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Pesticides as Endocrine Disruptors on the Reproductive Health of Females

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ABSTRACT
Excessive use of pesticides and insecticides, unscientific cultivation, industrialization, urbanization, deforestation, improper sanitation, enormous population growth, global climatic changes, and lack of environmental awareness had led to the development of a huge health and economic crisis The hormonal and cellular functions of an organism are dramatically altered under chronic exposure to pesticides. Some pesticides can disrupt the female endocrine system by disrupting the hormonal balance required for proper reproductive function. Hormone synthesis, hormone release and storage, hormone transport and clearance, hormone receptor recognition and binding, hormone post-receptor activation, and central nervous system function are all examples of stages of hormonal regulation where disruption can occur. Effects of pesticide exposure in vitro and on experimental animals in vivo are identified using these mechanisms. Potential effects of endocrine-disrupting pesticides on the female reproductive system, such as hormone concentration regulation, ovarian cycle abnormalities, and reduced fertility, are also common. Pesticide exposure has been linked to menstrual cycle disruptions, decreased fertility, a longer period to pregnancy, spontaneous abortion, stillbirths, and developmental defects which may or may not be due to the disruption of female hormonal function. Since pesticides are made up of a variety of different substances with different structures and toxicity, it's likely that some of the mechanisms mentioned above are involved in the pathophysiological pathways that explain the role of pesticide exposure in ovarian cycle disruptions, eventually leading to fertility problems and other reproductive effects.
Keywords: Pesticides, hormonal imbalance, endocrine disruption, toxicity, developmental defects

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INTRODUCTION

Pesticide use has risen slightly year after year over the last few decades, with over 4 million tonnes used globally in 2017. Asia (52.8%), followed by the United States (30.2%), and Europe (13.8%), had the largest amount of pesticide used. While these chemicals increase crop yields and provide economic benefits by reducing pest-borne diseases, their negative effects on human health and the environment continue to be studied, and less toxic alternatives are being established to mitigate these effects. Pesticide exposure, either alone or in combination, by environmental degradation, could have serious acute and chronic consequences for living organisms. Its use in agriculture is growing every day, and it's becoming a confounding problem due to the introduction of new chemical compounds (1). While there has been a lot of research linking pesticide exposure at work with fertility issues in men, there haven't been many studies done on women. One explanation may be that men are more likely to be exposed to pesticides because they apply them, while women are only exposed through re-entry activities. Another explanation may be that female fertility is more difficult to measure than male fertility (2). The ovarian cycle hasn't been studied as thoroughly as spermatogenesis in men. High levels of physical activity, age, stress, smoking, and caffeine consumption are all potential causes of ovarian disorders (3). Chemicals like benzene and polychlorinated biphenyls (PCBs) can also affect the menstrual cycle. There's also evidence that some pesticides may cause ovarian dysfunction (4). Farr et al. recently investigated the connection between pesticide exposure and menstrual cycle characteristics. They discovered that women who worked with pesticides that were suspected of being hormonally active had a 60–100% higher chance of having long cycles, missed periods, and intermenstrual bleeding than women who had never worked with pesticides (5). In another research, women who were exposed to pesticides or worked in agriculture-

related industries had a higher risk of infertility (6). Knowledge on the ways in which pesticides can impair hormonal function, as outlined in this study, can be used to generate new hypotheses for studies on pesticides' effects on the ovarian cycle, both in toxicological and epidemiological settings, in the future. Therefore, the purpose of this review is to provide an overview of the various ways pesticides can disrupt the hormonal function of the female reproductive system, specifically the ovarian cycle, leading to infertility.

NATURE OF SUBFERTILITY

Subfertility is characterized as the inability to conceive after 12 months of normal, unprotected sexual contact, and it affects roughly 10% to 15% of all couples in the Western world (7). According to a World Health Organization (WHO) multi-center survey, the issue was predominantly male in 20% of subfertile couples and predominantly female in 38% of the cases, while 27% of subfertile couples had anomalies in both men and women, and the remaining 15% had no apparent cause of infertility (8). Five types of subfertility disorders are distinguished (9).

Male subfertility

In 20–25 % of couples, low sperm concentration decreased motility, and/or irregular morphology of sperm are the leading causes of infertility. Male subfertility is described as a reduction in the female partner's ability to conceive (10).

Ovulation problems

Subfertility is caused by ovulation problems in another 20–25 % of couples, making it a common cause of infertility in women. Ovulation disorders manifest as prolonged or absent menstrual cycles, which can be confirmed by measuring reproductive hormones (10).

Defects in the interaction of spermatozoa and cervical mucus

The sperm cannot enter the oocyte if the cervical mucus is abnormal. Cervical aggression is thought to be a cause of infertility in 10–15% of couples, according to some scholars, while others deny it even exists (11).

Disturbances of the tuboperitoneum

Subfertility is caused by tubal disruption and/or obstruction, hydrosalpinx, pelvic adhesions, and endometriosis in 10–30% of couples. In certain cases, these issues are caused by infections (10).

Unexplained Subfertility

The age of a woman is a significant factor in her infertility. When a woman reaches the age of 35, her chances of being infertile rise from 10% to 30%. This is especially important nowadays, as a growing number of women postpone pregnancy until later in life when normal female fertility is declining due to an increase in chromosomal aberrations in the oocytes. Hormonal balance, particularly in relation to the ovarian cycle, is another important factor in female fertility. Stress, extreme body weight (too low or too high), caffeine intake, diet, and excessive exercise can all have an effect on a woman's hormonal equilibrium and, as a result, her ovulatory pattern. Hormonal diseases are also less likely to cause hormonal imbalances and ovulatory problems, like pituitary gland disorders. However, there is evidence that endocrine-disrupting chemicals like PCBs and certain pesticides may alter the hormonal balance and increase the risk of subfertility(12).

POTENTIAL EFFECTS OF PESTICIDES ON FEMALE REPRODUCTION

Hormone disruption's potential impact on the female reproductive system

Hormone concentrations and balance are critical for the female reproductive system to work properly. Endocrine disruption can cause problems in the reproductive system, including changes in hormone concentrations, abnormal ovarian cycles, and reduced fertility (13). Because the majority of these studies are based on experimental animals, it's important to remember that the estrus cycle in animals only partially resembles the ovarian cycle in humans and that the phases (proestrus, estrus, metestrus, and diestrus) differ. Estrus is the time when a woman's sexual response is at its peak, which usually coincides with ovulation. Diestrus occurs during the estrus cycle's luteal phase when the female is not responsive to the male and progesterone levels are high.

Hormone concentrations are altered

Hormonal balance, or the right amount of sexual hormones, is critical for female reproduction and fertility. Changes in estrogen or progesterone levels might throw this balance off. Several herbicides have been shown to lower estrogen levels. After large doses of hexachlorobenzene (14), ovulatory levels of estradiol were lowered in monkeys, and serum progesterone concentrations throughout the luteal phase were suppressed in a dose-dependent manner (15). Exposure to methoxychlor can also lower progesterone levels, notably during the estrus phase of the estrous cycle in rats (16).

Inconsistencies in the ovarian cycle

The female ovarian cycle is determined by a complicated interaction of hormones and is the consequence of a balanced collaboration between multiple organs. Ovarian cycle irregularities include ovarian cycle disruptions (e.g., a prolonged cycle, protracted estrus) as well as ovulation issues (deferred ovulation or anovulation).

Ovarian cycle disruptions

In rats, organochlorine chemicals have been shown to disrupt the estrus cycle. After rats were given methyl parathion, the number of estrus cycles and the duration of each phase of the estrus cycle were dramatically reduced (17). In rats, atrazine, an estrogen receptor antagonist, can modify estrous cyclicity, causing a prolongation of the estrous cycle and an increase in the number of days in estrus (18). Carbofuran influenced the estrus cycle by reducing the number of estrus cycles and the length of each phase, which might be due to a direct action on the ovary or a hormonal imbalance caused by the hypothalamus- pituitary-ovarian axis (19).

Problems with ovulation

Estrogen-like endocrine disruptors may be able to prevent ovulation in the same way that contraceptive pills do. The pituitary gland's midcycle surge of LH serves as the physiological trigger for the mammalian female's ovulation process. Any substance that interferes with the LH surge has the potential to be a reproductive toxin (20). Because atrazine suppresses LH secretion, it can cause anovulation (21). Chlordecone inhibited the proestrus LH surge in rats (22), while Muller et al. discovered that hexachlorobenzene can prevent ovulation in rhesus monkeys. Anovulatory cycles were shown to have low estrogen levels in this investigation.

Fertility issues

Fertility in humans is a delicate mechanism that can be affected by a variety of factors, including hormonal imbalances caused by pesticides. In most research, however, it is unclear if poor fertility is caused by hormonal imbalances or other toxins (23). A physiological consequence of the acrosome reaction is that the insecticide lindane changes sperm tolerance to progesterone in vitro, which could be a factor in infertility in lindane-exposed women (24). Mancozeb and methyl parathion exposure can cause a decrease in uterine weight, which can affect implantation (25). Mancozeb, methoxychlor (16), heptachlor (26), and chlordimeform (27) can all inhibit implantation.

DISRUPTION OF THE FEMALE HORMONE FUNCTION

Interference with hormone synthesis

Both hormones have different chemical structures and go through a different synthesis process with a slew of different steps. If one of the substances or links in the hormone synthesis chain is disrupted, the hormone may not be formed or may have different properties. In vitro, certain pesticides, such as fenarimol, prochloraz, and other imidazole fungicides, can inhibit estrogen biosynthesis by inhibiting CYP19 aromatase, preventing the conversion of androgens to estrogens (28).

Interference with hormone storage and release

Interference with hormone storage and/or release is also listed as a mechanism of action in the concept of EDCs. Catecholamine hormones (such as norepinephrine) are stored in the adrenal medulla's granular vesicles and in presynaptic terminals in the central nervous system. As a result, they can be made available on request. Steroid hormones, on the other hand, are not retained intracellularly in secretory granules and are readily synthesized after gonad stimulation with gonadotropin. Chlordimeform and amitraz, both formamidine pesticides, have been shown to inhibit norepinephrine binding to alpha 2-adrenoreceptors (29). The preovulatory rise in the pulsatile release of GnRH and the resulting ovulatory surge of LH are both dependent on norepinephrine (30).

Interference with hormone transport and clearance

Pesticides have been linked to steroid hormone clearance, which occurs primarily in the liver, according to studies. Each hormone has a different clearance rate, which is influenced by compounds that alter the function of liver enzymes involved in hormone clearance. Many pesticides activate the liver enzymes monooxygenase and UDP-glucuronosyltransferase, resulting in increased pesticide clearance as well as testosterone clearance (31). *In vivo*, DDT analogs, for example, are active inducers of hepatic microsomal monooxygenase activity, which degrades endogenous androgens and leads to androgen receptor-mediated suppression (32).

Interference with hormone receptor recognition and binding

Hormones fly from the point of release in the bloodstream to specific tissues to deliver their messages. Hormones bind to receptors so that the message can be decoded. Only a certain form of hormone may bind to a specific receptor because hormone and receptor have such a tight fit. A variety of environmental

factors can influence this process by mimicking natural hormones (agonists) or blocking receptor binding (antagonists). The latter mechanism is dependent on total or partial receptor blocking. Since the affinity of endocrine disruptors for the estrogen receptor is typically several times lower than that of 17-beta-estradiol, this mechanism only works when the endocrine disruptor concentration is large (33). Cooper et al. found that lindane can effectively block the response of estrogen-dependent tissues and that this apparent anti-estrogenic effect is responsible for the ovarian function disruptions observed in rats (34). *In vitro* and *In vivo*, the fungicide vinclozolin and two of its metabolites bind to the androgen receptor and function as androgen receptor antagonists (35).

Interference with hormone post-receptor activation

When an agonist binds to its receptor, a series of events occur that cause the required cellular response for signal transduction across the membrane or, in the case of nuclear receptors, the start or alteration of DNA transcription and protein synthesis (36).Lindane has been shown to minimize protein kinase-C activation and decrease phosphatidylinositol turnover in the membrane. Indirect mechanisms, such as downregulation, can affect steroid hormone receptor activation, as seen after TCDD exposure (37).

Interference with the Thyroid function

Pesticides such as chlorophenols, chlorophenoxy acids, organochlorines, and quinones have been shown to disrupt thyroid gland function and lower thyroid hormone levels in the blood. (38) Thyroid hormone deficiency may impair the catalytic activity of hepatic cytochrome P450 monooxygenases, altering hepatic androgen metabolism (39).

Interference with the Central Nervous System

In the integration of hormonal and behavioral activity, the central nervous system (CNS) plays a critical role. Disturbances in these finely tuned systems can have a significant impact on normal adaptive behavior and reproduction. Since several pesticides are considered to be neurotoxic, it's possible that they may interfere with the CNS's organizing operation by disrupting brain cell functions (36). In rodents, low-dose exposure to o,p-DDT, and methoxychlor, for example, has been shown to result in decreased hypothalamic and pituitary activity (40).

THE EFFECTS OF PESTICIDE USE ON THE FEMALE REPRODUCTIVE SYSTEM

The studies discussed thus far have mostly included laboratory animals *(In vivo*) or cell cultures *(In vitro*). Animal and in vitro tests are often used as early signs of possible reproductive or developmental consequences. However, because of variations in exposure levels (41), fertility problems, metabolism, age, and lifespan, the health risks for human populations can be significantly different, making it difficult to extrapolate from animal effects to effects that would be anticipated in women (33). Only a threat is revealed when a pesticide's potential for harm is recognized. The likelihood of this pesticide having a biological effect is determined by its properties, but the effect will only occur when exposure exceeds a certain amount level (41). Endocrine disruptors that accumulate in the body may eventually reach higher threshold levels required for biological effects to manifest. Specific and sometimes brief time periods occur in the complex processes of the menstrual cycle, ovum formation, fertilization, implantation, and the growth and development of the fetus, in which these processes may be especially susceptible to low-dose endocrine disruptor exposures (33). Another challenge in human research is that endocrine disruptors can be introduced to people in a variety of ways, including iatrogenic exposure, endogenous estrogens, natural compounds with estrogenic or androgenic activity (bioflavonoids), and environmental endocrine disruptors including pesticides. It's also possible that endocrine disruptor interactions play a role when multiple exposures are present (42). As a result, epidemiologic findings seldom refer to particular pesticides, and firm conclusions regarding the causality of endocrine disruptor effects on female reproductive systems are missing. Still, we'll offer a brief rundown of epidemiological studies that have found links between pesticide exposure and reproductive effects, which may be attributable to female hormone disruption.

Disruptions of the menstrual cycle

Certain pesticides have hormonal or ovotoxic properties that adversely affect the reproductive system in humans as well as animals (pocer, p).The effects of pesticide exposure on the menstrual cycle were studied in two studies. Both studies discovered links between DDT and a DDT metabolite in the blood (43) and short periods and undefined 'menstrual disturbances' (44). According to a new report, women who currently use pesticides have longer menstrual cycles and are more likely to skip periods than women who have never used pesticides (45). In addition, relative to women who had never used pesticides, women who used likely hormonally active pesticides had a 60–100% higher chance of having long cycles, missed periods, and intermenstrual bleeding.

Infertility

Infertile women were found to be three times more likely to have been exposed to pesticides (45) and nine times more likely to have worked in agriculture in a study conducted in the United States. Another research discovered no links between infertility and self-reported overall pesticide exposure, agricultural employment, or living on a farm in the two years preceding the diagnosis. Where only exposure to herbicides was considered, however, there was a connection (47).

Pregnancy elapsed time

Three research looked at the impact of pesticide exposure on the time it took couples to become pregnant [time-to-pregnancy,TTP], which is influenced by disruptions in the reproductive cycle, from gametogenesis to embryonic survival (48). Curtis et al. found no clear pattern of associations in Canada, although certain pesticides were suspected to be linked to prolonged TTP (49). TTPs were found to be substantially prolonged in female greenhouse workers when they were exposed to high levels of pesticides (50).

Abortion/stillbirth that occurs unexpectedly

According to several studies, the risks of spontaneous abortion and stillbirth (51) were significantly increased among women who were exposed to pesticides at work and/or worked in the agricultural sector. Furthermore, two reviews found various indications that pesticide exposure may lead to spontaneous abortion and/or stillbirth (52), but it is uncertain if this should be considered an endocrine-disrupting impact (53).

Deficiencies in growth

In a large cohort study, a link between birth defects and agricultural work was discovered (54). Agricultural work was linked to orofacial clefts, hypospadias (55), absolute anomalous venous return (55), spina bifida (57), and limb reduction defects in studies focused on particular birth defects (58), though one study contradicted the connection with limb reduction defects (59). Pesticide exposure during the first trimester of pregnancy nearly doubled the risk of cleft lips and palates in offspring, according to a well-conducted Finnish study of women employed in agricultural occupations (60). There was also a small rise in the probability of CNS defects. It was once again impossible to create a cause-and-effect relationship between these defects and pesticide exposure.

CONCLUSION

Pesticides can impact the hormonal function of the female reproductive system, notably the ovarian cycle, in a variety of ways, as discussed in this review. Pesticides are made up of a multitude of distinct chemicals with variable structures and toxicity levels that can function in a variety of ways. As a result, it's quite likely that some of the aforementioned processes are involved in the pathophysiological pathways explaining pesticide exposure's role in ovarian cycle disturbances, which eventually lead to fertility problems and other reproductive harm. The studies discussed have the drawback of being primarily animal and cell culture experiments in a laboratory setting. Although extrapolating effects seen in laboratory animals to those seen in people is difficult, they are frequently the first indication of a chemical's possible reproductive consequences. As a result, we looked into epidemiological studies that connected pesticide exposure to menstrual cycle abnormalities, reduced fertility, longer time to pregnancy, spontaneous abortion, stillbirths, and developmental problems. However, the bulk of these studies lacked specific information on pesticide exposure and the pathophysiological mechanisms at work. We must also keep in mind that the capacity of a pesticide to cause harm is based on the dose, timing, and length of exposure. Pesticide exposure in the workplace, however, appears to impair the female reproductive system. The information offered in this study on how pesticides modify hormonal function might be used to generate specific ideas for future research on pesticides' effects on the ovarian cycle, both in toxicological and epidemiological settings.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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