Literature Review

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EXPOSURE TO TOXIC AGROCHEMICALS AND DEVELOPMENT OF CONGENITAL MALFORMATIONS: A SCOPING REVIEW

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ABSTRACT

Objective: to assess whether maternal and paternal exposure to toxic agrochemicals throughout life causes congenital malformations.
Method: a scoping review was carried out on the PUBMED, CINAHL, EBSCO, MEDLINE, LILACS, SciELO, BDENF, Web of Science and ATHENA databases between August and September 2019 and updated in December 2020. A cohort and case control study were included, which addressed the effects of parents' exposure throughout their lives to toxic agrochemicals which caused congenital malformation outcomes.
Results: the review covered 32 studies published between 2005 and 2020. The main malformations presented are related to the reproductive system, nervous system, musculoskeletal system, transverse limb deficiencies, digestive system and other malformations such as fetal growth restrictions, cleft palate and congenital heart disease. The most investigated toxic agrochemicals in the studies were the herbicides represented by atrazine.
Conclusion: maternal and paternal exposure to toxic agrochemicals can be associated with greater chances of children being born with congenital malformations, especially those related to the male reproductive system.

DESCRIPTORS: Congenital, hereditary and neonatal diseases and anomalies. Toxic agrochemicals. Pesticides. Review.

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EXPOSIÇÃO AOS AGROTÓXICOS E O DESENVOLVIMENTO DE MALFORMAÇÕES CONGÊNITAS: REVISÃO DE ESCOPO

RESUMO

Objetivo: avaliar se a exposição materna e paterna aos agrotóxicos ao longo da sua vida causa malformação congênita.
Método: realizou-se uma revisão de escopo nas bases PUBMED, CINAHL, EBSCO, MEDLINE, LILACS, SciELO, BDENF, *Web of Science* e ATHENA entre agosto e setembro de 2019 e atualizadas em dezembro de 2020. Incluíram-se estudo de coorte e caso controle que abordaram os efeitos da exposição dos pais ao longo da sua vida aos agrotóxicos e ocasionaram desfechos de malformação congênitas.
Resultados: a revisão abrangeu 32 estudos publicados entre 2005 e 2020. As principais malformações apresentadas estão relacionadas ao aparelho reprodutor; sistema nervoso, sistema musculoesquelético, deficiências transversais dos membros, sistema digestório e outras malformações como as restrições do crescimento fetal, fenda palatina e doenças cardíacas congênitas. Os agrotóxicos mais investigados nos estudos foram os herbicidas representados pela atrazina.
Conclusão: a exposição materna e paterna a agrotóxicos pode estar associada a maiores chances do nascimento de crianças que apresentem malformações congênitas, principalmente às malformações relacionadas ao sistema reprodutor masculino.

DESCRITORES: Doenças e anormalidades congênitas, hereditárias e neonatais. Agrotóxicos. Pesticidas. Revisão.

EXPOSICIÓN A AGROTÓXICOS Y DESARROLLO MALFORMACIONES CONGÉNITAS: REVISIÓN DE ALCANCE

RESUMEN

Objetivo: evaluar si la exposición materna y paterna a los agrotóxicos a lo largo de la vida causa malformaciones congénitas.
Método: se realizó una revisión de alcance en las siguientes bases de datos: PUBMED, CINAHL, EBSCO, MEDLINE, LILACS, SciELO, BDENF, *Web of Science* y ATHENA, entre agosto y septiembre de 2019, actualizada en diciembre de 2020. Se incluyeron estudios de cohorte y de casos control que abordaban los efectos de la exposición a lo largo de la vida de los padres a agrotóxicos que ocasionaron resultados de malformaciones congénitas.
Resultados: la revisión abarcó 32 estudios publicados entre 2005 y 2020. Las principales malformaciones que se hicieron presentes están relacionadas al aparato reproductor, al sistema nervioso, al sistema musculoesquelético, a deficiencias transversales de las extremidades y al sistema digestivo, además de otras malformaciones como ser restricciones en el crecimiento fetal, fisura palatina y enfermedades cardíacas congénitas. Los agrotóxicos más investigados en los estudios fueron los herbicidas, representados por la atrazina.
Conclusión: la exposición materna y paterna a los agrotóxicos puede estar asociada a mayores probabilidades de que los hijos nazcan con malformaciones congénitas, principalmente las relacionadas a aparato reproductor masculino.

DESCRIPTORES: Enfermedades y anomalías congénitas, hereditarias y neonatales. Agrotóxicos. Pesticidas. Revisión.

INTRODUCTION

Diverse scientific evidence indicates that the environment can be related to the occurrence of congenital malformations such as anomaly of the limbs, orofacial fissures and failure in male urogenital development, in addition to spontaneous abortions, which can be accentuated when the parents are exposed to toxic agrochemicals. These congenital malformations are included in the list of congenital anomalies that can be defined as structural or functional changes that occur during intrauterine life[1–2]. Nearly 50% of the congenital anomalies are not linked to a specific conditioning factor. However, there are known causes that can be related, such as socioeconomic, demographic and environmental factors, infections, genetic factors and maternal nutritional status[3].

Although some of the active ingredients of the agrochemicals are classified as moderately or slightly toxic, based on their acute effects, it is necessary to consider that the chronic effects can occur in months, years or even decades after exposure, manifesting in several diseases, such as tumors, congenital malformations, and endocrine, neurological and mental disorders[4]. In the vast areas of monocultures, agrochemicals are sprayed by means of tractors and airplanes on the crops, affecting not only the "pests" in the plantations, but also the soil, surface water, air, rain and food, as well as workers, surrounding residents and animals[5].

The Brazil is the largest consumer of toxic agrochemicals in the world[5]. Based on this problem, the objective of this study was to assess whether maternal and paternal exposure to toxic agrochemicals throughout the life causes congenital malformations. This research included 32 studies, the quality of the evidence was considered as level 4, that is, with evidence from well-designed cohort and case control studies[6]. Among the papers selected in the research, there are 12 research studies carried out in the USA and 3 in Brazil, showing anomalies related to the reproductive system (hypospadias, cryptochidism and micropenis)[7–17], to the nervous system[12,18–24] and other malformations[25–35,36–38].

METHOD

A scoping review was carried out following the method recommended by the Joanna Briggs Institute[39] according to the theoretical framework proposed by Arksey and O'Malley[40]. This type of research consists of an exploratory review aimed at mapping, in the scientific production, relevant studies in a given area, following the steps of the scoping review: 1. Identification of the research question; 2. Identification of relevant studies; 3. Selection of studies; 4. Data extraction; and 5. Summary and reporting of results. 6. The sixth consultation step, considered optional, was not used in this study[39,41].

The research question for this study was elaborated according to the PCC[39] mnemonic combination (P: *Population* – mother or father exposed to toxic agrochemicals; C: *Concept* – congenital malformation; C: *Context* – the world), with the following guiding question being established: Is maternal and paternal exposure to toxic agrochemicals throughout life associated with congenital malformations in children?

One of the data sources consulted was the Virtual Health Library, which included the following databases: International Literature in Health Science (MEDLINE), *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (LILACS), *Base de dados da Enfermagem* (BDENF), Cumulative Index to Nursing and Allied Health Literature (CINAHL). The searches for the publications indexed in the virtual libraries included: National Library of Medicine (PUBMED), EBSCO, Scientific Electronic Library Online (SciELO), Web of Science and *Université Paris-Est Créteil Val de Marne* (ATHENA. In order to guarantee research integrity, the researchers reviewed the reference lists of the selected articles to identify other possible relevant studies.

The following controlled terminology descriptors recommended by the Medical Subject Headings (MeSH) and/or the Health Sciences Descriptors (*Descritores em Ciências da Saúde*, DeCS) were

selected: *Congenital, Hereditary, and Neonatal Diseases* and *Abnormalities; Congenital diseases; Congenital malformations; Neonatal Diseases; Agrochemicals; Pesticides*. All of these terms were searched for in their equivalences in Spanish, French and Portuguese. The search strategy used followed the definition of each corresponding database. The Boolean *AND* operator was used with the following combinations: "*Congenital, Hereditary, and Neonatal Diseases* and *Abnormalities" AND Pesticides; Pesticides AND "congenital anomalies"; Pesticides AND "congenital malformations"; Pesticides AND "neonatal diseases"*; "*Congenital, Hereditary, and Neonatal Diseases* and *Abnormalities" AND Agrochemicals; Agrochemicals AND "congenital anomalies"; Agrochemicals AND "congenital malformations"; Agrochemicals AND "neonatal diseases".* The searches were performed between August and September 2019 and updated in December 2020.

The refinement of the articles found was based on the eligibility criteria. The pre-established inclusion criteria were as follows: cohort and/or case control study, published in Portuguese, Spanish, English and French, which studied the effects of maternal and/or paternal exposure to toxic agrochemicals throughout life on congenital malformations. No time limit was established and duplicate studies, reviews, meta-analyses, theses, dissertations and books were excluded.

In addition to this, to systematize the process of inclusion of the studies, the PRISMA Extension for Scoping Reviews[42] methodology was chosen. The studies were pre-selected from reading the titles and abstracts, and the final sample was reached based on reading the articles in full, according to the flowchart shown in Figure 1.

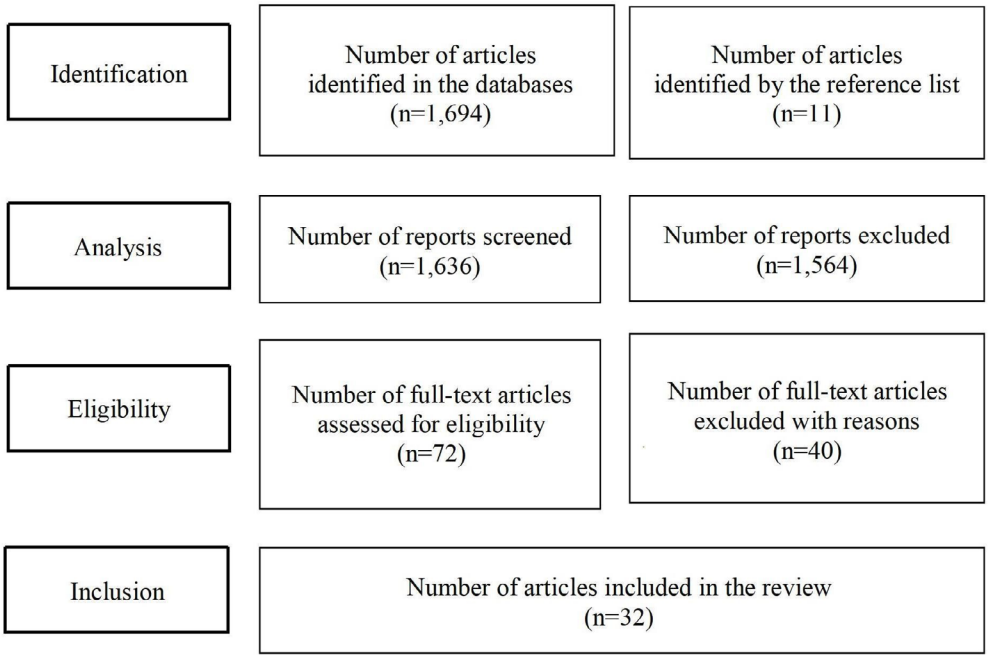

Figure 1 – Flowchart of the selection of studies that compose the research according to PRISMA ScR[42]

In the data extraction stage, an instrument structured in Microsoft Excel was used, which allowed mapping the essential elements of the studies, such as author, year of publication, country where the study was conducted, journal, type of study, description of the sample, outcome and the level of evidence of the study[6]. The data were extracted in a double-independent fashion and, in case of dissent, a third reviewer was contacted. In this way, in order to present an overview of the entire material, the presentation of the results was elaborated in a chart with the main characteristics of the studies, organizing a numerical description of the results and a thematic description according to the nature of the research.

RESULTS

After the process of evaluation and selection of articles, 32 studies were included in the scoping review[7–38]. These were published between 2005 and 2018 (Chart 1). The results were presented with a description of the characteristics of the studies, and the main congenital malformations evidenced from the selected studies and the most frequently identified toxic agrochemicals in the studies are described.

Chart 1 – Characterization of the articles according to author, year of publication, country where the study was conducted, type of study, sample, assessed outcome and level of evidence. Porto Alegre, RS, Brazil, 2020. (n=32)

Country	Type of study	Description of the sample	Assessed outcome	Evidence level
France[10]	cohort	1,068 pregnant women	Malformations of the reproductive system	IV
Brazil[8]	cohort	2710 male born	Cryptorchidism, hypospadias and micropenis	IV
France[27]	cohort	579 pregnant women	Fetal growth restriction	IV
USA[19]	control case	92 cases and 56 controls	Holoprosencephaly	IV
USA[11]	control case	165 cases and 165 controls	Cryptorchidism	IV
USA[24]	control case	291 cases for 2,745 controls	Spina bifida	IV
USA[17]	control case	343 cases of hypospadias and 1,422 male controls	Hypospadias	IV
USA[29]	control case	372 cases for 3,720 controls	Choanal atresia or stenosis	IV
USA[26]	control case	871 cases and 2,857 controls	Craniosynostosis, gastroschisis, diaphragmatic hernia and transverse limb deficiencies	IV
USA[21]	control case	502 cases and 2950 controls	Neural tube defects	IV
USA[23]	control case	367 cases and 785 controls	Anencephaly, spina bifida with and without cleft palate	IV
USA[32]	control case	156 cases for 785 controls	Gastroschisis	IV
USA[15]	control case	646 cases and 1493 controls	Hypospadias	IV
USA[7]	control case	20 cases and 28 controls	Hypospadias	IV
USA[33]	control case	4 controls for one case, with 805 cases for 3,616 controls	Gastroschisis and abdominal wall defects	IV
Brazil[25]	control case	219 cases for 862 controls	Congenital malformations	IV
Brazil[38]	control case	137 cases for 274 controls	<5 years with congenital malformations	IV
Brazil and India[20]	control case	35 cases 35 controls (mother and baby)	Congenital anomaly due to neural tube defects	IV
India[16]	control case	80 boys with hypospadias and 120 controls	Hypospadias	IV
India[31]	control case	cases of fetal growth restriction: 50; control: 50	Fetal growth restriction	IV

Chart 1 – Cont.

Country	Type of study	Description of the sample	Assessed outcome	Evidence level
France[14]	control case	225 cases of hypospadias and 225 controls	Hypospadias	IV
Netherlands[36]	control case	1174 cases and 5602 controls	Congenital heart diseases	IV
Netherlands[37]	control case	387 cases were defined as non-syndromic clefts,1,135 chromosomal and 4,352 malformed non-chromosomal controls	Cleft lip	IV
Mexico[13]	control case	Mother-baby binomial Newborns diagnosed with cryptorchidism (n=41). 41 controls with deciduous testicles	Cryptorchidism	IV
Mexico[18]	control case	184 case women and 225 control women	Neural tube defects	IV
Ethiopia[35]	control case	136 cases and 273 control	Congenital malformations	IV
Hungary[34]	control case	2,263 cases and 6,789 controls	Congenital heart diseases	IV
Paraguay[30]	control case	66 cases and 66 controls	Congenital malformations	IV
Greece[12]	control case	29 children with hypospadias and 49 fathers	Hypospadias	IV
Egypt[28]	control case	242 cases of congenital malformations and 270 controls	Congenital malformations	IV
China[22]	control case	80 fetuses or newborns with NTDs, while the controls were 50 healthy newborns	Neural tube defects (NTDs)	
Italy[9]	control case	80 mothers with babies with hypospadias and 80 mothers with healthy controls	Hypospadias	IV

Description of the studies

The largest number of publications was in the years 2014[12,21,23–25,29,32] (n=7), 2020[10–11,19,34–36] (n=6), 2011[8,15,16,22,27–28] (n=6) and in 2010[7,9,13,18,33] (n=5). As for the country where the studies were developed, most were from the United States[7,11,15,17,19,21,23–24,26,29,32], (n=10) followed by studies in Brazil[2,25,38], (n=3), France[10,14,27] (n=3), India[20,31,16] (n=3) and Mexico[13,18] (n=2) (Chart 1). For being an inclusion criterion, most of the studies were case-control studies[7–8,10,26–38] (n=29) and only three studies were cohort[8,10,27] (n=3) (Chart 1). In the 32 studies, the quality of the evidence was considered level 4, that is, with evidence from well-designed cohort and case control studies[6].

Below are four categories generated to meet the study objective: malformations related to the reproductive system, in which the main malformation found was hypospadias, followed by cryptorchidism and micropenis; malformations related to the nervous system such as neural tube defects (anencephaly, spina bifida), cleft palate and other malformations, such as fetal growth, digestive and musculoskeletal system restrictions, such as gastroschisis, choanal stenosis, transverse limb defects, cleft palate were also found. A fourth category with the toxic agrochemicals most frequently identified in the studies was also established.

Malformations related to the reproductive system

Among the 32 studies analyzed, twelve demonstrated an association between exposure to toxic agrochemicals and the occurrence of outcomes related to the reproductive system. Of these studies, hypospadias appeared more frequently (n=8)[7–9,12,14–17], followed by cryptorchidism (n=3)[8,11,13] and micropenis (n=1)[8]. The association between prenatal exposure to organochlorines and the occurrence of cryptorchidism was found through a case-control study. In addition to this, organophosphate levels in serum lipids of mother with children with cryptorchidism were analyzed, as well as in a control group of mothers of children with descending testicles; and the newborns' umbilical cord blood samples were studied. The levels of organochlorine metabolites were found in greater amount among mothers of newborns with cryptorchidism than among mothers of children with testicular descent: OR=1.79, 95% CI (1.34 - 2.24)[13].

According to a cohort study carried out in northeastern Brazil, the prevalence of newborns diagnosed with micropenis with maternal and paternal exposure to household pesticides was investigated. Exposure was assessed using a questionnaire, testosterone analysis and molecular gene analysis. Of the newborns monitored, 56 malformations were identified, with cryptorchidism (n=23), hypospadias (n=15) and micropenis (n=18). Most of the parents of these newborns reported exposure to toxic agrochemicals during paid and unpaid work, with 80.36% of the mothers and 58.63% of the fathers. This study indicated that exposure to disruptors of the endocrine system before and during pregnancy indicates that fetal contamination can be a risk factor for the development of male external genital malformation[8]. In the case control study carried out in Ethiopia, women exposed to pesticides during pregnancy were twice as prone to having children with congenital malformations (OR=3.19; 95% CI=1.31, 10.96)[35].

In a study carried out to assess the association between consumption of atrazine in water and hypospadias through a population-based control case, exposure to atrazine was measured using a maternal questionnaire on water and drinking water consumption (OR=1.00; 95% CI), estimating the total maternal consumption of atrazine (OR=1.02; 95% CI). In this study, the association between hypospadias and daily maternal exposure to atrazine during the critical window of genitourinary development was weak or null[17].

When associated with exposure to organophosphates and hypospadias, through the analysis of organophosphate metabolites in the blood and hair collected from children with hypospadias and their parents, it was verified that they had higher values than the general population, suggesting that exposure to organophosphate and organochlorine pesticides can be a potential risk factor for hypospadias[12].

A study[9] verified the association between maternal environmental exposures to endocrine disrupting toxic agrochemicals and the occurrence of births diagnosed with hypospadias. Through a control case, an association was verified between maternal exposure to a class of endocrine disrupters (OR=2.44; 95% CI) and (OR=4.11; 95% CI) for more than one class. The high plasma concentration of hexachlorobenzene (OR=2.44) can be related to the development of hypospadias in the newborn[9].

Regarding exposure to organochlorines, scholars[16] conducted a case control study assessing the risk of hypospadias. The evaluation took place using the blood samples collected from the children to assess the levels of organochlorines and polymorphism in the CYP1A1, GSTM1 and GSTT1 genes. The results showed that exposure to high levels of organochlorines increased the risk of developing hypospadias[16]. In 2005, Morera et al[14]. conducted a case-control study, with 225 cases (n=225) and 225 controls (n=225), to assess exposure to pesticides during the prenatal period and the occurrence of hypospadias. Thus, they concluded that exposure to toxic agrochemicals increased the chances of developing hypospadias in the newborn (OR=1.54; CI=0.83-2.84)[14].

However, according to the other studies[7,15], it was not possible to identify an association between exposure to toxic agrochemicals and the risk of hypospadias. Onde of the studies[15] concluded that occupational exposure to fungicides, insecticides and herbicides in the maternal periconceptional period was not associated with an increased risk of hypospadias (OR=0.78; 95% CI=0.61-1.01), while other authors[7] showed no association between maternal exposure to toxic agrochemicals and hypospadias, as they found no statistically significant results when studying maternal exposure to brominated, polychlorinated biphenyls and other pesticides and the occurrence of hypospadias in their children.

In addition to this, in the case control study[11], whose objective was to analyze maternal exposure in early pregnancy to organochlorines and an association with the risk of cryptorchidism, no statistically significant associations were found. As was the case in the cohort carried out by other authors[10], where no association was also found between the use of this input and the occurrence of malformations related to the reproductive system.

Malformations related to the nervous system

Of the studies analyzed, seven[18–24] showed an association between exposure to toxic agrochemicals and the occurrence of outcomes related to the Central Nervous System (CNS) in newborns. The association between maternal exposure to organochlorines and neural tube defects in newborns was verified through a case-control study. Blood levels of dichlorodiphenyldichlorethylene (DDE), total hexachlorocyclohexane (t-HCH) and endosulfan in mothers in the case group and in newborns with neural tube defects were significantly higher. Mothers who had children with NTDs were 11.3 times more likely to have DDE levels above the median concentration of the control group[20].

In China, conducted a study[22] to investigate the association between the occurrence of neural tube defects in newborns due to the exposure of pregnant women to toxic agrochemicals. The levels of agrochemicals were analyzed in placentas of pregnant women who had children with neural tube defects. Placental concentrations of polycyclic aromatic hydrocarbons (PAHs), organochlorine pesticides, polychlorinated biphenyls, dichlorodiphenyltrichloroethane (DDT) and hexachlorocyclohexane (HCH) were significantly higher in the placentas with newborn NTD outcome. Thus, the risk for increased PAH levels was 4.52 times greater (95% CI=2.10–9.74) for any neural tube defect, in addition to 5.84 (95% CI=2.28-14.96) and 3.71 times (95% CI=1.57–8.79) of increased risk of anencephaly and spina bifida, respectively[22].

Authors[21] analyzed the occurrence of NTDs in newborns of pregnant women who were exposed to toxic agrochemicals in the preconception and up to two months after conception. There was a positive, although not significant, association for the combined classes of insecticides and herbicides referring all types of NTDs. As for the joint classes of insecticides, herbicides and fungicides, there was a significant association for all NTD cases, with greater occurrence of anencephaly and encephalocele[21].

In relation to other malformations related to the nervous system, an increased risk of newborns having anencephaly, spina bifida, cleft lip without or with cleft palate or cleft palate was identified in pregnant women with early exposition to toxic agrochemicals. The estimate was made based on residential proximity in places with application of agrochemicals. Petroleum derivatives contributed to the increase in the occurrence of anencephaly; herbicides, specifically hydroxybenzonitrile, for spina bifida; and 2,6-dinitroaniline herbicides and dithiocarbamate methyl isothiocyanate, for cleft lip or palate. However, none of the 26 chemical products analyzed had an Odds Ratios with an associated confidence interval, although this environmental factor may be a condition for the onset of these diseases[23].

In a case-control study conducted in Mexico, authors[18] evaluated the exposure of pregnant women to toxic agrochemicals and the emergence of defects in the neural tube of their newborns.

According to the authors, interviews were conducted with the women for research on education, smoking and folate use. The women who used some chemical substance in their backyards were twice as likely to have newborns with neural tube defects (95% CI=1.2–3.1) when compared to women without these reported exposures. In addition to this, the women in the case group also reported living less than 0.35 km from cultivated fields than women in the control group (OR=3.6; 95% CI=1.7-7.6). Thus, the information regarding exposure to toxic agrochemicals increases the risk for the emergence of defects in the neural tube, especially of anencephaly in newborns[50].

A study carried out in the USA identified an increased risk for the development of holoprosencephaly in children whose mothers were exposed to pesticides during the pre-conception period or during pregnancy (OR=2.60, 95% CI=0.84-8.68). No association was found for occupational exposures to pesticides during pregnancy (OR=1.15, 95% CI=0.11-11.42)[19].

Other malformations

In addition to malformations related to the reproductive and nervous systems, articles were also found referring to malformations related to fetal growth restrictions (n= 2)[27,31], to the digestive system (n=3)[29,32–33], to the musculoskeletal system (n=1)[26], to the circulatory system (n=2)[34,36], and congenital anomalies in general (n=5)[25,27,30,35,37].

In France in 2011, authors[27] conducted a study between 2012 and 2016, using urinary biomarkers to detect exposure to atrazine before the 19th gestational week and its possible adverse events for pregnancy. As a result, they found metabolites of this herbicide in between 20% and 40% of the samples, and the presence of these metabolites was positively associated with fetal growth restriction and small head circumference according to gender and gestational age[27].

Also on fetal growth restriction, authors[31] produced a study that sought to identify genes present in pregnant women with fetal growth restriction that interact with organochlorines, looking for the cause of the restriction. For this, the study used blood samples from the mother and the umbilical cord. Among these samples, significantly higher levels of organochlorines were found in the cases when compared to the controls[31].

Regarding the digestive system, scholars[33], conducted a case-control study to determine periconceptional exposure to toxic agrochemicals, finding an association between the development of gastroschisis and the distance of the maternal residence from places with high exposure to pesticides. As a result, gastroschisis was positively associated with those who lived <25 km from places with high exposure (OR=1.6). However, authors[32] verified that gastroschisis was also positively related to maternal occupational exposure to insecticides, herbicides and fungicides (OR=1.88; 95% CI). However, contrary to the results found by scholars others[33], the study carried out in California[32] did not identify any association between exposure to triazines and gastroschisis or a standard profile related to women having children with gastroschisis.

The study carried out in the USA[29], sought to identify the residential exposure of women to toxic agrochemicals and its relationship with choanal atresia or stenosis; it was found that the children of mothers with high exposure accordingly had an increase in choanal atresia or stenosis (OR=1.79; 95% CI)[29]. In relation to the occurrence of cleft palate and maternal occupational exposure to solvents and pesticides, a case-control study showed that maternal exposure to pesticides significantly increased the chance of developing cleft palate (OR=1.7; 95% CI)[37].

In Paraguay, a study[30] sought to determine the association between the prenatal risk factors and the occurrence of congenital anomalies. An association was observed between malformations with distance <1 km of the residence from fumigated fields (OR=3.75; 95% CI) and direct maternal exposure to pesticides (OR=4.51; 95% CI)[30].

In relation to congenital malformations in general, in a hospital in Mato Grosso do Sul, a Brazilian state that has agribusiness as the basis of its economy, one study[38] investigated the association between parental exposure to pesticides and the occurrence of congenital malformations in children. Thus, a positive association was observed between exposure to toxic agrochemicals and the occurrence of congenital anomalies, associated with low maternal education (OR=8.40; 95% CI)[38]. Another Brazilian study carried out in Mato Grosso do Sul[25] sought to analyze the occurrence of congenital anomalies in the municipalities with the greatest exposure to toxic agrochemicals. Thus, significant associations were observed related to exposure to agrochemicals in the post-fertilization period (OR=1.66; 95% CI and OR=1.88; 95% CI) and in the periconceptional period (OR=2.04; 95% CI).

In relation to paternal exposure to toxic agrochemicals and the occurrence of congenital anomalies, a case-control study[28] analyzed that certain occupations during the periconceptional period can increase the chances of the occurrence of congenital anomalies. Parental occupation with pesticides, solvents, solder smoke, lead, working with video displays and computer monitors was studied, with a verified greater chance of having children with congenital anomalies in occupations with exposure to pesticides (OR=3.42; 95%CI=1.97-5.92), solvents (OR=5.63, 95% CI=2.77-11.42) and solder smoke (OR=2.98; 95% CI=0.99-8.54), in addition to inbreeding, which was considered a risk factor (OR=1.91, 95% CI=1.25-2.92)[28].

Regarding the malformations related to the circulatory system, a case-control study carried out in Hungary found a positive association between paternal exposure to pesticides (OR=1.66, 95% CI=1.03-2.69) and alkylphenolic compounds (OR=1.95, 95% CI=1.30–2.93) and the occurrence of patent ductus arteriosus. However, another case-control study, conducted in the Netherlands, found no association between maternal occupational exposure to pesticides and the occurrence of cardiac abnormalities[34].

Pesticides

As for the toxic agrochemicals most frequently identified in the studies, it is worth mentioning that the Atrazine herbicide was the most reported (n=11)[8,17,21,24,26–27,29–30,33,36–37], followed by 11 studies that investigated organochlorines[7,9–11,13,16,20–23,31].

The exposure to and/or application of toxic agrochemicals was verified in (n=8) studies[14–15,25,28,30,37–38,52]. Insecticides was examined in six studies[8,15,21,24,26,36] and fungicides, in four studies[15,24,26,37]. Only two studies investigated organophosphates[21,32].

DISCUSSION

The toxic agrochemicals considered to be endocrine disruptors include insecticides, herbicides and fungicides. These inputs are used in agriculture, aquaculture and domestic uses, whose residues have been found in food, drinking water and water bodies[43]. Some classes of agrochemicals present estrogenic and/or anti-estrogenic activity, such as organochlorines and pyrethroids; and androgenic and/or antiandrogenic activity, such as organochlorines, organophosphates and atrazine. The endocrine disrupting toxic agrochemicals act by binding to specific steroid hormone receptors (estradiol, testosterone and progesterone), thus being able to inhibit or activate enzymes that act in the synthesis and metabolism of hormones, disrupting the function of the hypothalamus and pituitary[44].

Congenital malformations are the second leading cause of infant death in Latin America according to data from the World Health Organization[45]. A Brazilian study identified that the largest association found between the increase in the cryptorchidism malformation from the 1993-2004 period to the 2004-2014 period was in the state of Paraná. The researchers suggest that, for being endocrine disruptors, some toxic agrochemicals are suspected of influencing the sexual differentiation of the fetus and other sex hormone-dependent outcomes and that they can be related to the fluctuation of female and male hormones during pregnancy[46].

In the USA, it was verified[47] that women exposed to different classes of toxic agrochemicals obtained different levels of significant risk associated with the having children with hypospadias. A study[48] from Spain, on the other hand, evidenced that most of the agricultural workers studied had a high relative risk of fetal death due to congenital anomalies. In a case-control research study in the Netherlands[49], paternal exposure to pesticides was significantly associated with cryptorchidism. A research study conducted in Paraguay[9] found a relationship between congenital anomalies and exposure to toxic agrochemicals. A Brazilian study[10] also found that maternal exposure to toxic agrochemicals during pregnancy was associated with congenital anomalies in the cities studied in the state of Mato Grosso, suggesting that populations intensely exposed to agrochemicals are at higher risk of fetal malformations.

In Mexico, a study[13] evaluated mothers and children born with cryptorchidism and exposure to organochlorines and concluded that exposure to toxic agrochemicals was higher among the mothers with children who were born with cryptorchidism than among mothers of children with descended testicles. In a study[30] carried out in Argentina, some risk factors for the emergence of congenital malformations were identified, among them distance of the house from the fumigated fields being less than 1 km (OR=3.75; 95% CI=0.98-14.31) and direct maternal exposure to pesticides (OR=4.51; 95% CI=1.77-11.46). This corroborates the articles[18,23] which identified that homes close to crops and direct contact of pregnant women to toxic agrochemicals can cause neural tube defects and consequences for the nervous system.

In an ecological study conducted in Brazil, it was concluded that Brazilian states with high consumption of toxic agrochemicals presented an increase of 100% and 75%, and that those with mean consumption, an increase of 65% and 23%, respectively, in the risk of congenital anomalies in the CNS and in the Cardiovascular System at birth, when compared to low-use states[51]. Thus, it is reinforced that the environmental factors, especially exposure to toxic agrochemicals, can contribute to the emergence of congenital malformations related to the central nervous system, according to the articles[18,20–21,23].

In this context, in a case-control study[24] parental exposure to toxic agrochemicals and the onset of spina bifida in newborns were analyzed. The parents' joint occupational exposure to agrochemicals (herbicides, fungicides and insecticides) was positively associated with spina bifida (OR=1.5; 95% CI=0.9-2.4) when compared to the infants without parental exposure[24]. Among the articles of this study, herbicides were the most reported for the occurrence of congenital malformations together with insecticides and fungicides, not only for neural tube defects[21,23], but also for other malformations such as those related to the reproductive system and to the gastrointestinal tract[15,26].

Corroborating the findings of this study, a systematic review[53] that sought to identify the risk factors related to maternal exposure and congenital malformations found similar results, as well as higher prevalence of cardiovascular, gastrointestinal, genitourinary, musculoskeletal and nervous system malformations[53]. Regarding the results found related to gastroschisis, a study carried out in the USA identified the prevalence of this malformation in cases coming from places with excessive use of pesticides for restricted use. In addition, a study[54] carried out in Campinas, São Paulo, also linked exposure to toxic agrochemicals during pregnancy with the occurrence of gastroschisis.

In a Brazilian study[55] carried out between 2004 and 2006 in *Nova Friburgo*, state of *Rio de Janeiro*, higher prevalence of congenital malformations, low birth weight and low Apgar score in newborns in rural areas of the city were identified. The study also highlighted the occurrence of cleft palate as the third most prevalent outcome[55].

The occurrence of congenital anomalies related to exposure to pesticides was also reported in a study conducted in South Africa. Through a control case study, it was concluded that newborns from mothers exposed to toxic agrochemicals were seven times more likely to develop some congenital anomaly when compared to newborns from mothers who did not suffer exposure[56].

Among the agrochemicals most used in articles analyzed in a systematic review study, atrazine, methyl bromide, cyanazine, DDT, dicamba, DDE and HCB were found[53]. Atrazine is one of the most widely used agricultural herbicides in the last 50 years in the United States of America and, in Brazil, it was the fourth most commercialized active ingredient in 2018[17,57]. Among the effects on health are dysregulation of the endocrine system, cardiovascular diseases and genitourinary malformations[17,58].

It is also worth mentioning some limitations of this study, such as the language of the search and inclusion strategies, since studies published in other languages and in other databases may not have been included using the strategy presented. Therefore, the impact of cultural diversity may suffer from this limitation. The authors acknowledge that important studies may have been omitted.

CONCLUSION

The implications of this study for the practice can be seen in the sense of strengthening the evidence related to the association between exposure to toxic agrochemicals and congenital malformations. With this review, it was concluded that maternal and paternal exposure to agrochemicals can be associated with greater chances of children being born with congenital malformations, especially those related to the male reproductive system.

A gap identified by the study is the low number of relevant papers published worldwide, mainly by the USA, Brazil and China, which are the main consumers of toxic agrochemicals. It is believed that this study will contribute to giving visibility to the theme and, thus, collaborate in the prevention of the population's exposure to toxic agrochemicals and in the birth of children with congenital malformations. In addition to this, it will contribute to the prevention and tracking of congenital anomalies during Nursing care, mainly during prenatal care through Nursing consultations in Primary Health Care.

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