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The Epidemiology of Disasters and Adverse Reproductive Outcomes: Lessons Learned

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A disaster has been defined as a disruption of human ecology that exceeds the capacity of the community to function normally. Little is known about the adverse effects of natural disasters on reproductive outcomes. Important lessons can be derived from several disasters caused by human factors, such as the Minamata Bay disaster. Adverse reproductive outcomes include infertility, early pregnancy loss, stillbirths, congenital malformations, and serious developmental disabilities such as cerebral palsy and mental retardation. Recent disasters like the Chernobyl and Bhopal explosions have provided important lessons on the need for accurate and sound information about the risk of prenatal exposures for adverse reproductive outcomes. To study questions of adverse reproductive outcomes and disasters requires a well-planned approach. It should include early development of surveillance for adverse reproductive outcomes, analytic studies on the risk of disasters from direct and indirect effects, sensitive methods to measure early pregnancy loss, and long-term follow-up programs to assess outcomes such as developmental disabilities.

Introduction

During this century, natural and human-generated disasters have contributed to many fatalities and many cases of a lifetime disability (*1*). During the past decade, much attention has been focused on the epidemiology of disasters (*1–3*), but little attention has been given to their potential for causing adverse reproductive outcomes in humans. Several human-generated catastrophic events have provided important lessons on how to study and search for adverse effects of disaster on human reproduction. This article is a review of the current knowledge about the reproductive health hazards associated with disasters and a description of the lessons learned.

Background

The committee of experts in charge of preparing the activities for the International Decade for the Reduction of Natural Disasters has endorsed the empirical definition of a disaster as a disruption of human ecology that exceeds the capacity of the community to function normally. In this article, disasters are classified into those resulting from natural events and those generated by humans. Natural disasters include geophysical events, such as earthquakes and volcanoes, and weather-related events such as tornadoes, heat waves, cold spells, floods, and hurricanes. Human-generated disasters include famines, air pollution, industrial incidents, fires, and nuclear reactor incidents.

To study whether disaster can cause adverse reproductive outcomes, researchers require three basic elements: methods to measure exposures, methods to measure outcomes, and sound methods for analyzing data. To assess the current knowledge of disasters and their relationship with adverse reproductive outcomes, three questions must first be answered: *a*) What toxic exposures are related to the disaster? *b*) What adverse reproductive outcomes have been studied? *c*) Are the study methods sound?

Exposures. Disasters can cause harm to humans through primary exposure (e.g., radiation from a nuclear incident) or through secondary exposure (i.e., stress, post-disaster outbreak of infectious diseases). Both primary and secondary exposures should be considered when evaluating the potential risk for adverse reproductive outcomes from disasters. In the absence of epidemiologic study results, knowing the exposure may provide physicians with some basis for making a qualitative assessment of the potential risk. For example, if the emission of volcanoes contains large silica particles, the chances of that material causing an adverse reproductive outcome is small because its inert nature has a low probability of being aspirated into the bronchial tree and is unlikely to be absorbed.

Adverse Reproductive Outcomes. To study adverse reproductive outcomes, specific definitions for each outcome and appropriate methods of data collection should be developed. The term "reproductive hazards" includes events or agents that affect reproductive or sexual func-

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tion. Examples of outcomes resulting from reproductive hazards include depressed libido, impotence, irregular menstrual cycles, and infertility. A developmental hazard is an agent or event that leads to the death of the conceptus or to structural abnormalities, altered growth, or functional deficiency of the offspring. Each of the consequences of a developmental or reproductive hazard is an adverse reproductive outcome.

Fertility. Some adverse reproductive outcomes, particularly those leading to decreased fertility, are difficult to detect without a sound methodologic approach. In studies of large human populations, fertility serves as a surrogate for several adverse reproductive outcomes, such as sperm dysfunction, implantation failures, or early pregnancy loss. Early pregnancy detection by highly sensitive laboratory methods can be helpful in studying early pregnancy loss.

"Fecundability" is a new term that is defined as the probability of pregnancy during each menstrual cycle for couples who are intending a pregnancy. This measure has been suggested as a measure of fertility when pregnancy can be detected as early as 25 days after the last menstrual period. Canfield et al. (*4*) have developed a sensitive and specific assay for human chorionic gonadotropin (hCG). It can detect pregnancy at about 25 days after the start of the last menstrual period. This is a significant improvement over the average of 29.5 days for conventional radioimmunoassay techniques. Baird et al. (*5*) have suggested the method of Canfield et al. as a potential and feasible approach to studying the effects of environmental agents on fertility; however, this method still needs more testing in communities.

Early Pregnancy Loss. Early loss of the conceptus is the earlier detectable developmental effect of a reproductive hazard. Having a standard technique for diagnosing pregnancy very early is crucial for researchers who study early pregnancy loss. The time at which pregnancy is recognized varies greatly. Wilcox et al. (*6*) found that 22% of the pregnancies detected by the hCG test described by Canfield ended in a pregnancy loss before pregnancy would have been clinically recognized. Among all pregnancies detected with the Canfield test, 31% ended in early pregnancy loss. The rate of spontaneous abortion and early pregnancy loss varies with the gestational age at which pregnancy is recognized. Researchers who study the relationship between pregnancy loss and environmental factors must use standard methods to detect pregnancy and adverse pregnancy outcomes.

Birth Defects. To study birth defects related to disasters, some type of surveillance is needed. In any population between 2% and 3% of the live-born infants have a serious birth defect. A study of the relationship between disasters and birth defects needs either to include a suitable comparison population or to make a comparison between a community before and after a disaster. Källén (*7*) has reviewed the methods of studying birth defects and environmental exposures.

Infant Mortality. A parameter that can be followed with relative ease in a population is infant mortality. This measure of the health status of a community is almost universally studied and results are generally available. In any study of the causes of infant mortality, the difference between infant mortality before and after a disaster can serve as a crude measure of adverse reproductive outcomes.

Developmental Disabilities. Human teratogens are known to cause developmental disabilities. Prenatal exposure to methyl mercury causes adverse outcomes which include cerebral palsy, seizures, and mental retardation (*8*). Another human teratogen, rubella, causes deafness and cataracts that could lead to blindness (*9*). Maternal alcohol use during pregnancy causes neurobehavioral abnormalities and other developmental disabilities (*10*). To study developmental disabilities related to disasters, a registry and long-term follow-up is needed. Disabilities such as cerebral palsy may not become evident until the age of 2 years. Mild mental retardation may not be recognized until the child enters school.

Study Methods. Understanding the reproductive hazards resulting from a disaster requires the use of surveillance and epidemiology. Gregg (*11*) has defined surveillance as the dynamic, continued scrutiny of health-related events through the systematic collection, tabulation, and analysis of health data. Epidemiology is the basic science of public health. Epidemiologists study the cause and determinants of disease. Through the tools of surveillance and epidemiology, one can study the conditions resulting from a disaster, the risks associated with those conditions, and the potential prevention strategies. Because the study of some adverse reproductive outcomes requires sequential urine testing to detect pregnancy early, it is important to plan those studies well before the occurrence of a disaster.

Natural Disasters

Little is known about the direct or indirect effect of geophysical events such as earthquakes and volcanoes on human reproduction. Few studies were found that addressed adverse reproductive outcomes after natural disasters. The following sections summarize these studies.

Earthquakes. Weissman and co-workers studied the influence of seismic activity on pregnancy outcome among residents of Haifa, Israel (*12*). They studied the number of deliveries and premature rupture of membranes during the 48 hr after five earthquakes of a magnitude that could be felt by most of the population. The comparison group consisted of babies delivered during the 2 weeks preceding the seismic activity. They found an increase in delivery rates during the 48 hr following the earthquakes and a significant increase in the premature delivery rate. Fuginaga et al. found an increased rate of malformations among the offspring of Sprague-Dawley rats who were pregnant during a major earthquake in Northern California (*13*).

Volcanoes. Records show that more than 100 volcanoes had severe or frequent eruptions during the twentieth century (*14*). Potential effects of volcanic eruptions can derive from the gases emitted, the physical destruction of the volcano, or the secondary effects of the destruction.

The most common emissions from volcanoes are silica crystals, which are inert and not easily inhaled.

Floods. The physical force of a flood is only one of its hazards. Flooding can cause displacement of pathogenic organisms, which could lead to outbreaks of infectious diseases. The moisture and humid climatic conditions can lead to growth of potentially hazardous organisms in stored foods. Sinha found that 40 of 60 samples of maize collected from a flood-affected area in the Bhagalpur district of India were contaminated with *Aspergillus flavus* and had levels of aflatoxin B_1 above the recommended 20 μg/kg (*15*). Many samples contained a mixture of aflatoxin B_1, B_2, and G_1. Some aflatoxins have estrogenic activity, but none are confirmed human teratogens.

Floods also may bring pollutants that can result in adverse reproductive outcomes and other health hazards. Janerich et al. described a time-space cluster of leukemias, lymphomas, and spontaneous abortions associated with a 1972 flood in the state of New York (*16*). No specific agents that could have caused the cancer or spontaneous abortions were identified.

Tornadoes. We found no data on any relationship between tornadoes and adverse reproductive outcomes.

Heat Waves. The main health effects of heat waves are heatstroke, heat exhaustion, heat syncope, and heat cramps. Heatstroke is generally defined as delirium, stupor, or coma associated with a core temperature of 40.6°C or greater resulting from high environmental temperatures. Syncope, exhaustion, and cramps are the lesser effects of heat exposure. Mortality associated with heat waves have been well documented (*17*). The elderly, the poor, and the very young are at high risk, particularly in inner cities. Few data exist on heat waves and the risk to the human fetus.

Considerable evidence exists, however, showing that raising the core temperature by more than 3°C is teratogenic in several species of animals (*18*). In rats, elevations in core temperature averaging 3.6°C were associated with reduced brain weight and microcephaly. Other abnormalities observed were fetal resorptions, growth retardation, anencephaly, eye abnormalities, palatal defects, and limb defects.

No conclusive evidence exists that hyperthermia is a teratogen in humans. There are many case reports of birth defects among mothers who experienced hyperthermia, defined as maternal fever of 40°C or greater for at least 24 hr. Results of several epidemiologic studies have also suggested an association between maternal febrile illness and neural tube defects (*19*). Clarren et al. studied maternal fever during pregnancy among participants of the United States Collaborative Perinatal Study (*20*). A total of 165 babies were identified whose mothers had at least one episode of hyperthermia during the first trimester. None had the pattern of birth defects reported in case reports of hyperthermia and malformations.

Saxen et al. (*21*) conducted a case–control study of central nervous system defects and orofacial malformations in Finland. No association was found between maternal habits of sauna use and malformations (*21*). Note also that in Finland, where sauna use is almost universal, the rates of anencephaly and spina bifida are among the lowest in the world (*22*).

A potential protective effect among humans is the ability to maintain a stable core temperature when the environmental temperature is very high or very low. Harvey et al. (*23*) studied the time required to raise the core temperature to 38.5°C. None of the women in the study could tolerate remaining in the hot tub for enough time to increase their core temperatures to 39.9°C which suggests that the core temperature is preserved through some type of adaptive mechanism (*23*).

To find out if heat waves are associated with a risk for adverse reproductive outcomes, further studies are needed. Researchers in such studies should look for a relationship between the core temperature of pregnant women during heat waves and their pregnancy outcomes.

Human-Generated Disasters

Human-generated disasters have contributed to the understanding of the effect of environmental hazards on human reproduction. The disaster at Minamata Bay in Japan provided data that showed for the first time a link between a chemical environmental exposure and adverse reproductive outcomes. Bertazzi (*3*) has classified human-generated disasters into the acute incidents that can hurt many people in a short time, such as the Bhopal and Chernobyl explosions, and the incipient disasters where the outcomes may be revealed well before the source of exposure is recognized, for example, the Minamata Bay incident. Both types of disaster may have significant consequences to human reproduction.

Famines. The unavailability of food and resulting hunger is a major worldwide problem. Famine often results from war or failure of the food distribution system, not from climatic disasters (*24*). There is a large body of literature about famine and the reproductive process. A study of the Dutch famine of 1944–1945 provided much insight into the effects of famine on human reproduction (*25*). Stein and Susser (*25*) studied five parameters of pregnancy outcome including postpartum maternal weight, birth weight, placental weight, birth length, and birth head circumference. All the adverse pregnancy outcomes attributable to the famine occurred in women who were in their third trimester of pregnancy at the time of the famine. The adverse effects were associated with consumption of less than 1500 calories of food per day. During the Dutch famine, on average, maternal weight declined by 4.3%, birth weight declined by 9%, placental weight declined by 15%, length at birth declined by 2.5%, and head circumference declined by 2.7%. These average measurements increased after pregnant women began receiving adequate nutrition.

Vitamin deficiencies have been associated with adverse reproductive outcomes. Warkany (*26*) showed that maternal vitamin A deficiency in the rat, rabbit, and pig can cause malformations. Results of a recent randomized clinical trial showed that daily supplementation with 4 mg of folic acid before pregnancy and during the first trimester can prevent 71% of the recurrence of a neural tube defect among babies of mothers who had a previously affected child (*27*). These results suggest that certain nutrients such as folic acid have a specific role in human embryogenesis. It appears that a subgroup of the study mothers who had a baby with a neural tube defect may have an increased requirement for folic acid, since all study mothers had normal serum levels of folic acid. Recent studies also suggest that micronutrients in the mother's diet may be a more important contributor to birth weight than maternal weight gain (*28*).

Nuclear Reactor Incidents. The introduction of nuclear fission as an energy resource led to the construction throughout the world of many commercial nuclear reactors to produce electricity, and since then several serious incidents involving release of radiation and toxic substances have occurred. The reproductive hazards caused by exposure to radiation have been studied extensively (*29,30*).

A secondary effect of a disaster may result from lack of accurate information about reproductive hazards or misunderstanding of the risks. After the Chernobyl disaster, Bertollini et al. (*31*) studied the number of births in three regions of Italy. The regions were Lombardia in the north, Lazio in central Italy, and Campania in the south. The estimated effective levels of radiation among adults in Italy were about 60 mRem, with adults in the north having an average of 70 mRem and in the south an average of 50 mRem. The natural background radiation is about 200 mRem per year. Therefore, the increased radiation represented only about a third of the exposure from background radiation. There is little evidence that low-level radiation increases the risk for radiation teratogenesis (*29,32,33*). However, the authors found about a 7% reduction throughout Italy in the number of births during the first three months of 1987. They also documented a decrease in planned pregnancies and a small increase in induced abortions during the first weeks after the incident. Increases in the number of induced abortions in Greece (*34*) and Sweden (*35*) after the Chernobyl incident were also documented.

Chemical Exposures: Lessons Learned as a Result of Finding New Human Teratogens

Congenital Minamata Disease

In 1955, an unknown neurologic disease was discovered in a fishing village in Minamata Bay, Japan (*8*). It took 4 years to document that the congenital neurologic condition was due to methyl mercury poisoning from a nearby plant that produced acetaldehyde.

Affected children were born to mothers that seemingly showed no adverse effect from the methyl mercury. The babies appeared normal at birth, but at 6 months of age they showed some abnormal neurological signs. These included severe developmental delay, the persistence of primitive reflexes beyond 6 months of age, growth retardation, abnormal cerebellar signs such as dysarthria and ataxia, and many other signs and symptoms associated with spastic diplegia and spastic tetraplegia (*8*). In contrast to cerebral palsy caused by other symptoms, children with cerebral palsy caused by methyl mercury exposure *in utero* are more likely to have mental retardation and cerebellar disturbances.

The first lesson learned from this episode was that chemical agents can cause birth defects and developmental disabilities. Up until that time scientists believed that the human fetus was protected by the placental barrier. The second lesson learned was that a chemical agent can have a significant effect on the developing fetus without adversely affecting the mother.

In general, the mothers of the affected children did not show evidence of toxicity. The third lesson learned was that surveillance systems of birth defects and developmental disabilities would have helped detect the cluster of cerebral palsy and birth defects in the affected communities earlier. It took about 3 years from the time the first cases were identified to the time the source and relationship between the effluent of a nearby plant and the disease among the villagers around Minamata Bay was confirmed.

Birth defect surveillance systems have helped shorten the time from the occurrence of a cluster of birth defects to the time when the medical community recognizes the teratogenic risk. That was the experience with valproic acid (*36*). In September 1982, Robert presented to the members of the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) her observations of an association between the occurrence of spina bifida and the prenatal use of the anticonvulsant valproic acid. The members of the ICBDMS quickly reviewed the occurrence of spina bifida among mothers who had epilepsy and the use of valproic acid (*37*). In summary, women who took valproic acid during pregnancy were 20 times more likely to have a baby with spina bifida than women who did not take valproic acid. The risk of having a baby with spina bifida was therefore 1%, instead of the 1/1000 in the general population. The Italian group of the ICBDMS also reviewed their data on valproic acid and spina bifida and found a similar association (*38*). The findings of Robert, the Italian group, and the ICBDMS were shared with the manufacturer of valproic acid. In the United States, a letter was sent to all registered physicians alerting them of the risk of valproic acid. The labeling on bottles of valproic acid was changed to add the risk of spina bifida. The time from the first observations of Robert to the time when information was disseminated to health professionals was about 3 months.

Bhopal

Some important lessons can be learned from Bhopal regarding the study of adverse reproductive outcomes. The major lesson of the Bhopal disaster is that national and international resources can be mobilized to study the acute and chronic effects of disasters. Many studies have been published about Bhopal, including one on its effect on reproductive outcomes. Bhandari and colleagues studied pregnancy outcomes among women exposed to isocyanide during the Bhopal explosion (*39*). They found that 24% of pregnant women exposed to the explosion had a spontaneous abortion, compared with about 6% in a comparison group, a 4-fold increase in the rate of spontaneous abortions. The investigators did not find an increased risk of stillbirths or congenital malformations. The slight increase observed in perinatal and neonatal mortality was not statistically significant. Goswami et al. focused their study on chromosomal variations among persons exposed to isocyanide as a measure of genetic damage (*40*). They found no difference in the rate of chromosomal variation between subjects exposed to isocyanide and those who were not. Daniel et al. studied the spermatogenic function of subjects heavily exposed to isocyanide and did not find a significant effect on sperm count, sperm motility, seminal cytology, or the number of F-bodies (*41*). Kanhare et al. studied the morphology of placentas from pregnant mothers exposed to isocyanide from the Bhopal explosion (*42*). They found that placentas from exposed mothers weighed less than placentas of mothers who were not exposed. Investigations of immunologic, mutagenic, and genotoxic effects were also conducted (*43*).

Summary

Little is known about the potential adverse reproductive outcomes resulting from most natural disasters. Improving the understanding of the adverse reproductive effects of disasters requires as much preparedness as that required for emergency response to prevent mortality and morbidity. Here we outlined potential approaches to studying adverse reproductive outcomes. We recognize that disasters usually cause chaos and that, in general, the resources to handle disasters are limited. The first concern during a major disaster is saving life and property. Preparation for disasters, however, should also include developing systems to assess reproductive outcomes.

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