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The Physiopathology of Endometriosis: Pollution and Dioxin

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Abstract
Reports in the literature of an increasing incidence of endometriosis in industrialized countries and increasing problems with pollution in these countries leads to speculation about a possible link between one of the most harmful components of pollution, dioxin, and endometriosis. To establish this link, we need to examine three issues more closely: What are the effects of dioxin, what is the true incidence of endometriosis, and what is the nature of the association between endometriosis and dioxin. This report reviews current thinking on these issues.

Origin and Effects of Dioxin

Dioxin is a name for a family of heterocyclic hydrocarbons that are by-products of many industrial processes such as the blanching of paper, creation of herbicides, or incomplete combustion. The reference compound is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), known as a reproductive toxin, an immunotoxin, a neurotoxin, and a carcinogen. Dioxins are metabolically stable, and accumulate in the environment and in animal tissues. Dioxins are consumed by humans and animals when eating the flesh of fish and other animals who were exposed to this environmental toxin. Dioxins are known to be excreted in breast milk.

Known or putative effects of TCDD include death, wastage, lymphoid and gonadal atrophy, hepatic toxicity, metaplasia, chloracne, diabetes, and endometriosis. The effects of dioxin vary with age of the exposed animal and with the species; for example, mice are more sensitive to its effects than are rats.

In humans, dioxins are known to alter gene expression [1], and to affect the genes involved in inflammation and differentiation. A major effect of dioxin is immunologic; dioxin can inhibit T lymphocytes and cytokine production, and decrease natural killer cell activity [2, 3]. Dioxin can act as an antiestrogen, or as a weak estrogen, and may thereby affect endometriosis [4]. Acute effects in vivo include the binding of dioxin to the aryl hydrocarbon receptor, a ligand-activated transcription factor that has been found in many tissues, including the uterus.

It is tempting to speculate about a possible link between the increasing exposure to dioxins in the industrialized countries and the increasing reports of endometriosis in many of these same countries. To establish this link, we need to examine these issues more closely.

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Is the Incidence of Endometriosis Increasing in Women?

The possible relationship between endometriosis and industrialization is a clear cause for concern. In industrialized countries, endometriosis is often called the 'career woman's disease.' In some areas of Russia, the rise in the incidence of endometriosis parallels that of pollution levels. In baboons in Kenya, the incidence of endometriosis in rural areas is 7%, whereas it rises to 25% in urban cities such as Nairobi.

The reported prevalence of endometriosis has increased in industrialized countries, according to the literature, from 25 to 30% in the 1970s, and 30 to 40% in the early 1980s, to as high as 80% in the late 1980s. Although the prevalence seems to be increasing, it is important to determine whether this trend is caused by a recognition bias. For example, an increasing incidence of endometriosis could be the result of more scrutiny for small, microscopic lesions. Increasing reports of deep endometriosis may result from the increased recognition of this clinical entity among gynecologists and registrars because of more widespread use of menstrual clinical examinations and laparoscopic excisions.

Another possible indicator of the prevalence of endometriosis is the indication for hysterectomy, which can be traced in statistical databases in some industrialized countries. In the United States, the incidence of endometriosis reported as an indication for hysterectomy has increased. One must be careful when interpreting such data, however, as there could be a bias towards more common use of surgical hysterectomy in some countries. Until more data are available, it is difficult to disregard the possible sources of bias from increased recognition of, and screening for, endometriosis.

Is Endometriosis Linked to Dioxin Exposure?

There is some evidence to support the claim that dioxin exposure is related to the development or worsening of endometriosis.

Animal Studies

Rodent models of endometriosis and dioxin show acute effects, but the interpretation is unclear. In a study by Cummings et al. [5], TCDD produced a dose-dependent increase in the diameter of surgically induced endometriotic lesions in mice and rats up to 12 weeks after the implantation surgery. Ovarian weight decreased in the rats, but not in the mice, and histologic evaluation showed ovulatory arrest at 12 weeks. In addition, TCDD caused suppression of cell-mediated and humoral immunity. A study by Yang and Foster [6] examined the effects of dioxin on surgically induced endometriosis in ovariectomized mice treated with high doses of estradiol. In this case, the researchers found that continuous exposure to TCDD caused a regression of the endometriotic lesions.

In a long-term controlled study of 24 rhesus monkeys by Rier et al. [7], groups of monkeys were exposed to no dioxin (control) or 5 or 25 parts per trillion (ppt) dioxin for 4 years. Groups exposed to dioxin had biopsy-proven accumulation in adipose tissue. At the end of the study (10 years after termination of dioxin exposure), the incidence of endometriosis was directly correlated with dioxin exposure, and the severity of the lesions was dose related (table 1). Seven monkeys died, 3 of endometriosis and 4 of unrelated causes. Although unrelated to dioxin exposure, the similarity in the delayed effect of total body irradiation is striking.

There has been a correlation established between the development of endometriosis and proton radiation in rhesus monkeys [8]. The shortest period of time between development of endometriosis and irradiation was 7 years.

Human Evidence

Extremely high levels of serum dioxin, greater than 56,000 ppt, were measured by Mocarelli et al. [9] in selected residents of Seveso, Italy, who developed chloracne after an explosion of a chemical manufacturing plant in 1976. A later study conducted by Bois and Eskenazi [10] in 1994 confirmed that the most heavily exposed Seveso residents had concentrations of dioxin in their body fat that exceeded the highest levels reported in Rier et al's study of rhesus monkeys. Further epidemiologic studies in these populations may help to establish an association between dioxin exposure and endometriosis.

Studies of dioxin exposure in women with endometriosis have found a possible link between endometriosis and dioxin. In a study by Mayani et al. [11], 8 of 44 (18%) infertile women with endometriosis were found to have detectable levels of dioxin in their blood, compared with 1 of 35 (3%) infertile woman without endometriosis ($p = 0.04$; fig. 1).

It is presently unknown whether the accumulation of dioxin in human breast milk should warrant any change in the recommendations for breast-feeding of infants. There is a large, ongoing study in the Netherlands, designed to determine any adverse effects of dioxin in human breast milk.

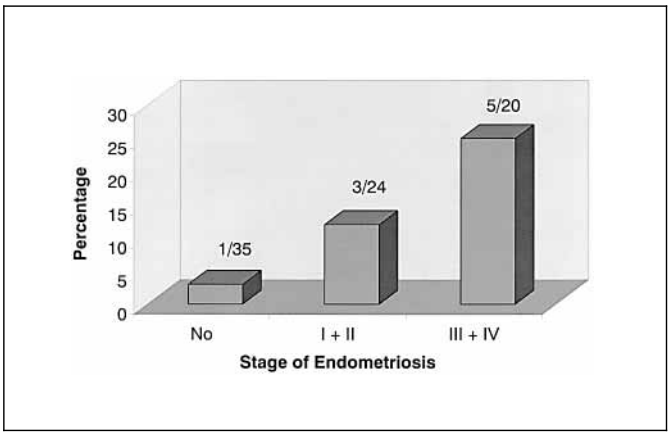

Fig. 1. Dioxin concentrations in women with endometriosis. (Data from Mayani et al. [11].)

Table 1. Endometriosis in rhesus monkeys with long-term (4-year) exposure to dioxin

Dioxin exposure	Stage of endometriosis				
	None	I	II	II	IV
Control	4	2	0	0	0
5 ppt	2	2	0	2	1
25 ppt	1	0	1	1	4

Table values are numbers of monkeys with the characteristic. Data from Rier et al. [7].

Possible Mechanisms

Endometrial growth is regulated by steroid hormones, cytokines such as tumor necrosis factor and interleukin 1, and a complex interaction of epithelial cells, stroma, and lymphoid cells. Several mechanisms may explain the development of endometriosis after exposure to dioxin. Dioxin may adversely affect the immune system, interfering with cytokine production and changing the composition of the peritoneal fluid to promote angiogenesis and growth. Alternatively, cellular changes or genetic predisposition may predispose an individual to the immunologic modulation caused by dioxin exposure, leading to infiltration and adhesion of endometrial cells in the peritoneum.

Along with decreasing natural killer cell activity in plasma and peritoneal fluid, and promoting a decrease in cellular toxicity, dioxin may stimulate peritoneal fluid macrophages and thus affect angiogenesis and local concentrations of cytokines and growth factors. These factors may act synergistically to promote the development or worsening of endometriosis.

Conclusions

It is presently unknown whether dioxin causes endometriosis in humans. Circumstantial evidence would suggest that endometriosis prevalence and severity could be related to pollution. Further large-scale studies, with a careful attention to controlling for possible sources of bias, are necessary to clarify this relationship.

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Discussion

Prof. Terakawa: What was the direct cause of death in the three monkeys with endometriosis?

Prof. Koninckx: In the group of 24 monkeys entered into the study, seven have died. Three died from severe endometriosis due to bowel obstruction, while four died from unrelated causes.

Dr. Tsutsumi: Dioxin is also a problem in Japan. I think maternal milk may be more contaminated in Japan. How do you think we should advise women who ask us about the merits of breast feeding?

Prof. Koninckx: We do not have any conclusions at this moment. It is very important and that is why I referred to the study going on in the Netherlands. If you take the dioxin story very seriously in endometriosis, you should say that breast feeding is not to be recommended, or even go a step further and recommend women to express milk and throw it away to remove as much dioxin from their body as possible. It is too early, however, for this conclusion.

Dr. Ota: You said a major effect of dioxin in endometriosis is immunologic, with dioxin causing immunologic abnormalities. However you also said NK cell activity is decreased, but when we look in general at immunological abnormalities in peripheral blood, we do not find such severe abnormalities; for example, the number of T cells over B cells. Could you comment on this discrepancy.

Prof. Koninckx: We have two kinds of data. First the data which look at acute effects. This involves giving dioxin for a few weeks and seeing what happens. Acute effects in vitro include binding to the receptor and nuclear effects. But the long-term effects of these acute changes will require many years to assess. What I tried to do today was to move from acute effects on endometrial cells and growth to say there is something which takes a lot of time to develop, and then suddenly, as soon as a strategic point is reached, further effects develop. There are many examples in medicine of effects not identified for many years. For instance, the association between maternal X-rays and leukemia, maternal diethylstilboestrol and gynecologic cancers in the female children. Often it is difficult to explain what is going on, but it can appear to be accumulated effects or due to point mutations similar to oncologic theories at this moment.

Dr. Ota: Does dioxin induce adenomyosis in the same way as its effect on endometriosis?

Prof. Koninckx: You probably notice that I did not use the words adenomyosis today. Adenomyosis within the uterus is something which is there and causes pain and bleeding, but it is poorly understood. At present, with MRI studies, we see condensation of inner layer, contractures of the inside of the uterus, and a whole series of endometrial muscle relationships. If I had to speculate at the moment, I would say that many of these uterine tumors have a fragile area of breakage on chromosomes 12 and 14. At the moment, we are looking in the same area for endometriosis.

Dr. Kanzaki: You identified some special areas in Russia which have a high incidence of severe endometriosis. Does any specific form of pollution appear to be more causative for this; for instance, radiation?

Prof. Koninckx: Endometriosis is high in Moscow, but epidemiologic studies are needed because, in Russia, there hasn't been a lot of population movement and there are areas of high and low pollution. Some areas are so polluted that no one lives there now, or will for a long time.

Prof. Taketani: You know a lot of the pathology of endometriosis in the rhesus monkey so my question is whether there is any relation between infertility and occurrence of endometriosis in these animals? If this is the case, I hypothesize that dioxin may compromise the reproductive function of rhesus monkeys leading to infertility. This infertility may then be the reason for the high occurrence of endometriosis. Thus dioxin may not be directly related to endometriosis, but rather associated indirectly, via its effect on infertility.

Prof. Koninckx: In the animal studies, the monkeys were not used for reproduction so we do not know whether they were infertile. However there is some data which I did not show from baboon studies performed at the same time. A series of baboons were immunosuppressed for a period of almost 6 months, treating them with the same dose as administered to patients after a kidney transplant. I was sure that we were going to find an increase in endometriosis and was surprised to find no evidence for this. Thus, short-term results show that immunosuppression in animals with endometriosis does not increase disease, but we have no data on long-term effects.

Prof. Taketani: If the etiology of endometriosis is linked to the immunosuppressive effect of dioxin, why is it that this immunosuppression does not lead to other pathologies such as cancer development and infection? I wonder why dioxin disturbs the immune system exclusively concerned with the development of endometriosis and nothing happens elsewhere.

Prof. Koninckx: The problem of dioxin is not solely linked with endometriosis as it has also been shown to cause diabetes. Maybe endometriosis has an unfortunate combination of being an immunologic disease, but with a very strong hormonal regulation, and dioxin works on the three levels, genetic, immunologic and as a hormone regulator modulator of receptors. When it acts in all three areas, it may lead to endometriosis.