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REVIEW ARTICLE

Pesticide exposure and its effects on intrauterine and postnatal development

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Abstract

Background: *The period between conception and the first two postnatal years is critical and marks the individual, largely determining their health and disease patterns.* **Objective:** *To review the effect of pesticide exposure in utero and in the 1st years of life.* **Materials and methods:** *The scientific literature in relation to the subject was reviewed, both in animal models and in humans.* **Results:** *The presence of various types of pesticides in umbilical cord blood and in meconium is well documented in newborns worldwide, including Mexico. Pesticides have been associated with low birth weight, and various birth defects at the heart, gastrointestinal tract, genitourinary system, musculoskeletal system, and neurodevelopmental disorders. These substances may play a role in the increase in cases of autistic disorder.* **Conclusions:** *Despite the evidence, there are no public policies in many countries, including Mexico, to control the sale and use of pesticides. It is required to prevent exposure to these substances in the population and to do follow-up studies in mother-child pairs where exposure is suspected.*

Keywords: *Pesticides. Exposure. In utero. Postnatal. Toxicity.*

Exposición a plaguicidas y sus efectos en el desarrollo intrauterino y posnatal

Resumen

Introducción: *El periodo comprendido entre la concepción y los primeros dos años posnatales es crítico y marca al individuo, determinando en buena parte sus patrones de salud y enfermedad.* **Objetivo:** *Hacer una revisión sobre el efecto de la exposición a plaguicidas en útero y en los primeros años de vida.* **Material y métodos:** *Se revisó la literatura científica en relación con el tema, tanto en modelos animales como en humanos.* **Resultados:** *La presencia de diversos tipos de plaguicidas en la sangre de cordón umbilical y en meconio está bien documentada en recién nacidos en todo el mundo, incluyendo México. Los plaguicidas se han asociado con bajo peso al nacer y diversos defectos congénitos a nivel cardiaco, del tracto gastrointestinal, sistema genitourinario y sistema musculoesquelético, así como a trastornos en el desarrollo neurológico. Estas sustancias pueden tener participación en el incremento de casos de trastorno autista.* **Conclusiones:** *A pesar de las evidencias, no existen en muchos países, incluyendo México, políticas públicas para controlar la venta y uso de plaguicidas. Se requiere prevenir la exposición a estas substancias en la población y hacer estudios de seguimiento en binomios madre-hijo donde se sospeche exposición.*

Palabras clave: *Plaguicidas. Exposición. In utero. Posnatal.*

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Introduction

The critical period between conception and the first 2 postnatal years marks the individual and determines their lifelong health and disease patterns[1]. Exposure to adverse conditions at these stages of development is associated with a pro-inflammatory profile, increased risk of autoimmune diseases (multiple sclerosis and rheumatoid arthritis) and allergic diseases, type 2 diabetes mellitus, obesity, and psychiatric disorders[2]. Among the main factors associated with adverse events in early life, nutritional, psychosocial, infectious and environmental toxic factors stand out. We review the role of early exposure to pesticides.

Methodology

The PubMed database was searched with the keywords: pesticides, *in utero* exposure, postnatal exposure. Scientific articles based on experimental work in animals and epidemiological studies in humans were included in the styudy.

Review

Time of exposure

Exposure to pesticides during the different stages of pregnancy, or even during the formation of the ovules in the mother, can have different consequences. Exposure in the first trimester of pregnancy can condition the loss of the product, while if the exposure is during organogenesis, defects in formation of organs and systems are expected[3].

Exposure can be direct (use of pesticides in agriculture) or indirect (ingestion of contaminated food and water). Infants are mainly contaminated by hand-mouth contact (75%). Pesticides have an affinity for lipid-rich tissues, especially the brain. Neurogenesis, neuronal migration and differentiation, synaptogenesis, and plasticity are strictly controlled; the disruption of these processes can cause permanent non-repairable damage, especially because the protective biological barriers (placental and blood-brain) are immature[4].

Study matrices

In newborns (NBs), prenatal exposure to pesticides can be monitored using different matrices (umbilical cord blood, hair, and meconium). Meconium is collected non-invasively, from birth to the third postnatal day; it forms from the 12th week of gestation and provides a wide window of fetal exposure. Toxicants can be detected in fetuses from week 17[5].

The study of 396 meconiums from newborn infants in Canada, with mass spectrometry, showed 72 different compounds; 30 were quantified, including caffeine, acetaminophen, methylpareben, and pesticides (<2%)[6].

In the Philippines, meconium samples from 638 NBs were analyzed. The exposure rate detected in meconium was 23.8% for propoxur, 1.9% for pretilachlor, 1.9% for cypermethrin, 0.8% for cyfluthrin, 0.6% for DDT and 0.3% for malathion and bioallethrin; while in umbilical cord blood positivity to propoxur was only observed in 1.9% samples, and hair samples were only positive to chlorpyrifos in 0.2% of cases[7].

In Egypt, the meconium analysis in newborn children of agricultural workers showed the presence of pretilachlor 54.7%, DDT 57.4%, lindane 50%, chlorpyrifos 35.8%, diazinon 53.7%, malathion 49.5%, bioallethrin 34.7%, α cypermethrin 41.1%, and β-cyfluthrin 21.5%. Exposure *in utero* was associated with low birth weight[8].

Prenatal exposure

It has been associated with congenital heart defects[9], structural defects of the gastrointestinal tract, genitourinary system[10], musculoskeletal system, and neurodevelopmental disorders[11]. In North Carolina, exposure to residential pesticides was associated with hypospadias in the case of mepiquat chloride, paraquat, and pendimethalin; while cardiac atrial septal defects were associated with glyphosate, cyhalothrin, s-metolachlor, mepiquat, and pendimethalin[12].

Organochlorine pesticides

They are lipophilic and apolar and accumulate in adipose tissue. Of particular note are DDT (dichlorodiphenyltrichloroethane), hexachlorocyclohexane, its gamma (lindane) isomer, aldrin, dieldrin, heptachlor, mirex, chlordecone, endosulfan, and chlordane. They are divided into three groups, DDT and its derivatives, the benzene group and the cyclodiene group. DDT activates voltage-gated sodium and potassium channels, changes the permeability of the neuronal membrane to potassium and sodium ions, with secondary dysfunction consisting of repetitive shocks that result in muscle contractions, seizures, and death[13]. In the benzene group, lindane is an antagonist of the gate-gamma-aminobutyric acid (GABA) of chloride channels, thereby blocking the transmission of the nerve impulse at the neuromuscular level,

Cyclodiene is neurotoxic because inhibits GABA-receptor-regulated chloride transport[13].

In Veracruz, Mexico, the levels of organochlorine pesticides in the umbilical cord blood of children born in 2009 were evaluated, and the presence of β-hexachlorocyclohexanes (β-HCH), p, p'DDE and p, p'DDT was demonstrated[14].

Waliszewski et al. measured the concentration of organochlorine pesticides in serum and adipose tissue of exposed Mexican women, and in the serum of the umbilical cord of their children, which showed that these substances cross the placental barrier and tend to reach a balance in the concentrations between mother and fetus[15]. Additional studies carried out in Mexico have shown an association between levels of the metabolites pp'DDT and β-HCH, both in mothers and in NBs diagnosed with cryptorchidism, as part of an endocrine disruption process produced by these pesticides[16].

In China, the analysis of maternal blood and umbilical cord blood in 81 mother-child pairs showed that prenatal exposure to DDT, β-HCH, hexachlorobenzene and mirex was associated with low birth weight[17].

In pregnant mice, experimental exposure to pp'-DDE and β-BHC had a disruptive effect on reproductive function, including decreased uterine nesting, increased ano-genital distance, and increased numbers of females with beta-endorphin drop in the placenta. In addition, a reduction in the weight gain of pregnant females, a decrease in the liver weight in the products and an increase in the adverse events of pregnancy were observed[18].

Organophosphate pesticides (OP)

These phosphoric acid esters are the most widely used pesticides worldwide[19]. They block and inactivate cholinesterases and consequently cholinergic hyperstimulation occurs. Among the best known are methamidophos, parathion, Chlorpyrifos, dimethoate, fenthion, monocrotophos, and malathion. Chlorpyrifos is used at home to control cockroaches, fleas and termites and in flea collars for pets. In the field, it is used for tick and pest control. Volatilization, spills, and waste disposal allow this pesticide to enter the environment after application. Applied to the ground, it adheres to the particles, with little probability that it will be detached from them and pass to the groundwater. Chlorpyrifos enters natural waters in small quantities and remains near the surface, with subsequent evaporation due to its low affinity with water. Volatilization is the main dissemination mechanism. Once in the environment (soil, air, or water), chlorpyrifos breaks down due to sunlight, bacteria, or other chemical processes. However, in urban areas it can persist for a long time, inside or outside home. Less than 3% is absorbed through the skin. However, in infants crawling in recently fumigated areas, skin exposure and inhalation of its vapors are a serious hazard[20]. In New York City, it was used in greater amounts than in all agricultural communities in the state, to such an extent that it was detected in 70% of blood samples collected at the time of delivery, both from mothers and their newborn children[21]. In mice, chlorpyrifos increases intestinal permeability by altering the zonule occludens-1 with entry of lipopolysaccharides and a subclinical inflammatory state[22]. These mice gain more weight at the expense of fat and have lower insulin sensitivity, suggesting that pesticides may contribute to diseases associated with inflammation, especially obesity[23]. The Environmental Protection Agency of the United States of America (EPA) banned its sale for domestic use in 2000[24], but was until August 2021, that finally EPA issued a final rule banning all food uses of chlorpyrifos[25].

OP pesticides disrupt the basic cellular machinery that controls neuronal maturation and alters the formation of axons and synapses in early stages of brain development in mice and humans, which can produce subsequent behavioral and cognitive alterations[26]. Exposure even at low levels, *in utero* or during childhood, adversely affects fetal growth, and neurodevelopment[27,28]. NBs exposed *in utero* have low birth weight, decreased stature, and a smaller head circumference compared to unexposed children. High prenatal urinary concentration in the mother has been associated with increased abnormal reflexes in the newborn[29].

Illegal domestic application of methyl parathion has been associated with poor short-term memory performance, impaired attention in children, and behavior problems[30]. In mice, pre and postnatal experimental exposure to Malathion conditions alterations in the activity of catalase, glutathione superoxide dismutase, glutathione-S transferase, and glutathione peroxidase; causes increased peroxidation of lipid membranes and an anxiogenic state and poor social interaction in exposed pups[31]. Exposed animals can develop hyperinsulinemia, hyperlipidemia, and obesity[32].

In a study of 536 women and 254 of their children, with follow-up for 3 years, the proportion of children with delay in the high-exposure group, compared to the low-exposure group, was 5 times higher for the psychomotor development index and 2.4 times higher for the

mental development index[28]. Prenatal exposure to OP has been associated with ADHD and other neurological disorders in children, especially men[33].

Carbamate type insecticides

Carbamates are used as insecticides, herbicides and fungicides[34] and also act as acetylcholinesterase (ACE) inhibitors. The N-methyl carbamate that is derived from carbamic acid causes carbamylation of ACE at the neuronal synapse and at the neuromuscular junctions[35]. Unlike OP, carbamate-inhibited ACE recovers spontaneously after several minutes.

Among the insecticides in this group, aldicarb, carbofuran, thiocarbamide, carbaryl, methiocarb, diethofencarb, fenobucarb, oxamyl, methomyl, pirimicarb, propoxur, and trimetacarb stand out. In the production of carbamate pesticides such as carbaryl, aldicarb, methomyl and carbofuran, intermediate chemicals such as methyl isocyanate or MIC (CH3N = C = O) are formed. Isocyanates are aliphatic or aromatic compounds with a double bond. MIC is capable of interacting with DNA and inducing malignancies in murine models[36]. The Bhopal population suffered severe exposure to MIC in 1984. These individuals showed Robertsonian translocations, on acrocentric chromosomes 13 and 21, and on chromosomes 5, 9, 11, 14, and 16[37].

Exposure to MIC in mice reduced progesterone levels in pregnant females with subsequent loss of the product[38]. In MIC exposed ovarian epithelial cell lines, early loss of TRF2 protein was observed in relation to telomeric dysfunction with premature senescence and microsatellite instability[39]. There are reports from the 70's, which describe changes in the electroencephalogram of perinatal rats exposed *in utero* to propoxur[40]. Recently, a study in rats exposed to carbofuran, *in utero*, showed that it hinders the development of oligodendrocyte progenitor cells and their differentiation in the hippocampus, both *in vitro* and *in vivo*. This is associated with abnormal expression of genes and proteins that participate in the regulation of oligodendrocyte development and the induction of apoptosis. Therefore carbofuran has a deleterious effect on myelin compaction at the hippocampus level leading to cognitive defects in exposed rats[41].

In a study carried out in children (8-15 years old) with attention-deficit/hyperactivity disorder (ADHD) and controls, children with ADHD showed by magnetic resonance images, alterations in the compaction of myelin mainly in the corpus callosum and the main pathways of the left hemisphere and these alterations were directly related to the severity of ADHD[42]. It would be interesting to analyze whether there is a relationship between exposure in utero to these pesticides and ADHD.

Pyrethroid insecticides

From pyrethrum (partially refined extract of chrysanthemum flower), pyrethrins with insecticidal action are obtained; pyrethroids are synthetic compounds derived from the pyrethrin molecule. They interfere with ionic transport in the axonal membrane, acting on the sodium and potassium channels. These events produce altered neuronal function, which causes repetitive nerve discharges that result in paralysis and death[43].

Pyrethroid insecticides widely used in the domestic environment have a high specific toxicity for insects; however, at higher doses they also cause neurotoxicity in mammals, especially at critical stages in neurological development, including the intrauterine stage and the first postnatal years[44].

In a Mexican cohort of 187 newborn children, a metabolite of pyrethroids (3-phenoxybenzoic acid) was detected in 46% of maternal urine samples. The children of the participants with the medium and high ranges of 3-phenoxybenzoic acid concentration had a lower score on the mental development index compared to the low range[45].

Phenylpyrazoles

Fipronil is the main representative of this group and as an ectoparasiticide is the best-selling flea killer in the world. It blocks the channels of γ-aminobutyric acid (GABA) and glutamate (GluC). Intoxicated insects develop a state of hyperexcitation, both nervous and muscular; it has a high affinity for the GABA receptor of insects and shows effects on GluCs, which do not exist in mammals; blocks GABA-regulated chlorine channels.

A Korean research group reported the results of exposure to fipronil and its metabolite, fipronil sulfone in utero, in 59 mother-child pairs and in 51 biological parents. Fipronil sulfone was detected in the serum of mothers, fathers and in umbilical cord blood, but not fipronil itself. Fipronil sulfone levels were related directly to the mother's body mass index, prior to pregnancy, and inversely with the levels of T3 in umbilical cord blood and the Apgar score at 5 min. The fact of finding it in both parents suggested residential exposure[46].

On the other hand, butylene fipronil, which acts at the GABA receptor, induces cytotoxicity in murine

PC12 nerve cells, which lack the GABA receptor. This cytotoxic action is mediated by induction of cell arrest in the G0/G1 phase and apoptosis. It also induces generation of reactive oxygen species, activation of SP16-CDK4/6-cyclin D1 and of the mitochondrial apoptotic pathway[47]. In 2017, millions of chicken eggs contaminated with fipronil were recalled from the European market.

Neonicotinoids

They act selectively and irreversibly on nicotinic acetylcholine receptors in insect nerve cells, paralyzing them and causing their death. The main neonicotinoids for use in pets and livestock are dinotefuran, imidacloprid, nitenpyram, and thiamethoxam. Imidacloprid and fipronil have been linked to progressive bee mortality and reduced pollination, with consequent damage to agriculture. Some agricultural products with these active substances have been withdrawn from the market in the USA and France.

A study in which mice received orally, acetamiprid and imidacloprid in the early postnatal period, showed a reduction in neurogenesis with an increase in type M1 microglia in the hippocampal dentate gyrus[48].

In utero and early postnatal exposures to imidacloprid resulted in reduced fecundity and body weight in adult male mice, but not in females. A decrease in the triglyceride level, an increase in motor activity and a decrease in aggressive behavior were found in comparison with controls. This suggests that lasting changes in behavior and brain function can be induced[49].

These findings are worrying and justify the study of the effects of neonicotinoids on other mammalian species, including humans.

Glyphosate

Glyphosate (N-phosphono-methyl-glycine) is the most widely used herbicide worldwide. Aminomethylphosphonic acid is one of its main metabolites. Glyphosate inhibits the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) that only plants and some microorganisms synthesize, so it was initially considered not toxic to mammals[50]. However, even low doses of glyphosate (1/5000 dilutions) affected the development of *Xenopus laevis* embryos, with alterations in the development of the cephalic and neural crest and shortening of the anteroposterior axis[51,52].

In a murine model, perinatal exposure caused a long-term epigenetic disruption of the uterine ERα gene, which could be associated with implantation failure induced by this substance[50].

In rats, neonatal exposure altered the neonatal and prepubertal uterine development, with an increase in the frequency of epithelial hyperplasia and the thickness of the myometrium, which could favor fertility disorders and the development of neoplasms[53].

Also in rats, low-dose perinatal exposure affected female reproductive performance, induced fetal growth retardation and structural congenital abnormalities in F2 offspring (conjoined fetuses and abnormally developed limbs)[54].

Chronic exposure during pregnancy and lactation in rats produced neurobehavioral alterations in the offspring with early onset of the cliff aversion reflex, early opening of the auditory canal, decreased locomotor activity, and anxiety levels[55]. Even chronic exposure to ultra-low doses can cause histologically and transcriptomic confirmed liver and kidney damage[56].

In female lambs exposed from day 1 to 14 postnatally, functional alterations of the ovarian follicles with increased proliferation of theca and granulosa cells and decreased expression of follicle-stimulating hormone receptor mRNA were observed on day 45, as well as decreased uterine cell proliferation, but without alterations in histomorphology or gene expression[57].

On the other hand, glyphosate inhibits EPSPS of the beneficial intestinal microbiota, since *Clostridium* spp. and Salmonella strains are resistant to Glyphosate. Therefore, it can cause dysbiosis. The abnormal growth of clostridia produces harmful metabolites in the brain, which can affect neurological development[58]. Although some authors argue that adjuvants and accompanying substances in formulations are responsible for toxicity, the truth is that glyphosate is not sold or used in its pure form. Targeted studies are required in exposed human populations.

Organic tin compounds (organotin)

They are used in the manufacture of pesticides and being endocrine disruptors, they are capable of decreasing the size of the testis and epididymis, as well as the sperm count. On the other hand, in females, they decrease the weight of the uterus and ovaries, prevent fetal implantation and reduce pregnancy rates. Uterine exposure produces accumulation of lipid droplets in the cytoplasm of Sertoli cells and in the gonocytes of male products, and induces precocious puberty in females[59].

Nanoparticles (NP) as insecticides

NP are able to alter cellular metabolism, causing cytotoxicity and interfering with specific cellular functions[60]. Recently the use of NP in aqueous suspensions, as insecticides (green-capped NP) have opened the door for a new area of research, the impact of these NP on mammals, and especially on humans. Exposure to silver NP has been shown to be toxic and led to morphological abnormalities and DNA damages on invertebrate and vertebrate organisms[61]. When D. Melanogaster was exposed orally, to sub-lethal doses of silver NP, accumulation of reactive oxygen species in the fly tissues led to ROS-mediated apoptosis, DNA damage, and autophagy[62].

Polystyrene NP can interact with drug-metabolizing cytochrome P450 isoenzymes, CYP3A4, CYP2D6, CYP2C9, and CYP2A1[63].

NP can reach the organs through systemic circulation, and depending on their size, shape, and chemical reactivity, they can cross the placenta and reach the embryo or fetus; also, they are able to cross the blood-brain barrier, or they can reach the brain through axonal transport along the olfactory nerve[64]. Therefore, the use of nanomaterials should be investigated from the point of view of toxicity in mammals, before exposing humans and other species to insecticides that contain them.

Combination of pesticides and various disorders

The analysis of the umbilical cord blood of 336 newborn children whose mothers lived in an agricultural area in China, showed that the children had 15 different pesticides on average, with a maximum of 48. It was observed that those born in summer had a greater number of pesticides than those born in winter[65].

A case-control study in an agricultural area of California, in the United States, showed that prenatal exposure to pesticides within 2000 m or less of agricultural fields was associated with an increase in cases of autism spectrum disorders: glyphosate (RM 1.16), chlorpyrifos (RM 1.13), diazinon (RM 1.11), malathion (RM 1.11), avermectin (RM 1.12), and permethrin (RM 1.10); however, for autism with obvious intellectual disability, the odds ratio was 30% higher. Exposure during the 1st year of postnatal life also played an important role in the development of autism[66].

Martinez and collaborators demonstrated in Mexico the presence of persistent, brominated and chlorinated organic compounds in breast milk, including polychlorinated biphenyl-type dioxins in women from urban areas, showing exposure to multiple POPs through lactation[67].

Carbamates are systemically absorbed and trans-placentally transferred to the fetus. Bendiocarb in individuals exposed during pregnancy produces changes in fetal immune cells, including dose-dependent decrease in regulatory-CD4T cells, increased cytokine production and inhibition of antigen-driven proliferation and may affects the response to vaccination in infancy[68].

The exposome is the totality of environmental exposures from conception to death[69]. The same subject is exposed to many potentially toxic substances, which are added or enhanced to translate into specific pathologies. In each region, the weight of a pollutant may be greater than in another and having an inclusive vision helps to establish priorities for remediation and prevention.

Conclusions

The available evidence shows that in utero exposure to pesticides may produce short and long-term systemic alterations, and damage to brain and endocrine development, partially explaining the increase in neurodevelopmental disorders, such as autism. At Mexico, studies of both, mother-child pesticide detection and follow-up, are scarce. Immediate preventive actions are essential.

In residential areas is required to use mechanical containment measures for mosquitoes (mosquito nets) and adequate garbage disposal to avoid pests. The use of insecticides is not recommended if there are children or pregnant women; housing less than 2000 m from agricultural fields is not advisable. The intake of pesticide residues should be reduced by washing and peeling fruits and vegetables. Efficient public policies are required to regulate the distribution, sale and use of pesticides in our country and to educate the population about the adequate use of these substances.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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