Environmental exposure to endocrine-disrupting chemicals and miscarriage

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Establishment of early pregnancy is the result of complex biochemical interactions between the decidua and blastocyst. Any alteration in this chemical dialogue has the potential to result in adverse pregnancy outcomes including miscarriage. Sporadic miscarriage is the most common complication of pregnancy and can be caused by multiple factors. While the most common cause of miscarriage is genetic abnormalities in the fetus, other contributing factors certainly can play a role in early loss. One such factor is environmental exposure, in particular to endocrine-disrupting chemicals, which has the potential to interfere with endogenous hormone action. These effects can be deleterious, especially in early pregnancy when the hormonal milieu surrounding implantation is in delicate balance. The purpose of this paper is to review the current evidence on the role of environmental toxins in reproduction. (Fertil Steril® 2016;106:941–7. ©2016 by American Society for Reproductive Medicine.)

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Sporadic miscarriage, the loss of an embryo or fetus before 20 weeks of pregnancy, is the most common complication of pregnancy, affecting approximately 15% of all clinically recognized pregnancies (1). A much larger percentage of pregnancies are impacted if preclinical losses are included. Of these clinical pregnancy losses, a large majority occur during the first trimester. A majority of these first trimester losses are secondary to genetic abnormalities in the conceptus. However, sporadic, euploid losses do occur. Risk factors for pregnancy loss include but are not limited to advanced maternal age, hormonal imbalances, immunological interactions, and uterine anatomic abnormalities (1–4). Certainly, lifestyle factors such as tobacco smoke and alcohol usage are generally well accepted as contributing causes of miscarriage (5–7). Exposure to other chemicals such as endocrine disruptors, heavy metals, or occupational chemicals has also been implicated in miscarriage. The sensitivity of embryonic tissue or fetal tissue to such compounds is far greater than that of adult tissue. This is in part because of the small size and totipotent nature of many of the cells in the embryo or fetus (8, 9). A single insult at these early stages of development can have deleterious effects on development.

Not only can environmental toxins impact the developing embryo, there is also a potential for alteration of the endometrium of pregnancy, that is, the decidua. Successful implantation requires a complex biochemical dialogue to occur between the blastocyst and decidua. These early interactions allow for implantation to occur and ultimately for establishment of pregnancy (10). Environmental alteration of these early uterine events can also disrupt an early pregnancy or potentially result in miscarriage or other adverse pregnancy outcomes. In particular, abnormal hormone signaling pathways could potentially affect not only the ability of a blastocyst to implant in the endometrium but also the ability of the decidua to communicate with fetoplacental unit in a normal way. Multiple industrial contaminants have the potential for endocrine disruption; these chemicals can impact the ability to become pregnant and sustain a healthy pregnancy. Other environmental contaminants have also been implied to have a causal effect on pregnancy loss; these include radiation exposure, heavy metals, agricultural chemicals, and industrial solvents. Given the scope of this review, our discussion will be limited largely to endocrine-disrupting chemicals (EDCs). EDC exposure may represent an additional cause(s) of sporadic or recurrent loss.

DDT

Perhaps one of the most well-known EDCs is DDT, or 1,1,1-trichloro–

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2,2′bis(p-chorophenyl) ethane. DDT was first synthesized in 1874. However, it was not recognized as a pesticide until 1939, when it was first used during World War II for protecting the military from malaria. It then became commercially available in 1945. DDT had widespread use and is credited for eradicating malaria from the United States and Europe. While other pesticides began to emerge, DDT was still the most widely used pesticide until the mid-1960s, when environmental impacts started to become apparent. Unfortunately, part of its efficacy as an insecticide is due to its persistence in the environment. Because of its chemical stability and lipophilic nature, DDT persists in the environment and results in accumulation and even bioconcentration within the food chain. Even today, DDT is widespread in the environment; in fact some countries are still using DDT in vector control (8, 11).

By the mid-1950s animal studies were beginning to suggest that DDT was causing poor reproductive outcomes. Effects were first noted in birds, with plummeting of some bird populations. The birds most affected are those that are at the top of the food chain, in particular those that are fish eating. One specific example is the Californian brown pelican. They were found to have 3,000 breeding pairs in 1960, but by 1969 there were only 300 pairs and only five chicks were viable (12, 13). This decline in bird populations became the impetus for Rachel Carson's *Silent Spring*. Other animal populations were affected such as fetal resorption in rabbits and miscarriage and stillbirth in rats. Ultimately, DDT was restricted or banned in most developing countries by 1970 (11, 14).

Early human studies of DDT suggested a possible correlation with cancer in general. However, with time, reproductive disorders became apparent. Similar to the bird population, human population declines were secondary to reproductive failures. In vitro studies have shown that DDT has estrogenic activity (15). Dichlorodiphenyl dichloroethene (DDE), a metabolite of DDT, has been shown to be an androgen receptor antagonist. The reproductive repercussions of DDT use have been multiple; these include a suggested role in decline in sperm counts, increase in time to conception, and even intrauterine growth restriction (11, 16, 17). Spontaneous abortion has been correlated with DDT exposure in multiple studies. Given the stability of DDT and its metabolites (in particular DDE), it is possible to correlate serum levels with pregnancy history. Most human studies on miscarriage and DDT have correlated DDT or DDT metabolites with pregnancy outcomes. Some studies show limited impact of DDT on miscarriage (11, 18, 19). These studies are limited by the timing of collection of samples and the timing of observation of pregnancy losses. In these studies, DDT and/or its metabolites were measured in blood or serum that was collected after the pregnancies had completed. The levels of DDT would have the greatest impact during the pregnancy, that is, during the exposure to the fetus. In addition, many of the samples were collected in the postpartum period when women were nursing their infants. Since breast feeding decreases the DDT levels in the serum (20), levels could be lower than what they were in pregnancy. In addition to timing of sample collections, many pregnancy losses could have gone unaccounted for since these studies are retrospective in nature. Only prospective studies that collect samples and data throughout menstrual cycles and detect early preclinical losses with bhCG levels can account for all the pregnancy losses associated with high levels of serum DDT.

However, these studies have been in patients with lower serum levels of DDT or DDE. Several studies have shown that there is also an increase in spontaneous miscarriage at higher concentrations of DDE (>15 μg/L) (11, 18, 19). One of the largest studies of DDT and DDE in relation to miscarriage to date was done by Longnecker and coworkers (20). They used serum from enrollees in the Collaborative Perinatal Project (1959–1965). These women were asked about their pregnancy history, and serum samples were frozen. Serum from 1,717 women who had a pregnancy history was analyzed for concentrations of DDT and DDE. Women were compared to a group who had serum DDE levels of <15 μg/L; exposures greater than 15 μg/L were divided into quartiles of increased exposure. Longnecker et al. found an adjusted odds ratio (OR) of miscarriage per 60 μg/L increase in DDE of 1.4 (95% confidence interval [CI], 1.1–1.6) (20). One flaw of these studies is that they are retrospective in nature and therefore are subject to recall bias. There are two studies that are prospective in nature that found similar effects. Korrick and coworkers found an OR for miscarriage of 1.13 (95% CI, 1.02–1.26) in a case-control study matching patients by age, smoking status, body mass index, and workplace exposures; they were then followed prospectively through pregnancy (18). Control patients had an ongoing pregnancy, whereas the cases had miscarried. Serum levels of DDT and DDT metabolites were measured. Patients who miscarried were found to have higher levels of DDE in their serum (22 vs. 12 ng/g) than controls (P=.025) (18). Another prospective study by Venners et al. followed Chinese textile workers prospectively with serum hCG levels (19). In this study DDT levels were drawn before conception. Venners et al. found that there was a relative odds of pregnancy loss of 1.17 (95% CI, 1.05–1.29) associated with a 10 ng/g increase in serum total DDT (19). Overall, these studies consistently show an increase in spontaneous abortion in patients with higher serum levels of DDT or DDT metabolites (Table 1) (11, 18, 20).

BISPHENOL A

BISPHENOL A (BPA) [2,2-bis(4-hydroxyphyenyl) propane] was first synthesized in 1891 as a synthetic estrogen for the pharmaceutical industry. It was taken out of production once a much more potent estrogen was developed, diethylstilbestrol. Then, in the 1950s, its production resumed as it was found to be useful as an epoxy resin and the basis for polycarbonate plastics. It is now one of the highest-volume chemicals produced worldwide. BPA is an estrogenic compound used in the manufacture of polycarbonate plastic and epoxy resins. The use of BPA is so widespread that it is estimated that 100 tons of this chemical are released into the atmosphere annually (24, 34). While BPA is used to manufacture plastics frequently used for food storage, studies have shown that this