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Endocrine disruptors and female fertility: a review of pesticide and plasticizer effects

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An ongoing interest in environmental exposures and female fertility has led to an increasing number of studies focusing on endocrine-disrupting chemicals (EDCs). Both natural and synthetic compounds have the ability to impact reproductive health by altering the structure and/or function of genes and proteins that facilitate normal ovarian and endometrial functions. This mini-review aims to summarize the effects of some of the most common EDCs on female fertility, including the effects of pesticides and plasticizer alternatives (phthalates, bisphenol A), based on available data in human studies. A literature search was performed using the key words "pesticides, fertility, reproduction, plasticizers, bisphenol A, phthalate, miscarriage, and in vitro fertilization." The data supporting EDCs' role in female infertility remain limited, but existing evidence suggests that exposure may have an adverse impact. Accumulating evidence in animal studies provides important insights into the mechanisms underlying EDC effects. As dose-response dynamics are better elucidated, understanding the effects of EDCs on female fertility will help in the development of guidelines for both industry and individuals. (Fertil Steril Rep® 2022;3:86–90. ©2022 by American Society for Reproductive Medicine.)
Key Words: Endocrine-disrupting chemicals, female fertility, pesticides, plasticizers

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Endocrine-disrupting chemicals (EDCs) comprise a diverse group of chemical compounds that have recently become a topic of interest because of their potentially harmful effects on human health. Some EDCs are naturally occurring compounds; however, most EDCs are synthetic and were released into the environment without any prior knowledge of their effects on human and animal health. These natural and synthetic compounds have the ability to alter the actions of endogenous hormones and as a result, EDCs may disrupt the functions of the endocrine system.

Although the term "endocrine disruptor" was first proposed 30 years ago, the United States Environmental

Protection Agency has now identified 1,482 man-made chemicals that are considered EDCs (1). More recently, the American College of Obstetricians and Gynecologists has partnered with the American Society for Reproductive Medicine to publish committee opinion regarding EDCs and reproductive health (2). Despite their identification, understanding their mechanism of action and potential negative health implications remain incomplete.

This review will focus on the effects of 2 common classes of EDCs on female fertility. An exhaustive review of EDCs and female reproduction and fertility is beyond the scope of this mini-review; our aim is to summarize the effects of 2 of the most common EDCs–pesticides

and plasticizer alternatives (phthalates, bisphenol A [BPA])–on the basis of available data in human studies (Table 1) (3–20).

MATERIALS AND METHODS

This review was conducted using a PubMed search for human studies published between 2001 and 2021 using the following keywords: pesticides, fertility, reproduction, plasticizers, bisphenol A, phthalate, miscarriage, and in vitro fertilization (IVF). In addition, reviews that cited original references were examined for relevant information. We included studies that looked specifically at reproductive outcomes in women, including time to pregnancy, pregnancy loss, and assisted reproductive technology (ART) outcomes, including oocyte yield, embryo development, clinical pregnancy rates, and live birth rates. We also included reviews of the mechanisms underlying the effects of EDCs in rodent models. Studies with primary outcomes of ovarian reserve testing that lacked reproductive outcome data were excluded from this review. We

https://doi.org/10.1016/j.xfre.2022.04.003

excluded studies focusing on the effects of EDC exposure on gynecologic diseases, such as polycystic ovary syndrome, endometriosis, and uterine leiomyomas, considered to be outside the scope of this mini-review.

EFFECTS OF EDCs ON FEMALE REPRODUCTION
Pesticides

Pesticides are commonly used in agricultural and household settings. Pesticides are used in large quantities—more than 1 billion pounds are used annually in the United States (2). Sources of contamination can be through ingestion, inhalation, or skin absorption, and the pathways of exposure can include food, water, air, dust, and soil (2).

Decreased fertility because of exposure to pesticides has been reported in several studies. Exposure to organochlorine pesticides was associated with decreased fecundability in 394 couples enrolled in a French birth cohort (4). Elevated cord blood levels of 3 organochlorine pesticides—dichlorodiphenyldichloroethylene (DDE), β-hexachlorocyclohexane (β-HCH), and hexachlorobenzene (HCB)—were associated with a longer time to pregnancy. After adjusting for maternal age, body mass index (BMI) and smoking status, fecundability was lower for the highest exposure levels of DDE (odds ratio [OR], 0.60 [0.42–0.84]; $P=.003$), β-HCH (OR, 0.49 [0.29–0.80]; $P=.005$), and HCB (OR, 0.67 [0.48–0.95]; $P=.02$) (4). Important limitations of this study include the use of cord blood as a surrogate for maternal exposure before pregnancy and reliance on subject recall for time to pregnancy. Additionally, the study design was limited to women who were already pregnant and, thus, likely underrepresented the less fertile couples.

Exposure to pesticides has also been shown to impact ART outcomes. Normal ovulation, healthy oocyte quality,

TABLE 1

Effects of pesticides and plasticizers on female fertility.

EDC	Exposure source	Negative effect on female fertility	No effect or positive effect on female fertility
Pesticides	Contaminated food, water, air, dust, and soil	Decreased ART clinical pregnancy and live birth rates (3)	
DDE		Decreased fecundability (3), fertilization rate, and number of high-quality embryos (4, 5). Increased risk of miscarriage (1)	No effect on ART pregnancy or live birth rate (5)
β-HCH		Decreased fecundability (3), fertilization rate, and number of high-quality embryos (4, 5)	No effect on ART pregnancy or live birth rate (5)
HCB		Decreased fecundability (3), fertilization rate, and number of high-quality embryos (4, 5)	No effect on ART pregnancy or live birth rate (5)
DDT		Increased risk of miscarriage (1, 6)	No association with number or quality of oocytes retrieved, fertilization rate, embryo quality, or pregnancy rate (7)
Glyphosphate			No association with miscarriage rate or time to pregnancy (8)
Plasticizers			
BPA	Contaminated food, consumer products, and packaging	Decreased oocyte yield (9, 10) and decreased normal fertilization (11). Increased risk of miscarriage (12–14)	No association with decreased fecundity (15, 16). No association with fertilization rates, proportion of high-quality embryos, embryo implantation, clinical pregnancy, or live birth rates (17)
DEHP	Used in consumer goods such as medical devices, cleaning/building materials, personal care products, cosmetics, pharmaceuticals, food processing, and toys	Decreased oocyte yield, clinical pregnancy rate, and live birth rate (18)	No effect on couple time to pregnancy (15)
MEP		Decreased odds of normal fertilization (11). Decreased fecundity (19)	No correlation between good-quality embryos on day 3 or blastocyst formation (11). No effect on couple time to pregnancy (15)
MBP		Decreased odds of normal fertilization (20)	No correlation between good-quality embryos on day 3 or blastocyst formation (11). No effect on couple time to pregnancy (15)
mcPP			Shorter time to pregnancy (15)

Note: DDE = dichlorodiphenyldichloroethylene; EDC = endocrine-disrupting chemical; HCB = hexachlorobenzene; HCH = hexachlorocyclohexane; DDT = dichlorodiphenyltrichloroethane; BPA = bisphenyl A; DEHP = di (2-ethylhexyl) phthalate; MEP = monoethylphthalate; MBP = monobutylphthalate; mcPP = mono (3-carboxypropyl) phthalate.

Vessa. EDCs and female fertility. Fertil Steril Rep 2022.

and subsequent embryo development are dependent on tightly regulated interactions between the oocyte and its surrounding somatic cells within the follicular microenvironment, which may be very sensitive to contaminant exposures. In women undergoing ART, higher follicular fluid DDE, HCB, and β-HCH levels were strongly negatively associated with fertilization rate ($P < .00001$) and the proportion of high-quality embryos relative to the number of oocytes retrieved ($P < .05$) (5). However, no associations were observed between follicular pesticide levels and clinical pregnancy or live birth rate, underscoring the importance of aspects other than the follicular microenvironment (e.g., uterine environment) in the establishment and maintenance of a healthy pregnancy. Although logistic regression analyses controlled for male subfertility as a confounder, paternal exposures were not assessed, and genetic testing of the embryos was not performed, which could have contributed to poorer quality embryos.

A recent subanalysis of the Environment and Reproductive Health prospective cohort study found an association between pesticide residue intake from the consumption of fruits and vegetables and pregnancy outcomes in women undergoing ART (3). In a cohort of 325 women undergoing 541 ART cycles, greater intake of high-pesticide residue fruits and vegetables was associated with 18% lower probability of clinical pregnancy (95% confidence interval [CI], 5%–30%) and 26% lower probability of live birth (95% CI, 13%–37%) (3). Although multivariate analysis adjusted for multiple confounding variables (e.g., age, BMI, smoking status, infertility diagnosis, residential pesticide exposures), reliance on the subject's self-reported food intake is an important limitation.

On the contrary, a study of 99 women found no association between exposure to the insecticide dichlorodiphenyltrichloroethane (DDT) and adverse ART outcomes (7). Higher levels of DDT in the follicular fluid were not significantly associated with a decrease in the number or quality of oocytes retrieved, fertilization rate, embryo quality, or pregnancy rate (7). Similarly, a review of epidemiologic studies assessing exposure to glyphosate, a common herbicide, found no consistent effects of glyphosate on reproductive health (8). Specifically, some studies examined both male and female self-reported exposure, spontaneous abortion rate, and time to pregnancy and found no significant correlation (8). Overall, contradictory findings may be due to different study populations (e.g., race/ethnicity, concurrent unmeasured environmental exposures, fertile vs. infertile women/couples, infertility diagnoses), methods of exposure assessment (e.g., direct measurement vs. subject recall), and/or the study of different pesticide compounds.

Multiple studies support an association between pesticides and early pregnancy loss but are limited by substantial delays (e.g., 2–6 years) between index pregnancies and measurement of serum pesticide levels (reviewed by Green et al. [1]). A more robust, prospective analysis measured the preconception serum DDT levels in Chinese textile workers between 1996 and 1998; after adjusting for age, BMI, and other occupational exposures, logistic regression revealed a 2.12 relative odds of early pregnancy loss (95% CI, 1.26–3.57) in the highest tertile serum DDT group compared with the lowest tertile (6). The particular strengths of this study include its prospective nature, recruitment of newly married nulliparous women actively trying to conceive, and use of daily urine human chorionic gonadotropin assays to prospectively detect conceptions, including early pregnancy losses occurring before clinical detection.

Although human epidemiologic studies cannot provide information on the mechanisms, rodent studies indicate that exposure to pesticides adversely affects ovarian function. In vivo exposure of CD-1 mouse antral follicles to methoxychlor, a pesticide commonly found in insecticides, resulted in decreased expression of steroidogenic enzymes and decreased ovarian steroid biosynthesis (21). In rats, exposure to methoxychlor during early development resulted in reduced expression of estrogen receptor β in preantral and antral follicles, important in the regulation of growth and maturation of ovarian follicles, granulosa cell differentiation, and luteinizing hormone responsiveness (22). In vitro studies exposing mouse oocytes to methoxychlor demonstrated increased formation of reactive oxygen species, lipid peroxidation, and aberrant mitochondrial distribution (20). A review of the mechanisms by which pesticides affect female reproductive function is provided by Zama and Uzumcu (22).

Plasticizers

Plasticizers are substances added to a material to produce or promote flexibility and to reduce brittleness. The major plasticizers include phthalates and BPA, which are present in food, packaging, and consumer products such as medical devices, cosmetics, pharmaceuticals, and toys (2). Exposure can occur through ingestion, inhalation, and skin absorption, similar to the pathways seen for pesticide exposure (23).

Prospective cohort studies to determine the effect of plasticizer exposures on natural conception have yielded inconsistent results. A survey of 229 women who had been part of the Danish First Pregnancy Planner Study from 1992–1994 found an association between urinary monoethyl phthalate levels and a longer time to pregnancy, with a fecundability ratio of 0.79 (95% CI, 0.63–0.99) (19). However, Buck Louis et al. (15) found no significant association between female urinary BPA or phthalate concentrations and time to pregnancy. Of note, the latter study used only a single urine measurement, and participants were mostly white, college-educated patients, limiting generalizability. Similarly, in a cohort of 2,001 pregnant women, Vélez et al. (16) found no association between urinary BPA or phthalate levels and time to pregnancy. However, this study relied on subject recall of time to pregnancy; further, the subjects had already achieved pregnancy, and the urinary BPA level was collected in the first trimester. Therefore, infertile women who may have had higher exposures to these chemicals were excluded (16).

An association between plasticizers and infertility has been described in multiple studies primarily focusing on plasticizers' effects on oocyte yield in women undergoing ART. Mok-lin et al. (9) found a negative correlation between urinary BPA levels and oocyte yield in 84 women undergoing ART, with an average 12% decrease in the number of oocytes

retrieved per log unit increase in specific gravity of urinary BPA (95% CI, 4–23; $P=.007$). Similarly, in 174 women undergoing ART, Ehrlich et al. (10) found a significant linear dose-response association between increased urinary BPA concentrations and decreased oocyte yield and normally fertilized oocytes ($P=.001$). In addition, Hauser et al. (18) evaluated di (2-ethylhexyl) phthalate metabolites in 256 women undergoing IVF. After controlling for age, BMI, smoking status, and primary infertility diagnosis, the urinary di (2-ethylhexyl) phthalate metabolite concentrations were inversely associated with oocyte yield ($P<.05$), clinical pregnancy ($P=.04$), and live birth rate ($P=.01$) after ART (18).

On the contrary, Deng et al. (11) measured urinary phthalate metabolites in 663 women undergoing IVF/intracytoplasmic sperm injection at a single center. Although increased urinary monobutylphthalate levels were negatively correlated with the odds of normal fertilization ($P<.01$), no significant correlation was found between any of the urinary phthalate concentrations and odds of a good-quality embryo on day 3 or blastocyst formation, clinical pregnancy rate, live birth rate, or early miscarriage rate (11). Similarly, another prospective cohort study of 256 women undergoing IVF found no association between the urinary BPA levels (measured in up to 2 urine samples collected before oocyte retrieval) and proportion of high-quality embryos, fertilization rates, implantation rates, clinical pregnancy or live birth rates (17). Although multivariate models adjusted for confounders such as age, race, and BMI, a major caveat is the measurement of these short-lived compounds in 1–2 urine or serum samples at the time of the IVF cycle, which may not reflect the true window of exposure in relation to folliculogenesis, embryo implantation, or during pregnancy. In addition, whether the results can be generalizable to those conceiving naturally is unclear.

With respect to miscarriage risk, Lathi et al. (12) conducted a prospective study of 115 women undergoing 68 clinical miscarriages. The median serum conjugated BPA concentrations measured during the missed menstrual cycle were significantly higher in women who had miscarriages than in those who had live births ($P=.014$) (12). A similar increased risk has been noted for both aneuploid and euploid miscarriages (12). Unique to this study was the timing of serum conjugated BPA measurement, collected during early pregnancy shortly after implantation. In a subsequent case-control study including 102 patients with recurrent miscarriage, urinary BPA levels were correlated with an increased risk of recurrent miscarriage ($P<.001$) (13). Although women with identifiable causes of recurrent miscarriage were excluded, embryo aneuploidy was not assessed. The study relied on subject recall of pregnancy history, and spot urine measurements were obtained after pregnancy, questioning the timing of exposure.

A smaller study by Sugiura-Ogasawara et al. (14) measured serum BPA levels in 45 women with a history of 3 or more consecutive first-trimester pregnancy losses and followed subsequent pregnancy outcomes over 16 months. The mean serum BPA levels were significantly higher in women with previous recurrent pregnancy loss ($P=.024$) compared with age-, BMI- and geographic location–matched controls, but higher serum BPA levels did not predict future miscarriage (14). However, the timing of BPA exposure relative to subsequent miscarriage was unclear. Further, none of the above studies have taken into account the potential effects of male exposures on embryo quality and miscarriage risk.

Studies in mice have elucidated the mechanisms by which plasticizers negatively impact female fertility and IVF outcomes. After Patricia Hunt serendipitously discovered an increase in mouse oocyte aneuploidy associated with damaged plastic cages and water bottles in 1998, her group later elucidated a dose-dependent increase in oocyte aneuploidy in mice treated with daily BPA (2, 22). Mechanistic studies for BPA demonstrating adverse effects of BPA exposure on hypothalamic-pituitary signaling, folliculogenesis, oogenesis, estrous cyclicity, and embryo implantation have been reported (reviewed by Zama and Uzumcu [22] and Ziv-Gal and Flaws [24]). In utero exposures impaired uterine morphology and function in offspring (24). Human in vitro studies have also demonstrated adverse effects of BPA on oogenesis; exposure of fetal oocytes to BPA resulted in defects in synapsis and recombination of homologous chromosomes and increased oocyte degeneration (23). In adult oocytes, BPA exposure resulted in impairment of the cytoskeleton and incomplete meiosis (23). Regarding phthalates, the mechanisms affecting female fertility in rodent studies include disruption of oogenesis and folliculogenesis, induction of deoxyribonucleic acid damage in oocytes, altered expression of gonadotropin and gonadotropin hormone-releasing hormone receptors, impaired steroidogenesis, and altered estrogen/androgen receptor signaling (reviewed in detail in the study by Hlisníková et al. [25]). Overall, these studies provide important insight into the mechanisms underlying decreased fertility after exposure to plasticizers.

CONCLUSION

The data supporting the role of pesticides and plasticizers in female infertility and miscarriage continue to grow as more interest in the field arises. Much of the human literature is based on epidemiological studies lacking mechanistic information, and results are varied, in large part because of methodological differences, populations studied (e.g., fertile vs. infertile couples), and assessment of exposures (e.g., metabolites studied and frequency/timing of assessment). However, the data overwhelmingly support an overall negative effect of these EDCs on female fertility, reviewed in detail in the report by Green et al. (1). Outside the scope of this review, but of equal importance, is the effect of male EDC exposures.

Exposure to specific EDCs such as pesticides, BPA, and phthalates should be minimized in couples trying to conceive, given the evidence for negative effects on fertility and overall health (2). Clinicians play a key role in counseling women about healthy lifestyles, including ways to minimize EDC exposures during the periconception and prenatal periods. Practical risk-assessment tools and specific recommendations to minimize EDC exposures are reviewed in detail in the study by Segal and Giudice (2), including choosing organic produce and "fragrance-free" products and using alternatives to plastic food containers. It is also critically important to consider racial/ethnic disparities in EDC exposures; because exposures

may be higher in nonwhite individuals, minimizing exposures provides particular opportunity for modifying risk in vulnerable populations who are already at increased risk of adverse reproductive health outcomes (25). As dose-response dynamics are better elucidated, understanding the effects of EDCs on female fertility will help develop guidelines for both industry and individuals and hopefully promote innovations in alternate compounds that do not harm fertility and health.

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