Infertility and Environmental Chemicals—Is There a Connection?

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Sperm counts plummeting!, Italian population growth stunted!, Infertility on the rise! These headline excerpts are taken from newspapers around the globe during the past decade, but are they accurate? If so, do environmental chemicals significantly contribute to such problems?

Reproduction in humans and other species is a complex process, involving normal anatomy, gametogenesis, embryogenesis, implantation, genetics, maternal health, and fetal growth, development and survival. A growing body of literature supports the idea that some environmental chemicals have detrimental effects on one or more of the components leading to normal reproduction, based primarily on wildlife studies, laboratory animal studies, and high-dose exposures of women and their fetuses to specific, individual chemicals (e.g., diethylstilbesterol, or DES).

Given that there are now more than 85,000 synthetic chemicals registered for use in the United States, the question naturally arises as to whether any of these, individually or in combination, even at low levels of exposure, may compromise normal reproduction in humans. Multiple, simultaneous chemical exposures, low-level exposures, duration of exposure, exposure in utero versus as an adult, and in a specific genetic context comprise significant challenges in assessing cause and effect of environmental chemicals on human health and, in particular, reproductive health. This article reviews what is currently known about environmental effects on human reproduction and provides recommendations for maximizing fertility potential.

FERTILITY TRENDS—IS INFERTILITY ON THE RISE?

The number of couples undergoing infertility treatment has risen significantly in the past two decades, primarily due to advances in reproductive technologies, increased availability of fertility services and these technologies, and a transient increase in the population of baby boomers who delayed childbearing. In first world countries with sound economies, birth rates have declined over the last decade, primarily by virtue of, as well as delayed childbearing. Whether infertility per se is on the rise has been controversial, although recent data support a worrisome trend.

The U.S. National Survey of Family Growth (1998) reported that the incidence of impaired fecundity (involuntary fertility compromise) rose significantly between 1982 and 1995 in all reproductive-age groups, but surprisingly with the biggest increase (42 percent) in women under 25, compared to 12 percent and 6 percent for women 25 to 34 and 35 to 44 years old.[1, 2]

Similar trends have been observed in Europe, where, as an example, 40 percent of young men entering the draft in Denmark have sperm counts beneath 40 million/cc, a level associated with infertility.[3] Concern that there may be an environmental link to infertility derives from (1) wildlife observations linking environmental chemicals to reproductive abnormalities; (2) geographic and temporal trends in human health conditions affecting fertility (variable sperm quality and count reductions, increased incidence of male genital birth defects—e.g., hypospadias and cryptorchidism—and an apparent rise in endometriosis); (3) laboratory studies demonstrating that many commercial chemicals cause fertility impairment in experimental animals, often at very low doses; and (4) findings that these substances are found in humans at levels comparable to those causing fertility impairment in animals.[4] Together, these lines of evidence suggest there could be an "involuntary" component in birth rate declines.[5]

FEMALE INFERTILITY

While infertility is an adult problem, its causes may have some roots during fetal development.[6] The female reproductive tract develops independent of sex steroids,

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although estrogen-like compounds may affect it. The long-term effects of in utero exposure to DES, for example, are well known to include anatomic abnormalities in the uterus (T-shaped) and Fallopian tubes (higher incidence of ectopic pregnancies) in women exposed to this estrogen analogue in utero. With regard to oocytes, the greatest number exists in the fetal ovary at mid-gestation (approximately 6 million), followed by atresia thereafter, resulting in approximately 2 million at birth and approximately 400,000 at puberty. Acceleration of oocyte depletion results in early menopause and compromised fertility.

Women whose mothers smoked while they were in utero have an earlier menopause, suggesting that maternal smoking results in loss of oocytes in the fetal ovary.[7] Animal studies support this conclusion, in that pregnant mice exposed to the polycyclic aromatic hydrocarbons (PAHs) in tobacco smoke have fetuses with a higher percentage of oocytes undergoing apoptosis, resulting in fewer oocytes at birth and premature ovarian failure.[8] The underlying mechanism involves PAHs binding to the aryl hydrocarbon (Ah) receptor in the ovary, triggering apoptosis.[8,9] Similar results have been observed in vitro with human ovarian explants.[8] Fertility compromise has also been reported in women who had high levels of DDT in their umbilical cord blood at birth, reflected in an increased time to pregnancy, compared to those with lower levels,[10] suggesting an in utero exposure, although the exact mechanisms are not clear. Enzymes important in metabolizing these and other chemicals may be polymorphic among individuals, and thus some individuals may be more susceptible to their effects, in female (and male) fetuses (and adults).

Exposures of adult women are also cause for concern, as smoking, for example, results in decreased oocyte numbers and early menopause, depending on the amount and duration a woman smokes. Smoking is strongly associated with an increased risk of miscarriage and ectopic pregnancy.[11] Among women needing in vitro fertilization (IVF) to conceive, twice as many IVF attempts are required for smokers as nonsmokers, and female smokers require higher doses of gonadotropins, have lower peak estradiol levels, fewer oocytes retrieved, more canceled cycles, lower pregnancy rates and higher miscarriage rates than nonsmokers.[11] Recently, a chemical used in polycarbonate and in the lining of cans, bisphenol A, has been shown to cause abnormal oocyte meiosis and markedly decreased litter size in adult female mice.[12] Whether this finding applies to women is uncertain at this time.

Infertility in women is commonly associated with endometriosis, a disorder in which the lining of the uterus is found primarily in the pelvis where it provokes an inflammatory response. A study in nonhuman primates revealed that severe endometriosis developed in rhesus monkeys exposed to tetrahydrochlorodibenzo-*p*-dioxin (TCDD or dioxin) at 5 to 25 ppt daily for four years.[13] The severity of the disease was dose dependent. Epidemiologic studies demonstrate that Belgium, a country with the highest levels of dioxin pollution, has the highest incidence of endometriosis and prevalence of severe disease.[14] In 1976 in Seveso, Italy, an acute exposure to dioxin occurred and women were evaluated for endometriosis 20 years later. A doubled, nonsignificant risk for endometriosis among women with serum TCDD levels of 100 ppt or higher was found; however, no dose response was detected. A recent case-control study of Italian and Belgian women of reproductive age, with and without endometriosis, showed no significant differences in dioxin-like compound body burdens between women with and without disease.[15] Overall, these data suggest that TCDD is probably not a significant factor in the etiology of most endometriosis cases, although acute versus chronic exposure, duration of exposure, and other constitutional issues (genetics, immune status) preclude categorical denial of an association or causation.

MALE INFERTILITY

Exposure of male fetuses to chemicals may have detrimental affects on their future fertility, including abnormalities of the reproductive tract and gametogenesis. Testicular descent occurs in utero by a hormone-dependent process, which, if compromised, can result in cryptorchidism and subfertility later in life. It is well known in wildlife and experimental animal models that exposure to "environmental estrogens"[16] results in cryptorchidism, as well as hypospadias, and men exposed to DES in utero have a high incidence of these disorders.[17] (Similar effects in wildlife have been observed with organochlorines.) While other chemicals with weak estrogenic activity are in the environment or in foods, whether they affect human reproductive tract development and reproductive potential is controversial.[18]

The number of sperm produced daily in the adult male is determined, in part, by the number of Sertoli cells that reach nearly their final numbers within the fetal testis. For fertility, about 100 to 200 million sperm must be produced daily so that 40 to 250 motile sperm/ml are within an ejaculate for optimal fertility. In utero exposure to DES results in decreased sperm counts in adult men, largely because of the effects on Sertoli cells. Maternal smoking is also associated with decreased sperm and Sertoli cells in male offspring, likely via apoptotic mechanisms similar to oocytes. In rats, in utero exposure to dioxin, which also binds to the Ah receptor, results in similar reduced sperm counts in adulthood. In utero exposure to phthalates (anti-androgens found in plastics and cosmetics) results in decreased sperm counts, lower testosterone, and testicular dysgenesis syndrome in animal models.[19] Whether this is true for humans is uncertain at this time.

There are several reports of adult men being exposed to environmental chemicals, with compromised sperm counts and infertility. For example, men

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employed in the production of particular pesticides have higher rates of infertility, and pesticide usage has been associated with male infertility in farmers.[20] However, other detailed studies have failed to find a significant association between pesticide exposure and male (or female) infertility.[18, 21] The question arises whether men exposed to low levels of ubiquitous chemicals face risks of fertility compromise. The jury is still out on this for men (and women).

PUTTING IT ALL TOGETHER

Environmental chemicals in certain unfortunate instances have had clearly defined effects on human fertility. The biggest challenge currently is to determine if a particular chemical in the mixture of chemicals to which we are all exposed, in utero or as adults, is detrimental to human reproduction. In contrast to prescription and over-the-counter drugs that undergo a rigorous evaluation, first in animals and then in humans, before they are permitted for human use, most chemicals have not undergone equivalent testing for effects on health, reproductive or otherwise, and of course reproductive testing would be unethical in humans. The dilemma is that we may not know about reproductive toxicity until large-scale epidemiologic body burden studies are conducted, such as the ongoing Centers for Disease Control and Prevention's (CDC's) National Report on Human Exposure to Environmental Chemicals, an ongoing $6.5 million survey measuring 145 chemicals in 2,500 people across the U.S. every two years.

In the late 1990s, the CDC began the world's largest survey of chemical exposure among the general population, the National Health and Nutrition Examination Survey (NHANES), which now provides biomonitoring data on typical exposures to chemicals, including pesticides, ingredients in cosmetics, plastics, and other components of daily life.[22] These data need to be mined for reproductive effects specifically, so that objective information can either confirm or refute risk. The new NIH National Children's Study, which will address some chemical exposure issues, will enroll more than 100,000 pregnant women and track the health of their babies through adulthood. This long-term study is expected to give important information about putative effects of chemicals on human health, including reproductive health, although the results will be far in the future.

PRECAUTIONARY PRINCIPLE

So, what to do in the meantime? Before the verdict is in, it seems that the most prudent action is precautionary prevention. The Women's Foundation of California Report (2002) highlights exposures that California women face in their daily lives—cosmetics, nail polish, hair dyes, gasoline, household solvents and cleaning solutions, and cigarette smoke (either primary or secondary), to name a few. Exposure to many of these is preventable or at least can be minimized, although no one knows how low is low enough. Men who have an occupational exposure (e.g., working directly with pesticides, glycol ethers, and other chemicals) are likely to have an increased risk for fertility compromise. While these and other chemicals are ubiquitous, and it is unlikely that they will disappear anytime soon, precautionary prevention holds the greatest promise to preserve the reproductive potential of this generation and generations to come.

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