group with the highest exposure to atrazine, compared to women living in counties included the group with the lowest exposure, while controlling for covariates. Analyses using the three exposure assessment approaches demonstrated odd ratios ranging from 1.20 (95% CI: 1.14–1.27) to 1.26 (95% CI: 1.19–1.32) for the higher exposure group compared to the lower exposure group [20].

In a study by Jaacks *et al*. [21], urinary concentrations of pesticide markers in early pregnancy (less than 16 weeks gestation) were investigated, and the association of these concentrations with preterm birth, low birth weight, and dwarfism at approximately 1 and 2 years of age was estimated; 3,5,6-trichloro-2-pyridinol (TCPY), a metabolite of chlorpyrifos and chlorpyrifos-methyl, and 4-nitrophenol, a metabolite of parathion and methyl parathion, were detected in almost all women; 3-phenoxybenzoic acid (3-PBA), a non-specific metabolite of several pyrethroids, and 2-isopropyl-4-methyl-6-hydroxypyrimidine (IMPY), a metabolite of diazine, were detected in 19.8% and 16.1% of the women, respectively.

The remaining four pesticide biomarkers were detected in less than 10% of the women. Women in the highest quartile of 4-nitrophenol were more than three times as likely to give birth prematurely compared with women in the lowest quartile; women in the highest quartile of 4-nitrophenol were also at greater risk of having a child born small for gestational age. Women with detectable concentrations of IMPY were at greater risk of having a child born with low birth weight compared with women with undetectable concentrations [21]. No association was observed between any of the pesticide biomarkers and dwarfism at 1 or 2 years of age.

Parvez [22] studied on glyphosate (GLY), the most widely used herbicide in the world, but the extent of exposure in pregnancy remains unknown. Its residues are found in the environment, in major crops, and in food consumed daily by pregnant women. Since GLY exposure in pregnancy may also increase the risk of fetal exposure, a birth cohort was set up to determine the frequency of exposure, potential routes of exposure, and association with fetal growth indicators and duration of pregnancy.

The mean age of the participants was 29 years, and most were Caucasian. Of the pregnant women, 93% had GLY levels above the detection limit (0.1 ng/mL). The mean urinary GLY was 3.40 ng/mL (0.5–7.20 ng/mL). Higher levels of GLY were found in women living in rural areas ($P = 0.02$). None of the drinking water samples had detectable levels of GLY. No correlations were observed with fetal growth indicators such as birth weight and head circumference. Higher levels of GLY in urine, however, were significantly correlated with underweight in infants.

In a study by Quintana *et al*. [23], neonatal, placental, and umbilical cord blood parameters were observed in pregnant women living in areas with intensive pesticide use. In rural populations, the proximity of areas with intensive use of pesticides is a risk factor for exposure to xenobiotics. Newborns of mothers living in a pesticide-intensive area (PIA) demonstrated changes, especially in terms of placental and neonatal morphometric patterns, biochemical parameters of umbilical cord blood (UCB), and/or biomarkers related to oxidative stress and oxidative damage. Samples were collected from 151 healthy pregnant women living in a rural area during pesticide spraying (GRSS) and non-spraying (GRNSS) seasons as well as from women living in an urban area (control group; CG); they were then grouped according to the type of delivery (vaginal or caesarean). In the vaginal delivery group, placental weight and placental index were higher in the GR group than in the CG group ($P = 0.01$), while in the cesarean delivery group, newborn weight was lower in the GRSS group than in the CG group [24].

The publications related to the exposure of pregnant women to pesticides in rural areas from 2009 to 2019 found in this study revealed the adversity caused by pesticide exposure to the health of pregnant women and their babies, such as problems in gestational weight gain, premature birth, low birth weight, presence of pesticides in the blood of both mother and newborn, presence of agricultural pesticides in the cerebral cortex of fetus, and miscarriage. For the majority of births, there is no statistically identifiable impact of pesticide exposure on birth outcomes. Mothers exposed to extreme levels of pesticides, however, have an increased likelihood of adverse outcomes.

Adequate surveillance of women's health in Brazil largely depends on the educational processes and practices of the institutions involved. Thus, it will be effective in providing adequate information and positive impacts on the society, the environment, and occupational education, with regard to the practices of pesticide use.

The strategy used in this study contributes to the dissemination of essential information to various sectors involved in the health-disease process of the population studied. The social control aimed at the evolution of surveillance actions and at a more assertive inspection in the agricultural sector. Furthermore, it assists in health promotion and the discussion to reduce the use of pesticides.

4. Final considerations

The literature consulted brings important scientific contributions on the deleterious impacts of pesticide exposure on the health of pregnant women living in rural areas. This integrative review showed that the exposure of pregnant women to pesticides in rural areas is, in fact, associated with the occurrence of a number of diseases in both mother and child.

Recent studies have shown that pesticides cause hormonal changes, deregulating the endocrine system and impairing the functioning of glands. The daily consumption of pesticides may also be associated with difficulties in pregnancy, infertility, early menopause, endometriosis, liver and kidney problems, and allergic reactions. In pregnant women, research has indicated a relationship between intrauterine exposure to pesticides and the onset of congenital malformations, abortions, and low birth weight, besides problems that may occur during childhood, such as early signs of puberty and early menarche. It is also associated with psychiatric disorders and cognitive disturbances.

Future prospective studies at individual level are needed to assess the potential impact of pesticide exposure on the health of pregnant woman and newborns.

Disclosure statement

The authors declare no conflict of interest.

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