

Introductory Remarks: Environmental and Endogenous Hazards to the Female Reproductive System

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The toxic action of environmental chemicals on reproduction and the toxiclike effects of ovarian hormones have been shown by numerous investigators. Some toxic effects of environmental chemicals on reproduction are through their action on hormonal secretion. Such effects on the endocrine system could provide additional approaches to investigations of toxicity of compounds. A better understanding of interactions of environmental chemicals with the endocrine system is needed. Therefore, it becomes important for a greater exchange of information and more interaction between toxicologists and endocrinologists.

Many factors, both environmental and endogenous, can have detrimental effects on the reproductive cycle and on the outcome of pregnancy. Recent papers (1, 2) have reviewed in considerable detail the role of environmental toxic substances on female reproduction. Data also exist from which it can be concluded that endogenous hormones can have toxic or toxiclike actions on reproduction. The present paper will point out some hazards from exogenous and endogenous substances on reproductive processes, while the following four papers will discuss in detail physiological and endocrinological mechanisms in female reproduction that could be susceptible to toxic agents.

Reproductive Hazards from Environmental Chemicals

This section is a brief summary of only a few examples of toxic chemicals on female reproduction. For extensive coverage of the area, see reviews by Sullivan and Barlow (1) and Longo (2). Chemical contamination of the environment not only presents risks to the current population and the unborn fetuses, but also presents hazards to future generations through mutations and due to

the persistence of some of the chemicals in the environment. A number of classes of chemicals and their effects on the reproductive system and the conceptus are summarized in Table 1.

From data in Table 1, it can be concluded that some chemicals have direct effects on the conceptus, while other materials alter reproduction through actions on different organs: hypothalamus, pituitary, ovary, or uterus. These alterations of reproduction could be through temporary or permanent changes in the endocrine system. Polybrominated biphenyls (PBB) and polychlorinated biphenyls (PCB) affect enzyme systems that metabolize steroids, and therefore affect circulating levels of steroid hormones (3). These altered hormonal concentrations would be expected to modify reproductive processes. Most toxic substances entering the maternal circulation can cross the placenta and result in various risks to the conceptus: death, congenital malformations, growth retardation, mental deficiencies, mutations and carcinoma.

Reproductive Hazards from Altered Endogenous Hormones

Brawer et al. (4) found that a single injection of a pharmacological level (2 mg/rat) of estradiol valerate resulted in a gradual progressive degeneration of axons and dendrites in the arcuate nucleus with

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Table 1. Examples of environmental agents that affect reproduction in the female.^a

| Chemical | Known effects on conceptus or reproductive function |
|---|--|
| Metals | |
| Lead | Abortion, mental deficiencies |
| Mercury | Abortion, menstrual disorders, birth defects |
| Cadmium | Retarded fetal growth |
| Selenium | Abortion |
| Organic pesticides, herbicides, organic solvents, etc. | |
| Dioxins | Abortion, birth defects, stillbirth |
| Polychlorinated biphenyls | Retarded growth, neural depression |
| Pesticides | Birth defects, mutation, neural alterations, ovarian dysfunction |
| Herbicides (2,4-D and 2,4,5-T) | Abortion, stillbirth, birth defects |
| Benzene, toluene | Menstrual dysfunction, anemia |
| Gases | |
| Carbon monoxide | Fetal death, brain damage |
| Ozone | Abortion, birth defects |
| Anesthetics | Infertility, birth defects |
| Radiation | |
| X-ray, gamma ray | Mutations, microcephaly, mental deficiencies |
| Drugs and hormones | |
| Thalidomide | Birth defects |
| Diethylstilbestrol | Vaginal adenocarcinoma in offspring |
| Alcohol | Neural deficiencies, growth retardation |

^aData from Sullivan and Barlow (1) and Longo (2).

an increase in the number of phagocytic microglial cells and reactive astrocytes. A constant vaginal estrus developed and the ovaries were small and polyfollicular. Production of constant estrus by exposure of rats to constant light produced similar degenerative changes in the arcuate nucleus (5). Removal of the ovaries prior to treatment with estradiol valerate or constant light prevented the alterations in the hypothalamus. These studies suggest a material of ovarian origin, probably estrogen produced during the acyclic polyfollicular condition, is the cause of degeneration in the arcuate nucleus. Degenerative changes in the arcuate nucleus occur at a slow rate during normal aging and the rate is reduced by ovariectomy (6). Therefore, it is demonstrated that normally an endogenous ovarian product has a toxiclike action on the arcuate nucleus. These changes in the arcuate nucleus with age could be responsible for normal termination of reproductive cyclicality and reproduction, which could be induced prematurely by exogenous environmental contaminants. The above study by Brawer et al. (4) is an example of a single exposure to an exogenous substance that produces a chronic change in secretion of an endocrine organ, which in turn causes degenerative changes in neural tissue.

Work from our laboratory has shown that altered patterns of physiological levels of endogenous estrogen have detrimental effects on the preovulatory oocyte and intrauterine environment of the rat

(7, 8). An early rise in estrogen in relation to the time of ovulation during a pentobarbital induced delay of ovulation resulted in increased developmental anomalies and embryonic death, as well as decreased fertilization and implantation rates. Absorption of the early endogenous release of estrogen with an antiserum to estradiol prevented the detrimental effects. The developmental defects could be reinitiated by treatment with diethylstilbestrol, a biologically active estrogen which does not bind to the antiserum. Table 2 contains a summary of data collected at midgestation during this latter study. Similar results were obtained in studies of preimplantation embryos, which demonstrated that estrogen-induced anomalies and death occurred as early as day 4 of gestation.

An early rise of plasma estrogen in relation to time of ovulation was recently found in old rats during those types of estrous cycles, which were shown to produce an increased incidence of developmental anomalies in the embryos (9). Therefore, modifications in secretory patterns of estrogen with advancing age could cause degeneration in the hypothalamus and in the preovulatory oocyte with subsequent developmental abnormalities. Such a mechanism is compatible with the increased incidence of birth defects that is found with advancing maternal age in women. Chemicals which delay the release of gonadotropic hormones or interfere with ovarian secretion of estrogen have potential for production of defective oocytes.

Table 2. Developmental defects due to an early preovulatory rise in estrogen.^a

| Treatment ^b | Implantation rate, % | Embryonic death, % | Recovered embryos, % | | |
|------------------------|----------------------|--------------------|----------------------|----------|-----------------|
| | | | Normal | Abnormal | Retarded growth |
| Control | 85 ^{e,d} | 5 | 92 ^c | 1 | 7 |
| PB | 43 ^e | 22 ^c | 57 ^d | 9 | 34 |
| ASE-PB | 89 ^e | 8 | 81 ^e | 1 | 18 |
| DES-ASE-PB | 75 ^d | 18 ^c | 70 ^f | 7 | 23 |

^a Data from Butcher and Pople (8).

^b PB-Pentobarbital-induced 2-day delay of ovulation, ASE = antiserum to estradiol on day 1 and 2 of the estrous cycle, DES = diethylstilbestrol on days 1 and 2 of the cycle; *n* = 146 to 427 embryos/group. Mean % in the same column without a common superscript letter are significantly different, *p* < 0.05.

Environmental chemicals accidentally introduced into the human food chain, such as PBB found in meat and milk in Michigan (3), have the potential of altering the endocrine system, if chronically present in the diet. These endogenous changes in hormonal concentrations or patterns have the potential of producing reproductive difficulties. Therefore, it is not only important to examine the acute effect of environmental chemicals on reproduction, but also the long-term effects induced through alteration in the endocrine system.

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