Fertility and the environment: endocrine disruption

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Summary

Extraordinary awareness, interest and concern have been aroused concerning the effects of environmental exposure on human reproductive and developmental health generally, motivated in part by the explosion of technologies to enhance fertility and minimise adverse pregnancy outcomes. At the same time, the intensified focus on reproduction and development is the result of growing concern about the effects of chemical, biological and physical hazards on health in general. This short review focuses on the history of environmental endocrine disruption, the mechanisms of action of endocrine disruptors, and current evidence of effects on reproduction and infant development. Policy implications and the ongoing efforts of research into exposure and the effects of endocrine disruptors are briefly addressed.

In the past 50 years, tens of thousands of chemicals have been synthesised and released – usually uncontrolled – into the general environment. Reports in the scientific literature and in the media have raised concerns that certain of these chemicals may produce adverse effects on wildlife and humans by interfering with the endocrine system. Some of the effects include reproductive and developmental abnormalities, increases in hormone-related cancers (breast, prostate, testis), and a decline in wildlife populations. The term *endocrine disruptors* is used to describe exogenous agents which act by mimicking or antagonising natural hormones in the body which are responsible for maintaining homoeostasis and fertility and controlling normal development.

The main classes of chemicals involved are phthalates, which are used in food packaging, dyes, insecticides, and pharmaceuticals; alkylphenols used in the production of industrial detergents; and organochlorine pesticides including DDT, which is already banned in most developed countries [1, 2]. Although in adults the endocrine system has the ability to recover from fairly significant disturbances, in the foetus even minor changes in hormone levels may have lifelong effects.

Because hormone receptor systems are similar in humans and animals, effects observed in wildlife species (e.g. alligators with stunted genitalia, male fish becoming hermaphroditic and female molluscs with penises) arouse concern regarding potential human health effects. Hence the current scientific debate centres on whether there is evidence of health effects or significant risks to the general human population from exposure to these chemicals.

Unfortunately, these challenges uncover a second aspect of the reproductive-environmental health problem – namely, the extraordinary paucity of useful information. Three decades ago, information was available on reproductive and developmental effects for only a small number of physicobiological, chemical, and biological agents and only on those effects that occurred at high levels of exposure. Physicians are ill-prepared to answer most of the questions concerning reproductive or developmental risks which may arise from environmental pollution in general.

Evaluating potential low-dose effects of environmental oestrogens (xenooestrogens) was identified as a major research priority which led to the Swiss research programme 'Hormonal active substances: Consequences on humans, animals and the ecosystem' (NFP 50).

Historical background

Endocrine disruption is not a new discovery. In the 1930s, studies in laboratory animals demonstrated oestrogenic properties of a number of industrial chemicals, including bisphenol A, now widely used in plastics, resins, and dental sealants. The feminising effect of the pesticide DDT in roosters was reported in the 1950s.

Although hormonally active chemicals are widely used for beneficial medical purposes, adverse effects have also occurred. In 1971, clinicians traced an epidemic of vaginal clear cell carcinoma in young women to maternal use of a synthetic oestrogen, diethylstilbestrol (DES), during pregnancy. DES daughters have an increased risk of reproductive and immunological abnormalities, while sons are at risk of genital anomalies and abnormal spermatogenesis [3]. In animals, and possibly in humans, DES alters male- and female-typical behaviour patterns. The example of DES indicates that the foetus, rather than the adult, may be most at risk from the adverse effects of hormonal disruption.

Mechanisms of action and foetal vulnerability

It is known that some pesticides and other industrial chemicals can directly bind to, or block, hormone receptors, thereby initiating or blocking receptor-activated gene transcription – the production of proteins from genetic information. Other environmental chemicals act indirectly on hormonal balance by altering hormone production, hormone transport on binding proteins, receptor numbers on target organs, or hormone transport metabolism. For example, polychlorinated biphenyls (PCBs) interfere with thyroid function via a variety of mechanisms, including increased metabolism of the thyroid hormone T_4, interference with T_4 delivery to the developing brain by displacement from the carrier protein, and interference with the conversion of T_4 to the active form of thyroid hormone known as T_3 [4].

During development, the foetus is particularly sensitive to hormonal fluctuations. Low-level exposure to hormones or toxicants may result in permanent

physiological changes not seen in adults exposed at similar levels. For example, mild hypothyroidism in adults is not expected to have long-term effects on the brain. In contrast, mild hypothyroidism during foetal and neonatal life causes disruption of neurotransmitters, nerve factors, nerve-cell growth, and normal energy production in the developing brain, altering cognitive and neuromotor development [5].

Potential health implications

Reported abnormalities in laboratory animals and wildlife exposed to endocrine-disrupting chemicals include feminisation of males, abnormal sexual behaviour, birth defects, altered sex ratio, lower sperm density, decreased testis size, altered onset of puberty, cancers of the mammary glands or testis, reproductive failure, and thyroid dysfunction.

Epidemiological studies have found associations between exposure to specific pesticides or industrial chemicals and thyroid stimulating hormone (TSH), testosterone, and prolactin levels in adults [6–8].

Some of these studies have also found significant associations with other relevant endpoints including diminished sperm quality, impaired sexual function, and testicular cancer [9, 10]. Some studies indicate that sperm counts worldwide have fallen by 2 % per year, and that the number of mobile sperm has fallen by 1 % a year over the past 20–30 years [11], while breast cancer in females has risen by 25 to 30 % since the 1940s. However, there is obviously no convincing evidence of a concomitant decrease in fertility which has been shown, e.g. in a study on the time trends in biological fertility in Britain [12].

Several studies have found associations between occupational solvent or pesticide exposure and subfertility or adverse effects on offspring, but it is not clear whether these are due to endocrine mechanisms [13]. Case-control studies have shown increased risks of cryptorchism (undescended testicles) and hypospadias (congenital defect of the penis) among the sons of farmers and/or women gardeners exposed to pesticides [14]. These findings are important because animal studies have revealed the same effects after exposure to oestrogenic or antiandrogenic chemicals.

There are few population-based epidemiological studies relevant to endocrine disruption. The studies that have been done are weakened by the inevitable time lag between exposure and clinical disease, difficulty in defining exposed and control populations, and poor retrospective assessment of exposure during the prenatal period. Moreover, limited understanding of the role of gene-environment interactions increases the likelihood that the susceptible subpopulations may remain unidentified. Perhaps as a result, epidemiological data concerning the relationship between breast cancer and tissue levels of certain organochlorides, such as DDT, its by-product DDe, PCBs, or dieldrin, are conflicting [15, 16].

Surveillance-based studies in the general population show increases in some potentially hormone-related conditions, such as hypospadias, cryptorchidism, sperm count, testicular and prostate cancer, or age at breast development. These increases are not completely explained by improved detection or reporting [17]. Although behavioural and nutritional factors are potential explanations for some of these observations, it is biologically plausible, and consistent with laboratory and wildlife evidence, that foetal exposure to endocrine-disrupting chemicals may play a role. Cancer and other health effects may manifest many years later as steroid hormones continue to stimulate cell growth and proliferation [18, 19].

Beyond endocrine disruption: policy implications

The topic of endocrine disruption has brought to the surface an underlying debate on the nature of scientific proof and decision-making about whether to take action in the face of scientific uncertainty. Some argue that there is no conclusive proof of human health effects from endocrine disruption at current exposure levels in the general population. Others point to suggestive evidence and warn that the consequences of interaction may be significant for future generations.

Detecting health effects from exposure to endocrine-disrupting chemicals is difficult and will continue to pose substantial challenges. Hormones act at extremely low (part-per-trillion) levels; therefore, even low-level exposure to hormonally active agents may be of concern, particularly during sensitive periods of foetal development when protective feedback loops have not yet developed. Endocrine-mediated effects may be subtle and are often delayed, making it difficult to link early life exposure to illnesses or conditions that may only become apparent in adulthood. Moreover, adverse impacts may be manifest primarily in populations rather than individuals. For example, slight overall declines in sperm density or intelligence may have little relevance for an individual but important adverse implications for the population [20]. Surveillance systems which focus on individuals rather than populations may therefore fail to detect early evidence of impacts until substantial damage has already occurred.

Low-level exposure to endocrine-disrupting chemicals are ubiquitous in today's environment. Persistent chemicals such as DDT, PCBs and dioxins are detectable in nearly 100 % of human blood samples, and even some of the shorter-lived potential endocrine disruptors, such as phthalates and other (non-DDT) organochlorine pesticides, are detected in general-population surveys of blood or urinary residues [21]. Despite substantial evidence of the impacts of endocrine-disrupting chemicals in human and wildlife, there is still considerable uncertainty about the severity and scope of the health threat. The ubiquitous nature of exposure, nontrivial potential health effects, and the difficulties inherent in quantifying those effects justify measures to mitigate exposure now, while the remaining scientific uncertainties are being addressed. This is the conclusion of the International Joint Commission (USA & Canada) with respect to Great Lakes water quality, and it serves as an instructive example of how to make policy under conditions of scientific uncertainty.

Therapeutic drugs may contaminate the environment due to metabolic ex-

cretion, improper disposal, or industrial waste [22]. A variety of drugs have been reported to have reproductive and developmental effects and most were measurable in drinking or river waters and sediments, suggesting that pharmaceutical products are widespread contaminants, with possible implications for human health and the environment. Concentrations measured in water may give rise to human exposure in the ng per day range, at least three to four orders of magnitude lower than those producing a pharmacological effect. Risks arising from acute exposure can therefore be regarded as unlikely. However, possible effects of life-long exposure have still to be determined [23].

Conclusion

Although it is emphasised that there are no data which unequivocally link infertility or hormone-dependent cancers to exposure of man to endocrine disruptors, it should be evident that a surprising number of known hormonally active chemicals are present in our modern environment. It is also clear that some of these chemicals do cause disorders (usually of reproduction) in a range of animals, especially aquatic life. Faced with this evidence it would seem both foolish and dangerous for us to conclude that man is not affected by such chemicals because we have no proof of this. Both our exposure to hormonally active environmental chemicals and development of disorders of the reproductive system are chronic rather than acute processes. If there is any causal relationship between these lifelong events it will obviously prove extremely difficult to establish (long latency period between exposure and event). The proposed research into possible links between trends in reproductive health and exposure to chemicals with known oestrogenic or related hormonal effects will (1) examine the extent of human exposure to oestrogen mimics; (2) develop a test for chemicals that may interfere with the action of natural oestrogen in the body; (3) develop a standardised national approach to measurement of sperm counts and assessment of sperm quality; (4) study the development of the male foetus in the first trimester to ascertain whether oestrogen mimics can influence the development of the testes; and (5) undertake epidemiologic studies of testicular and breast cancer.

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