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## PESTICIDE EXPOSURE AND HEALTH PROBLEMS AMONG WOMEN IN REPRODUCTIVE AGE: A LITERATURE REVIEW

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### ABSTRACT

*Pesticides are persistent organic pollutants that are resistant to environmental degradation and have a negative impact on human health and the environment. Exposure to chemicals from pesticides can be accepted by anyone, including women, both women of reproductive age and women who are pregnant. This study was a literature review study with a data collection process was carried out by obtaining articles relevant to the research objectives in the Pubmed, ScienceDirect, and Google Scholar databases. The keywords used include "Pesticide and reproductive health and women" and "pesticide and reproductive health and farmer and women". After that, 20 articles that match the research objectives were selected. Women who expose to pesticides during early pregnancy may increase the risk of adverse birth outcomes such as small for gestational age, preterm delivery, and low birth weight. The negative impacts of pesticides, that harmful for human health and the environment, are because of bad handling practices, lack of information about the toxicity, the availability of this chemical are so many although they are banned or unauthorized by the government, and that negative impacts are also larger but underestimated and underreported. Multiple recommendations can take to minimize pesticide's negative effect including application of the regulation, choosing alternative biopesticides, using personal protective equipment when applying the pesticides, and regular counseling on all aspects of pesticides.*

**Keywords:** pesticide, women, reproductive

### INTRODUCTION

Pesticides are used for controlling pests or weeds and vectors of disease. Pesticides also can improve crop productivity so the sales and profit increase because of the use of large amounts (Barrón Cuenca et al., 2019). Pesticide is one of the persistent organic pollutants (POPs) that is harmful for the environment and affects the population of plants, animals, and human health. Organochlorine pesticides (OCPs) are a class of insecticides and the most dangerous pesticides that are usually used in agriculture

(Djanggalina et al., 2020; van den Dries et al., 2018).

Some of the active Organophosphate Pesticides (OP) pesticides may remain on or in food after they are applied to food crops and individuals can expose this chemical through their daily diet (Van den Dries et al., 2019). The pesticides residues can be found in everyday foods and beverages that we consume such as water, fruit juices, wine, instance cooked meals, and animal feeds. Furthermore, it should be concern that washing and peeling cannot completely remove the residues. The residue of



pesticides were also been detected in human breast milk samples, and they must be noted about prenatal exposure and health effects in children (Nicolopoulou-Stamati et al., 2016). Pesticides are dangerous and harmful to living organisms and also a threat for human health. Long-term exposure to low levels of pesticides can increase reproductive disorders (Barrón Cuenca et al., 2019).

Pesticides induce reproductive and endocrine system disorders, delayed development of the nervous and immune systems, cancer and respiratory failure, and inborn defects. (Djangalina et al., 2020) The exposure of POPs correlates with a longer time to pregnancy, higher odds for infertility, a worse outcome in assisted reproduction, and earlier reproductive senescence. They can decrease fertility in humans and other animals (Björvang et al., 2021).

The type of pesticide used, duration of the application, route of exposure, and individual health status, including nutritional and skin conditions, determine possible health outcomes (Nicolopoulou-Stamati et al., 2016). The negative impact of pesticides, that can affect human health and the environment, are because of bad handling practices, lack of information about pesticide toxicity, the availability of this chemical are so many although they are banned or unauthorized by the government, and that negative effects are also larger but underestimated and underreported (Andersson & Isgren, 2021).

Some of the existing literature we found, only relate the impact of pesticide exposure to certain reproductive disorders. For this

reason, we conducted this literature review to specify the effect of pesticide exposure on women's reproductive health during reproductive age.

## RESEARCH METHOD

This article is a literature review article using a narrative literature review. The literature review is aimed to formulate the impact of pesticides on women's reproductive health. To collect the data, we obtain articles that relevant to the research objectives which is derived from 3 databases i.e. Pubmed, Google Scholar, and ScienceDirect with 2 keywords, namely: (1) pesticide AND reproductive health AND women; and (2) pesticide AND reproductive health AND farmer AND women.

The inclusion criteria that we used in this literature review are: (1) published articles; (2) published in the year 2014-2021; (3) open access and full text in English. Based on the results of the search, the number of literature reviews that we used in this article, as many as 20 articles covering observational study with cross-sectional studies, survey studies, and cohort studies. The results of this non-systematic review analysis are described in Table form matrix literature review in Table 1. Result synthesis is carried out by comparing the results of published studies.

## RESULT AND DISCUSSION

The results of the synthesis of several kinds of literature on efforts to provide the effect of pesticides for women that presented in Table 1.

**Table 1. Literature Review**

No	Authors, Years	Title	Sample	Method	Result
1	Dries et al., 2018	Determinants of organophosphate pesticide exposure in pregnant women: A population-based cohort study in the Netherlands	784 pregnant women	Six Dialkyl Phosphate (DAP) metabolite concentrations, the main urinary metabolites of Organophosphate Pesticides (OP), measured in the urine of pregnant women in the Rotterdam, Netherlands	DAP metabolite concentrations tended to be higher and seem to be associated with maternal age, married / living with a partner, underweight or normal weight, and high education. The main exposure is because of fruit intake and higher during the summer
2	Faria et al., 2014	Occupational exposure to pesticides, nicotine, and minor psychiatric disorders among tobacco farmers in southern Brazil	2400 women and men tobacco farmers	Identify the prevalence of minor psychiatric disorders (MPD) among tobacco farmers associated with pesticide Cross-sectional study with multivariate analysis using a hierarchical Poisson regression model	MPD prevalence is 12% among 2400 tobacco farmers and higher among women, workers aged 40 or over, difficulty in paying debts, tenants/employees, and low socioeconomic status. Tobacco farmers who use organophosphates had 50% more risk of MPD than those not exposed
3	Jaacks et al., 2019	Association of prenatal pesticide exposures with adverse pregnancy outcomes and stunting in rural Bangladesh	289 pregnant women	Eight pesticide biomarkers, urine, were collected from pregnant women participating in a birth cohort study. Anthropometry of the child at birth and 1-2 years of age was measured. Relative risk (RR) with 95% confidence intervals (CI) estimated with log-binomial regression	Women who expose to pesticides during early pregnancy may increase the risk of adverse birth outcomes such as preterm delivery, small for gestational age, and low birth weight. No association was found between any of the pesticide biomarkers and

					stunting at 1 or 2 years of age
4	Li et al., 2020	Association of urinary metabolites of organophosphate and pyrethroid insecticides, and phenoxy herbicides with endometriosis	619 reproductive-age women	This research is to determine the concentration of 11 pesticides, metabolites of organophosphate and pyrethroid insecticides, and phenoxy herbicides in urine samples collected from menstruating women using liquid chromatography-tandem mass spectrometry. Surgical visualization, laparoscopy, or laparotomy, together with histologic confirmation and magnetic resonance imaging (MRI) were used to define endometriosis diagnoses. Descriptive statistics and comparison of basic characteristics of women with and without endometriosis for each cohort were evaluated using the Student's-t-test and Mann-Whitney U test.	Pesticide metabolites, IMPY and TCPY, are associated with an increase in the odds of an endometriosis diagnosis. The exposure of diazinon (parent compound of IMPY), as well as chlorpyrifos and chlorpyrifos-methyl (parent compounds of TCPY), may be associated with increased odds of an incident endometriosis diagnosis.
5	Jurewicz et al., 2020	Exposure to pyrethroid pesticides and ovarian reserve	511 females aged 25-39 years who attend infertility clinics for diagnostic purposes, because of couple's infertility	This study is to assess the urinary concentration of pyrethroid metabolites, CDCCA, TDCCA, DBCA, 3-PBA, using the validated gas chromatography ion-tap mass spectrometry method. Urine and blood were collected from each woman at the time of recruitment. The female ovarian reserve was assessed by antral follicle count (AFC), the concentration of hormones: Anti-Mullerian Hormone (AMH), Follicle Stimulating Hormone (FSH), and estradiol (E2).	Urinary concentration of pyrethroid metabolites, 3-PBA, decreases the level of AMH and AFC and increases the FSH level when 3-PBA was treated as a continuous variable. Urinary level of CDCCA, TDCCA, and DBCA was not associated with any examined parameters of ovarian reserve (AFC, AMH, FSH, E2). Synthetic pyrethroids may affect female



				ovarian reserve. Ovarian reserve is the parameter that could be used to determine the potential of female fertility.	
6	Mora et al., 2020	Prenatal pesticide exposure and respiratory health outcomes in the first year of life: Results from the infants' Environmental Health (ISA) study	Pregnant women were enrolled in the ISA study from March 2010 and June 2011. Of the remaining 360 mother-child pairs	This study is to evaluate respiratory outcomes, confirm a diagnosis of Lower Respiratory Tract Infections (LRTIs) and wheeze during the first year of life because of the use of pesticides. The seven pesticide metabolites (including mancozeb) were measured in maternal urine samples collected repeatedly during pregnancy.	Ten percent of the children had at least one LRTI and 39% had at least one episode of wheezing during their first year of life. About 71% of children with a history of an LRTI also had wheezing. Prenatal exposure to mancozeb was associated with respiratory outcomes during the first year of life in infants living near banana plantations in Costa Rica.
7	Naidoo et al., 2011	Spontaneous miscarriages and infant deaths among female farmers in rural South Africa	911 women working in agriculture	This is a cross-sectional study that examined associations between demographic and occupational factors (agricultural activities, physical load, pesticide spraying) and self-reported spontaneous miscarriage and infant death using an interview survey.	Spraying pesticides during the first trimester of pregnancy has a higher risk of spontaneous miscarriage. This is related to the irrigation scheme, women's age over 40 years, drylands, farm ownership, and working hours of more than 10 years in drylands.
8	Pan et al., 2019	Selected persistent organic pollutants associated with the risk of	Chinese female population, including 157 cases and 217	This study is to explore the association between serum levels of Selected Persistent Organic Pollutants (POPs) and risk for Primary Ovarian	In control women, LH had a positive association with OCPs. In patients with POI, exposure to

		primary ovarian insufficiency in women	healthy controls	Insufficiency (POI). Serum concentrations of organochlorine pesticides (OCPs) and serum levels of reproductive hormones (FSH, LH, AMH, Estradiol) were measured.	OCPs was associated with lower levels of AMH. Exposure to PCBs and DDT could be the potential risk factors for POI in women.
9	Weder et al., 2020	Herbicide, fumigant, and fungicide use and breast cancer risk among farmers' wives	30.594 farmers' wife	This is a cohort study that examined the relationship between exposure to herbicides, fumigants, and fungicides and breast cancer among farmers' wives.	The results of the study showed that there were 1,081 cases of breast cancer out of 30,594 women where 38% of these women had used herbicides, fungicides, and fumigants during 15,7 years follow up. The risk of breast cancer increases in women who have used the fungicide benomyl, the herbicide 2,4,5-trichlorophenoxyacetic acid, and the husband's use of herbicide 2 propionic acid. This increased risk may be related to an increase in estrogen receptors in the tumor.
10	Engel et al, 2017	Insecticide Use and Breast Cancer Risk among Farmers' Wives in the Agricultural Health Study	30.594 farmers' wife	This is a cohort study that examined the relationship between exposure to insecticides and breast cancer among farmers' wives.	Pesticide use was not associated with an increased risk of breast cancer. The thing that increases the risk of breast cancer in the pre-menopausal period is the use of organophosphates chlorpyrifos or terbufos.
11	Hyland et al., 2022	Interactions of agricultural pesticide use near home during pregnancy and	458 maternal and youth pairs	This study is a longitudinal cohort study to examine the associations of pesticide mixtures and adolescent neurobehavioral	Little evidence found that pregnant women who live near agricultural pesticides application have a

		adverse childhood experiences on adolescent neurobehavioral development in the CHAMACOS study		development from pregnant women within 1 km application of agricultural pesticides and youth reported adverse childhood experiences	child who reported behavioral and emotional problems
12	Bjorvang et al., 2022	Follicular fluid and blood levels of persistent organic pollutants and reproductive outcomes among women undergoing assisted reproductive technologies	185 women aged 21-43 years old	This study is to analyze the level of follicular fluid and blood level of persistent organic pollutants collected from women with a median of 2 years of infertility who were seeking assisted reproductive technology (ART) treatment during ovum pick-up	Women who expose to persistent organic pollutants was associated with various effects such as lower antimullerian hormone, higher basal antral follicle count, and lower embryo quality,
13	Baumert et al., 2022	Urinary Concentrations of Dialkylphosphate Metabolites of Organophosphate pesticides in the Study of Asian Women and their Offspring's Development and Environmental Exposures (SAWASDEE)	330 pregnant farmworker women	This study is to analyze the metabolites of organophosphate insecticides, urinary dialkyl phosphate, during gestation	Farmworker women who work at a farm that requires intensive application of insecticides such as tangerines have higher levels of DEAP metabolites
14	Vargas et al., 2022	Exposure to common-use pesticides, manganese, lead, and thyroid function among pregnant women from the Infants' Environmental Health (ISA) study, Costa Rica	400 pregnant women	This study is to analyze the current use pesticide exposure of women from Infants' Environmental Health Study (ISA)	Women who expose to fungicides and insecticides were associated with changes in thyroid hormone concentration which may affect fetal development and child development during early life
15	Yang et al., 2021	Prenatal exposure to organochlorine	1039 mother-infant pairs	This study is to examine the associations between prenatal	Increasing cord serum level was associated

		pesticides and infant growth: A longitudinal study			exposure to organochlorine pesticides (OCPs), measured in cord serum, and infant growth	with increasing BMI z score and higher risk of overweight status in infants and seemed to be stronger in girls
16	Wielsoe et al, 2017	Serum levels of environmental pollutants is a risk factor for breast cancer in Inuit: a case-control study	77 breast cancer cases and 84 controls		This case-control study examined the associations between serum levels of persistent organic pollutants (POPs) and breast cancer with a focus on the highly exposed Greenlandic Inuit population	Serum levels of polychlorinated biphenyls (PCBs) and 16 perfluoroalkyl acids (PFAAs) in women with breast cancer were higher than in controls. PCBs and PFAAs levels are associated with an increased risk of breast cancer.
17	Chiu et al, 2017	Association Between Pesticide Residue Intake From Consumption of Fruits and Vegetables and Pregnancy Outcomes Among Women Undergoing Infertility Treatment With Assisted Reproductive Technology	325 women fertility center		This cohort prospective study is examined the association of preconception intake of pesticide residues in fruits and vegetables with outcomes of infertility treatment with assisted reproductive technologies	The lower probability of pregnancy and live birth is related to the intake of high pesticide residues from fruits and vegetables
18	Wesselink et al, 2020	Pesticide residue intake from fruits and vegetables and fecundability in a North American preconception cohort study	5.234 women		This cohort study is examined the association between dietary intake of pesticide residues and fecundability	Intake of fruits and vegetables exposed to high levels of pesticides does not significantly affect the fecundability of women who are trying to conceive
19	Cupul-Uicab et al, 2018	Exposure to DDT from Indoor Residual Spraying and biomarkers of inflammation	416 women		This study is examined the association between plasma concentrations of DDT and DDE with biomarkers of inflammation among	High levels of DDT and DDE in plasma concentrations are associated with increased concentrations of pro-



		among reproductive-aged women from South Africa		reproductive-aged women residing in homes sprayed with DDT through Indoor Residual Spraying (IRS)	inflammatory biomarkers in women of reproductive age which can lead to chronic inflammation.
20	Knudsen et al, 2018	Persistent organic pollutants and hematological markers in Greenlandic pregnant women: the ACCEPT sub-study	189 pregnant women	This study examined the association between serum persistent organic pollutants (POPs) and hematological markers in Greenlandic pregnant women.	Long-term and massive exposure to the persistent organic pollutant (POPs) is associated with increased immunosuppressant biomarkers in pregnant women

### The Effects of Pesticide for Women

There is a relationship between pesticide exposure and women's reproductive health during the reproductive period. Women's reproductive health is a complex system that affects the reproductive system and women's ability to reproduce. Exposure to pesticides in the long term can have an impact on endocrine disorders and hormonal dysfunction in the female reproductive system (Naidoo et al., 2011). Exposure profiles of pesticides to farmworker women can be different depending on the application of the pesticides and the residential location of farmer living. Pregnant farmworker women and women who work at a farm that requires intensive application of insecticides such as tangerines have higher levels of DEAP metabolites (Faria et al., 2014). Demographic factors like ethnicity, cultural marriages, and low education can also influence the use of pesticides in their agricultural activity (Baumert et al., 2022).

A study conducted in Netherland showed that the main exposure to OP pesticides in young urban women in the Netherlands is because of fruit intake and higher during the summer. Studies using urine samples of

pregnant women at a gestational age of fewer than 18 weeks, 18-25 weeks, and more than 25 weeks of gestation found that the average concentration of dialkyl phosphate (DAP) metabolites in the first trimester were 311 nmol/g creatinine, in the first trimester. In the second trimester it was 317 nmol/g, and in the third trimester, it was 310 nmol/g. Factors associated with an increase in the average level of DAP include getting older pregnant women, pregnant women with married status or living with a partner, underweight or normal weight (BMI <18.5 and 18.5-<25), higher education level, income level height, and pregnant women who do not smoke. Higher DAP levels were also found in summer. Consumption of 100 grams of fruit per day is known to increase 7% of total DAP levels during pregnancy (Van den Dries et al., 2018).

The results of other studies also show that food sources such as honey have the potential to contain organochlorine pesticides (OCPs) which are at risk of causing reproductive health problems. The results of this study indicate that the estimated HI values for adults (102.38), and children (90.33) were far above the threshold value of 1, indicating adverse

health effects. This can be attributed to the high toxicity of OCP residues. Effects that can occur due to high levels of lindane include impaired development and compromised maturation, decreased follicle survival, shortening in the menstrual cycle by approximately 4 days in women with the highest serum levels of DDT, chronic inflammation, and lower implantation rates which can cause female infertility (Cupul-Uicab et al., 2020). A high level of endosulfan caused degeneration in the endometrium leading to spontaneous abortions, as well as an increase in the calcium ion levels leading to improper muscular rhythm causing infertility in treated females. Exposure to organochlorine chemicals has significant associations between endometriosis and infertility (Ben Mukiibi et al., 2021; Sokoloff et al., 2016). However, a study conducted in North America showed that intake of fruits and vegetables exposed to the high level of pesticides does not significantly affect the fecundability of women who are trying to conceive (Wesselink et al., 2021).

One of the risk factors for endometriosis is the presence of endocrine-disrupting chemicals. Endocrine-disrupting chemicals can be caused by exposure to pesticides containing organophosphate, pyrethroid, and phenoxy acid pesticides (Li et al., 2020). The results of another suitable study showed that exposure to high concentrations of diazinon and chlorpyrifos was associated with a higher incidence of endometriosis. In contrast to previous studies, the risk of endometriosis was increased in younger, nulliparous, and women with lower socioeconomic status (Ben Mukiibi et al., 2021).

Massive exposure to pesticides in the form of insecticides, herbicides, fungicides, and fumigants on agricultural land can cause endocrine disorders. Exposure to

dichlorodiphenyltrichloroethane (DDT), polychlorinated biphenyls (PCBs), and 16 perfluoroalkyl acids (PFAAs) in pesticides resulted in inhibition of estrogen activity to induce breast tumors in a cohort study of farmers' wives who were exposed to pesticides through a spray, pesticide residues, and contaminated water. The risk of breast cancer increases in premenopausal women who are exposed to pesticides containing the organophosphates chlorpyrifos and terbufos (Engel et al., 2017; Werder et al., 2020; Wielsøe et al., 2017).

Other studies have also shown that synthetic pyrethroids are associated with infertility in women aged 25-29 years. The results of the study showed that levels of pyrethroid metabolites (CDDCA (cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid), TDDCA (trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid), 3PBA (3-phenoxybenzoic acid) and DBCA (cis-2,2-dibromovinyl-2,2-dimethylcyclopropane-1-carboxylic acid)) were associated with decreased concentrations of anti-Mullerian hormone (AMH), follicle-stimulating hormone (FSH) and estradiol (E<sub>2</sub>). Long-term use of pyrethroids can cause endocrine-disrupting chemicals (EDCs). These chemicals may interfere with the synthesis, secretion, binding action, or elimination of hormones responsible for reproduction (Chiu et al., 2018; Jurewicz et al., 2020). Another study about chemical exposure to women of reproductive age was conducted on women with a median of 2 years infertility who were seeking assisted reproductive technology treatment, especially organochlorine pesticides. Women who expose to persistent organic pollutants were associated with various effects such as lower

antimullerian hormone, higher basal antral follicle count, and lower embryo quality (Björvang et al., 2021, 2022).-

Exposure to pesticides during early pregnancy may increase the risk of adverse birth outcomes such as preterm delivery, small for gestational age, low birth weight, and a lower probability of live birth (Chiu et al., 2018; Jaacks et al., 2019). Another study showed that the risk of spontaneous miscarriages increases in pregnant women who are exposed to pesticides during the first trimester of pregnancy. This is due to the high exposure to pesticides, especially glyphosate and thiocarbamates on the drylands sprayed, and the increasing immunosuppressant biomarkers in pregnant women (Knudsen et al., 2018; Naidoo et al., 2011). However, other studies have shown that there is no relationship between pesticide exposure and the incidence of complications in pregnancy, especially gestational diabetes. The results of this study indicate that the content of organophosphorus (OP) and organochlorine (OC) in the first trimester of pregnancy have no impact on mitochondrial dysfunction and endocrine mechanisms in releasing insulin so that it does not affect the incidence of gestational diabetes (Shapiro et al., 2016).

The impact of pesticide exposure not only on pregnant women but also on the fetus in the womb. Pesticides exposure to pregnant women may affect thyroid function that very important for fetal brain development. Women who expose to fungicides and insecticides were associated with changes in thyroid hormone concentration. Although the changes were within clinical ranges, it must be a concern that the change may affect fetal development and child development during early life (Corrales

Vargas et al., 2022). Furthermore, the effect of organochlorine pesticides exposure to pregnant women who lives near the agricultural farm is also associated with their infant growth, at 12 and 24 months of age, such as increasing BMI z-score, higher risk of overweight, higher risk of lower respiratory tract infections and wheezing during their first year of life, and behavioral and emotional disorders such as hyperactivity and attention problem at ages 16 and 18 years (Hyland et al., 2022; Mora et al., 2020; Yang et al., 2021).-

Premature ovarian insufficiency (POI) is the loss of normal hormonal and reproductive function of ovaries in women before age 40 as the result of premature depletion of oocytes. The incidence of POI increases with age in reproductive-aged women, and it is highest in women by the age of 40 years. Studies show that exposure to polychlorinated biphenyls (PCBs) is associated with high levels of luteinizing hormone (LH), while exposure to organochlorine pesticides (OCPs) is associated with low levels of the anti-Mullerian hormone (AMH), which increases the risk of primary ovarian insufficiency (POI)- in women of childbearing age (Pan et al., 2019).-

## CONCLUSION

Based on the outcomes of the study, it is found that pesticide exposure has many various effects on women of reproductive health during reproductive age including endometriosis, premature ovarian insufficiency, infertility, breast cancer, spontaneous miscarriages, and impaired growth and development of the fetus in the womb. Multiple recommendations can take to minimize pesticide's negative effect including implementation of the regulation,



choosing alternative biopesticides, using personal protective equipment when to apply the pesticides, and regular counseling on all aspects of pesticides.

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