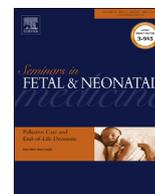




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Review

Counseling women and men regarding exposures to reproductive and developmental toxicants before conception or women during pregnancy



Robert L. Brent*

Thomas Jefferson University, Alfred I. duPont Hospital for Children, Room 308, A/R Building, PO Box 269, Wilmington, DE 19899, USA

S U M M A R Y

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It should be apparent that determining the reproductive risks of an exposure during pregnancy or the cause of a child's congenital malformations is not a simple process. It involves a careful analysis of the medical and scientific literature pertaining to the reproductive toxic effects of exogenous agents in humans and animals, as well as an evaluation of the exposure and the biological plausibility of the concern of an increased risk or a causal connection between the exposure and a child's congenital malformations. It also involves having available a detailed physical examination of the malformed infant or child and a review of the scientific literature pertaining to genetic and environmental causes of the malformations in question. Abridged counseling on the basis of superficial and incomplete analyses is a disservice to the family. Experienced counselors understand that their primary task is to educate the pregnant women or family members concerning the risk of an environmental exposure. The counselor should advise them on the options available, but not on which option to select.

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1. Introduction

In 1944, during World War II, I received my draft notice for induction into the armed forces, which would occur in mid 1945. At the age of 15 years, I applied to the University of Rochester, since I had passed all the high school senior courses which included advanced physics, biology and chemistry. In June 1944, I was a freshman at the University and obtained a part-time position at the Manhattan Project Research facility in Rochester in the genetics and embryology divisions. Whereas all the employees at the University of Rochester were investigating the biological effects of ionizing radiation and the entire research staff had the highest level of security clearance, none of the staff were aware that researchers in Los Alamos were attempting to develop an atomic bomb. After the war ended in 1945, the Manhattan Project became one of the Atomic Energy Commission (AEC) facilities at the University. In 1949, I entered medical school but continued my embryology radiation research. The head of the division, Dr James Wilson, offered me the opportunity to be his graduate student in the summer of 1950 and Wilson spent the summer intensively training me in all

the experimental techniques used in that division. At the end of the summer, Dr Wilson announced that he had accepted a position at the University of Cincinnati. Rather than close the division, the Administration appointed me the Head of the Division. I had a budget, a technician and secretarial support and I taught the University of Rochester medical students embryology during the next four years while I was in Rochester completing my medical and graduate degrees. During these four years my national and international counseling effort began at the University of Rochester.

The only other major AEC facility in the country interested in radiation effects on reproduction was at Liane Russell's excellent laboratory in Oak Ridge, Tennessee. However, she was extensively involved in pursuing her research. So the calls and letters all came to Rochester, and then to the Massachusetts General Hospital where I was a resident physician and the Walter Reed Army Institute of Research where I was the head of the Radiation Biology Section for my two years of Army service from 1955 until 1957. I arrived at The Jefferson Medical College in 1957 and have been there for 56 years. In the 1950s there were practically no educational programs in medical school or graduate school that pertained to the evaluation of the risks of reproductive and developmental toxicants or counseling families with regard to the presence or absence of risks from these exposures. The concept of professional counseling was still in its infancy.

* Tel.: +1 302 651 6880; fax: +1 302 651 6888.

E-mail address: rbrent@nemours.org.

2. The stages of medical and graduate school education in the USA: When did counseling with regard to reproductive and developmental toxicant exposure become a recognized and necessary skill?

Medical education in the USA received a major impetus following the publication of Abraham Flexner's (1910) monograph that was commissioned by the Carnegie Foundation for the Advancement of Teaching [1]. Prior to being contacted by the Carnegie Foundation, Flexner graduated from Johns Hopkins in 1885 at the age of 19 and crystallized in his mind the components of quality higher educational programs: small classes, personal attention and hands-on teaching. He returned to Louisville and founded a medical school using these principles. The graduates proved to be emissaries of what quality education can accomplish. It was these early successes that convinced the Carnegie Foundation that Flexner was the scholar who could improve medical education. Following the implementation of the Flexner Report many rural medical schools closed. Many physicians are unaware that Flexner was not a physician nor did he have an advanced degree. However, he was a brilliant teacher and scholar.

Over the next 50 years the Flexner model of medical education evolved into the bioscience model of medical education and medical practice. High quality basic science education and research 'could provide all the answers', so that physicians could diagnose, ameliorate, treat or cure medical problems with which they encountered.

Unfortunately, the bioscience model is incomplete and can result in a significant portion of the patient population being dissatisfied with their care. This was evident to George Engle at the University of Rochester. He was trained in psychiatry and internal medicines and published many articles about the biopsychosocial model of health care delivery that reflected his interest in psychosomatic medicine [2]. At the University of Rochester Engle established the 'medical psychiatric liaison service' staffed by internists and psychiatrists. Engle indicated that he would prefer having physicians with behavioral training rounding on the other clinical services rather than on the psychiatry service. Engle was adamant that you cannot ignore the impact of the environment on the patient's disease or the behavioral defenses available to the patient. It was clear that Engle believed that compassion and empathy were important components of the biopsychosocial model of medical care.

Carl Rogers [3–5] is probably the most important contributor to the elements of proper counseling since he emphasized the humanistic approach to psychological counseling. If the patients or contacts do not sense that the counselor is compassionate or empathetic, their interaction will be less than satisfactory. Exhibiting genuine compassion and empathy results in a client-centered interaction with much greater success in properly communicating and educating the contact. The client, patient or contact has to believe that the counselor believes that the contact deserves respect, which is demonstrated by exhibiting compassion and regard for the contact (unconditional, positive regard) [4]. The fundamental precepts of Rogerian counseling include congruence (being genuine in one's concern), empathy, and unconditional positive regard [4]. A widely accepted component of genuine concern in medical counseling is the responsibility of the counselor to provide core knowledge of the evidence addressing the issue in question. To be genuinely concerned is to seek and provide reliable information. A further adaptation of these principles involves providing an unbiased discussion of the facts surrounding the problem being addressed. Empathy requires some knowledge of, and sensitivity to, the social and cultural position of the persons being counseled.

During the first 50 years of the twentieth century, the rules of professional counseling were rarely articulated or taught. It was only after the writings of Engle and Rogers that the essential features of professional counseling were legitimized, whether it pertained to psychotherapy, medical care and especially for counseling contacts concerning reproductive and developmental risks from environmental exposures.

3. The history of providing counseling to pregnant women exposed to reproductive and developmental toxicants (teratogenesis, congenital malformations), and men and women with preconception exposures (mutagenesis in the gametes and in the offspring in the next generation)

Individual counseling is part of the practice of clinical medicine. However, at the beginning of the twentieth century there were very few individuals prepared to counsel patients with regard to the risk of reproductive, developmental and mutagenic toxicants.

Our laboratory has provided consultations dealing with the risk of various environmental toxicant exposures during or before pregnancy since 1950. In 1960 a group of 60 scientists interested in birth defects met at the Slone Kettering Institute in New York City to discuss their common interests in the causes of birth defects and decided to create a Birth Defects Society. In 1961 many of those scientists met in Cincinnati where the charter of the Teratology Society was drafted. Within the Teratology Society a proportion of the membership was interested in providing counseling to the patient population. There were diverse opinions as to whether individuals who provided counseling should receive training and pass a certification examination. That issue was never resolved. However, the problem was partially solved in the 1990s when the Organization of Teratology Services was formed, which frequently meets with the Teratology Society at the latter's annual meeting. In 2005, the name of OTIS was changed to the Organization of Teratology Information Specialists. In Europe the European Teratology Society (founded in the 1970s) and European Network of Teratology Information Services (ENTIS) define the counseling organizations in Europe having active scientific and counseling programs, as also happens in Japan and Australia. But none of these organizations professionally certifies individuals to provide counseling, although some members may be certified genetic counselors.

In North America there are many OTIS members and branches. The Mother Risk program (Motherrisk.org) headed by Dr Gideon Koren is located at the Hospital for Sick Children and the University of Toronto. In San Diego, Dr Kenneth Lyon Jones heads the largest program in California; and in Seattle, the TERIS program was initiated with a federal grant obtained by Dr Jan Friedman. With the advent of the Internet, consulting has become more rapid and efficient. In 2012 the Ask the Expert (ATE) website of the HPS (Health Physics Society) received about 2 400 000 hits. More than 700 000 prepared answers to questions were downloaded. More than 1800 contacts were still quite anxious after reading the website answers and requested a personal consultation. During 2012 our laboratory received its 25 000th consultation. We also receive consultations by letter, telephone and e-mail unrelated to the HPS website. From this extensive experience we have learned that many physicians and other health care counselors are not prepared to counsel patients concerning reproductive and developmental risks. Approximately 6–10% of the contacts concerned about various environmental toxicants had been provided inaccurate information that stimulated unwarranted anxiety that could have resulted in an unnecessary interruption of a wanted pregnancy.

4. Role of the counselor in advising families

The counselor must be cognizant of many patients' belief that congenital malformations are caused by a drug or medication taken during pregnancy. Counseling patients about reproductive risks requires a significant degree of both knowledge and skill. Physicians must also realize that erroneous counseling by inexperienced health professionals may be a stimulus to non-meritorious litigation [6–8].

Unfortunately, some individuals have assumed that if a drug or chemical causes birth defects in an animal model or in an in-vitro system at a high dose, then it has the potential for producing birth defects at any dose. This may be reinforced by the fact that many teratology studies reported in the literature using several doses have not determined the no-effect dose.

Ignoring the basic tenets of teratology (Box 1) appears to occur most frequently in the evaluation of environmental toxic exposures where the exposure was very low or unknown and the agent has been reported to be teratogenic at a very high dose or a maternally toxic dose in animal models. In most but not all instances, the actual population exposure is revealed to be orders of magnitude below the threshold dose observed in animal studies. This has occurred with 2,4,5-trichlorophenoxyacetic acid (2,4,5-T, also known as Agent Orange), polychlorinated biphenyls (PCBs), lead, cadmium, pesticides, herbicides, veterinary hormones and some industrial exposures.

Unfortunately, environmental disasters have been responsible for birth defects or pregnancy loss in exposed populations (methyl mercury in Japan, PCBs in the Orient, organic mercury in the Middle

East, lead poisoning in the nineteenth and early twentieth centuries) and there are examples of teratogenic drugs and chemicals having been introduced (Table 1) [10–17]. Therefore, we can never generalize as to whether a chemical or drug is safe or hazardous unless we know the magnitude and stage of the exposure.

Before their baby is born, parents may be concerned about the risks of various environmental exposures. If the child is born with congenital malformations they may question whether there was a causal relationship with an environmental exposure.

4.1. Scholarly evaluation

When a counselor responds to a parent's inquiry ('What caused my child's birth defect?'), the physician should respond in the same scholarly manner that would be utilized in performing a differential diagnosis for any clinical problem. Physicians have a protocol for evaluating complex clinical problems; i.e. 'fever of unknown origin', 'failure to thrive', 'congestive heart failure', or 'respiratory distress' (Box 2).

If a mother of a malformed infant had some type of exposure during pregnancy, such as a diagnostic radiological examination or medication utilized during pregnancy, the consulting physician should not support or suggest the possibility of a causal relationship before performing a complete evaluation (Box 3). Likewise, if a pregnant woman who had not yet delivered had some type of exposure during pregnancy, the consulting physician should not support or suggest the possibility that the fetus is at increased risk before performing a complete evaluation.

As mentioned previously, only a small percentage of birth defects is due to prescribed drugs, chemicals and physical agents (Tables 2 and 3). Even when the drug is listed as a teratogen, it has to have been administered during the sensitive period of development for that drug and above the threshold dose for producing teratogenesis. Furthermore, the malformations in the child should be the malformations that are included in the teratogenic syndrome produced by that drug. It should be emphasized that a recent analysis pointed out that there are no drugs with measurable teratogenic potential in the list of the 200 most prescribed drugs in the USA [17].

After a complete examination of the child and a review of the genetic and teratology medical literature, the clinician must decide on whether the child's malformations are due to a genetic cause or an environmental toxin or agent (Boxes 1 and 2; Table 1). The clinician may not be able to conclude, definitively or presumptively, the etiology of the child's birth defects. This information must then be conveyed to the patient in an objective and compassionate manner. A similar situation exists if a pregnant woman has been exposed to a drug, chemical or physical agent, since the mother will want to know the risk of that exposure to her unborn child. If one wishes to answer the generic question, 'Is a particular environmental drug, chemical or physical agent a reproductive toxicant?' then a formal approach is recommended that includes a five-part evaluation as described in Box 4.

5. Deficiencies in counseling education and methodology

Some physicians and other health professionals misinform their patients regarding the magnitude of the risk of environmental toxicant exposure during pregnancy [23,29]. Ratnapalan et al. [29] surveyed a large number of general physicians and obstetricians regarding the risk of abdominal computed tomography (CT) scan to pregnant women during the 6th week of gestation (Table 4). Experienced counselors understand that their primary task is to educate the pregnant women or family members concerning the risk of an environmental exposure. The counselor should advise

Box 1 Principles of teratology.

When evaluating studies dealing with the reproductive and developmental effects of any environmental agent, important principles should guide the analysis of reproductive human and animal studies. Paramount to this evaluation is the application of the basic science principles of teratology and developmental biology.^a

1. Exposure to teratogens follows a toxicological dose–response curve. There is a threshold below which no effect will be observed, and, as the dose of the teratogen is increased, both the severity and frequency of reproductive effects will increase (deterministic effect; tissue reaction).
2. The period of exposure is critical in determining what effects will be produced and whether any effects can be produced by a known teratogen. Some teratogenic effects have a broad period of sensitivity, others a very narrow one.
3. Even the most potent teratogenic agent cannot produce every malformation.
4. Most teratogens have a confined group of congenital malformations that occur after exposure during a critical period of embryonic development. This confined group of malformations is referred to as the syndrome that describes the agent's teratogenic effect.
5. Whereas a group of malformations may suggest the possibility of certain teratogens, they cannot definitively confirm the causal agent. On the other hand, the presence of certain malformations can eliminate the possibility that a particular teratogenic agent was responsible.

^aSource: Brent [52].

Table 1
Developmental toxicants: risks of congenital malformations and abortion in the human.

Developmental toxicant	Reported effects or associations and estimated risks	Comments ^a
Alcohol	Fetal alcohol syndrome: intrauterine growth retardation, maxillary hypoplasia, reduction in width of palpebral fissures, characteristic but not diagnostic facial features, microcephaly, mental retardation. An increase in spontaneous abortion has been reported but since mothers who abuse alcohol during pregnancy have multiple other risk factors, it is difficult to determine whether this is a direct effect on the embryo. Consumption of 6 oz of alcohol or more per day constitutes a high risk but it is likely that detrimental effects can occur at lower exposures.	Quality of available information: good to excellent. Direct cytotoxic effects of ethanol and indirect effects of alcoholism. Whereas a threshold teratogenic dose is likely it will vary in individuals because of a multiplicity of factors.
Aminopterin, methotrexate	Microcephaly, hydrocephaly, cleft palate, meningomyelocele, intrauterine growth retardation, abnormal cranial ossification, reduction in derivatives of first branchial arch, mental retardation, postnatal growth retardation. Aminopterin can induce abortion within its therapeutic range; it is used for this purpose to eliminate ectopic embryos. Risk from therapeutic doses is unknown but appears to be moderate to high.	Quality of available information: good. Anticancer, antimetabolic agents; folic acid antagonists that inhibit dihydrofolate reductase, resulting in cell death.
Androgens	Masculinization of female embryo: clitoromegaly with or without fusion of labia minora. Non-genital malformations are not a reported risk. Androgen exposures which result in masculinization have little potential for inducing abortion. Based on animal studies, behavioral masculinization of the female human will be rare.	Quality of available information: good. Effects are dose and stage dependent; stimulates growth and differentiation of sex steroid receptor-containing tissue.
Angiotensin-converting enzyme (ACE) inhibitors	The therapeutic use of ACE inhibitors has neither a teratogenic effect nor an abortifacient effect in the first trimester. Since this group of drugs does not interfere with organogenesis, they can be used in a woman of reproductive age; if the woman becomes pregnant, therapy can be changed during the first trimester without an increase in the risk of teratogenesis. Later in gestation these drugs can result in fetal and neonatal death, oligohydramnios, pulmonary hypoplasia, neonatal anuria, intrauterine growth retardation, and skull hypoplasia. Risk is dependent on dose and length of exposure.	Quality of available information: good. Antihypertensive agents; adverse fetal effects are related to severe fetal hypotension over a long period of time during the second or third trimester.
Caffeine	Caffeine is teratogenic in rodent species with doses of 150 mg/kg. There are no convincing data that moderate or usual exposures (300 mg per day or less) present a measurable risk in the human for any malformation or group of malformations. On the other hand, excessive caffeine consumption (exceeding 300 mg per day) during pregnancy is associated with growth retardation and embryonic loss.	Quality of available information: fair to good. Behavioral effects have been reported and appear to be transient or temporary; more information is needed concerning the population with higher exposures.
Carbamazepine	Minor craniofacial defects (upslanting palpebral fissures, epicanthal folds, short nose with long philtrum), fingernail hypoplasia, and developmental delay. Teratogenic risk is not known but likely to be significant for minor defects. There are too few data to determine whether carbamazepine presents an increased risk for abortion. Since embryos with multiple malformations are more likely to abort, it would appear that carbamazepine presents little risk because an increase in these types of malformations has not been reported.	Quality of available information: fair to good. Anticonvulsant; little is known concerning mechanism. Epilepsy may itself contribute to an increased risk for fetal anomalies.
Cocaine	Preterm delivery; fetal loss; placental abruption; intrauterine growth retardation; microcephaly; neurobehavioral abnormalities; vascular disruptive phenomena resulting in limb amputation, cerebral infarctions and certain types of visceral and urinary tract malformations. There are few data to indicate that cocaine increases the risk of first trimester abortion. The low but increased risk of vascular disruptive phenomena due to vascular compromise of the pregnant uterus would more likely result in mid-gestation abortion or stillbirth. It is possible that higher doses could result in early abortion. Risk for deleterious effects on fetal outcome is significant; risk for major disruptive effects is low, but can occur in the latter portion of the first trimester as well as the second and third trimesters.	Quality of available information: fair to good. Cocaine causes a complex pattern of cardiovascular effects due to its local anesthetic and sympathomimetic activities in the mother. Fetopathology is likely to be due to decreased uterine blood flow and fetal vascular effects. Because of the mechanism of cocaine teratogenicity, a well-defined cocaine syndrome is not likely. Poor nutrition accompanies drug abuse and multiple drug abuse is common.
Chorionic villous sampling (CVS)	Low, but increased risk of orofacial malformations and limb reduction defects of the congenital amputation type as seen in vascular disruption malformations in some series. The risk of abortion following CVS is quite low.	Quality of available information: fair. Excessive bleeding from the chorion is probably related in part to the experience of the operator. Further research is necessary to determine whether CVS is safer for the fetus at certain stages of gestation.
Coumarin derivatives	Nasal hypoplasia; stippling of secondary epiphysis; intrauterine growth retardation; anomalies of eyes, hands, neck; variable central nervous system anatomical defects (absent corpus callosum, hydrocephalus, asymmetrical brain hypoplasia). Risk from exposure 10–25% during 8th to 14th week of gestation. There is also an increased risk of pregnancy loss. There is a risk to the mother and fetus from bleeding at the time of labor and delivery.	Quality of available information: good. Anticoagulant; bleeding is an unlikely explanation for effects produced in the first trimester. Central nervous system defects may occur any time during second and third trimesters and may be related to bleeding.
Cyclophosphamide	Growth retardation, ectrodactyly, syndactyly, cardiovascular anomalies, and other minor anomalies. Teratogenic risk appears to be increased but the magnitude of the risk is uncertain. Almost all chemotherapeutic agents have the potential for inducing abortion. This risk is dose-related; at the lowest therapeutic doses the risk is small.	Quality of available information: fair. Anticancer, alkylating agent; requires cytochrome P450 mono-oxidase activation; interacts with DNA, resulting in cell death.
Diethylstilbestrol (DES)	Clear cell adenocarcinoma of the vagina occurs in about 1:1000 to 10 000 females who were exposed in utero. Vaginal adenosis occurs in about 75% of females exposed in utero before the 9th week of pregnancy. Anomalies of the uterus and cervix may play a role in decreased fertility and an increased incidence of prematurity although the majority of women exposed to DES in utero can conceive and deliver normal babies. In-utero exposure to DES increased the incidence of genitourinary lesions and	Quality of available information: fair to good. Synthetic estrogen; stimulates estrogen receptor-containing tissue, may cause

Table 1 (continued)

Developmental toxicant	Reported effects or associations and estimated risks	Comments ^a
	infertility in males. DES can interfere with zygote survival, but it does not interfere with embryonic survival when given in its usual dosage after implantation. Offspring who were exposed to DES in utero have an increased risk for delivering prematurely, but do not appear to be at increased risk for first trimester abortion.	misplaced genital tissue which has a greater propensity to develop cancer.
Diphenylhydantoin	Hydantoin syndrome: microcephaly, mental retardation, cleft lip/palate, hypoplastic nails and distal phalanges; characteristic but not diagnostic facial features. Associations documented only with chronic exposure. Wide variation in reported risk of malformations but appears to be $\leq 10\%$. The few epidemiological data indicate a small risk of abortion for therapeutic exposures for the treatment of epilepsy. For short-term treatment, i.e. prophylactic therapy for a head injury, there is no appreciable risk.	Quality of available information: fair to good. Anticonvulsant; direct effect on cell membranes, folate, and vitamin K metabolism. Metabolic intermediate (epoxide) has been suggested as the teratogenic agent.
Electromagnetic fields (EMFs)	The data pertaining to video display terminals indicate that the EMF exposures from these units do not present an increased risk for abortion or congenital malformations. The data on power line and appliance exposures are too varied to draw any conclusions, although the risks appear to be small or non-existent. Human exposures to video display terminals and power lines are quite low and are unlikely to have reproductive effects.	Quality of available information: fair. Pregnant animals exposed to EMF do not exhibit consistent or reproducible reproductive effects. There are still questions about biologic effects for frequencies and wave forms of magnetic fields that have not been adequately studied.
Fluconazole	Fluconazole, a triazole antifungal agent used to treat mycotic infections, is a widely administered medication for vaginal candidiasis. In this latter treatment, it is prescribed as a single dose of 150 mg and has not been associated with increased abnormalities or congenital defects in pregnancy series [18–20] Fluconazole is also used to treat more serious mycotic infections at doses of 400–800 mg/day on a continuous basis. During the 1990s, four case reports of infants exposed to this high-dose regimen of fluconazole had a distinct and consistent pattern of malformations [21] The constellation of defects consisted of craniosynostosis, orbital hypoplasia, and the rather unique skeletal manifestations of humeral radial synostosis and femoral bowing.	Quality of available information: fair.
Infectious agents	The cytotoxic effects and inflammatory responses resulting from fetal infections interfere with organogenesis and/or histogenesis. Fetopathic syndromes are related to the specific tissue localization, pathologic characteristics of the infectious agent and the duration of the infection in the embryo and fetus. In some instances the infection may be debilitating to the mother and indirectly result in pregnancy loss.	
Cytomegalovirus (CMV)	Fetal cytomegalovirus infection presents an increased risk for abortion but it does not appear that maternal genital infection increases the risk of abortion. Fetal infection occurs in about 20% of maternal infections. Intrauterine growth retardation: risk of brain damage is moderate after fetal infection early in pregnancy; characteristic parenchymal calcification.	Quality of available information: good to excellent. CMV damages organs principally by cellular necrosis.
Herpes simplex virus	Generalized organ infections, microcephaly, hepatitis, eye defects, vesicular rash. Maternal infection can be transmitted in utero or perinatally. Herpes simplex 2 is one of the few infections where it is agreed that the risk of abortion is increased.	Quality of available information: good. Fetal anomalies associated with herpes simplex virus infection appear to be due to disruption rather than malformation.
Human immunodeficiency virus (HIV)	The overall risk of vertical transmission of HIV is 25–40%. Fetal HIV infection and asymptomatic maternal HIV infection are not associated with adverse effect on fetal growth or development. Symptomatic maternal HIV infection, other sexually transmitted diseases and opportunistic infections may increase the risk of low birth weight or perinatal morbidity.	Quality of available information: fair to good. Prophylactic treatment with zidovudine does not appear to cause permanent adverse effects in the fetus.
Parvovirus B19	Infection can result in erythema infectiosum in children but in the fetus can result in hydrops fetalis and fetal death; congenital anomalies are likely to be very rare. The risk for stillbirth with hydrops has been clearly substantiated. An increased risk for abortion has been suggested, but is more difficult to substantiate.	Quality of available information: fair to good. Fetal infection is not frequent. Infection of red blood cell precursors causes severe anemia.
Rubella virus	Greater than 80% incidence of embryonic infection with exposure in first 12 weeks, 54% at 13–14 weeks, 25% at end of second trimester, and 100% at term. Defects include mental retardation, deafness, cardiovascular malformations, cataracts, glaucoma, microphthalmia. Diabetes mellitus or rubella panencephalitis may develop later in life. The abortigenic risk of maternal rubella is uncertain.	Quality of available information: excellent. Rubella has an affinity for specific tissues. Damage is caused by mitotic inhibition, cell death and interference with histogenesis by repair processes, resulting in calcification and scarring.
Syphilis	Defects in 50% of offspring after early exposure to primary or secondary syphilis and 10% after late exposures. Defects include maculopapular rash, hepatosplenomegaly, deformed nails, osteochondritis at joints of extremities, congenital neurosyphilis, abnormal epiphyses, chorioretinitis. Syphilis can increase the incidence of abortion.	Quality of available information: good. Fetal pathology is associated with maturation of the fetal immune system at about the 20th week.
Toxoplasmosis	Hydrocephaly, microphthalmia, chorioretinitis. Risk is predominantly associated with pregnancies in which the mother acquires toxoplasmosis. Epidemiological studies do not indicate that toxoplasmosis increases the incidence of early abortion, but congenital toxoplasmosis may be responsible for the stillbirth of severely affected fetuses.	Quality of available information: good to excellent. Toxoplasmosis is unlikely to contribute to the risk of repeated abortion.
Varicella-zoster	Skin and muscle defects; intrauterine growth retardation; limb reduction defects. No measurable increased risk of early teratogenic effects. Incidence of maternal varicella during pregnancy is low but risk of severe neonatal infection is high if maternal infection occurs in last week of pregnancy. There does not appear to be an increased risk of first trimester abortion.	Quality of available information: fair to good. Virus infection of fetal tissues can cause cellular necrosis.
Venezuelan equine encephalitis	Hydroencephaly; microphthalmia; central nervous system destructive lesions; luxation of hip. There are not enough data to determine whether infection presents an increased risk of abortion.	Quality of available information: poor to fair. Infection can cause cellular necrosis in fetal tissues but fetal infection is rare.

(continued on next page)

Table 1 (continued)

Developmental toxicant	Reported effects or associations and estimated risks	Comments ^a
Lead	There is no indication that serum lead levels <50 µg% result in congenital malformations in exposed embryos and fetuses but the developing central nervous system in the fetus and child may be susceptible to lead toxicity, resulting in decreased IQ and behavioral effects. Lead levels >50 µg% result in anemia, and encephalopathy can have serious effects on central nervous system development. Lead levels <50 µg% do not increase the risk of abortion.	Quality of available information: good. Whereas there are human studies indicating small deficiencies in IQ in patients with lead levels >10 µg%, there could be other explanations for these IQ differences. Furthermore, pathological findings have not been described in the brain at these levels.
Lithium carbonate	Although animal studies have demonstrated a clear teratogenic risk, the effect in humans is uncertain. Early reports indicated an increased incidence of Ebstein's anomaly, other heart and great vessel defects, but as more studies are reported the strength of this association has diminished. Lithium levels within the therapeutic range (<1.2 mg%) do not increase the risk of abortion.	Quality of available information: fair to good. Antidepressant; mechanism has not been defined.
Maternal conditions Diabetes	Caudal hypoplasia or caudal regression syndrome; congenital heart disease; anencephaly. Vascular lesions in long-standing diabetics may produce placental dysfunction and result in fetal growth retardation. Documented significant increased risk of abortion. The risk is greatest in untreated diabetics or in patients who are poorly controlled; insulin therapy protects the fetus.	Quality of available information: good. Results of in-vitro studies suggest that diabetic embryopathy has a multifactorial etiology. Adverse fetal effects have not been demonstrated with gestational diabetes.
Endocrinopathy	If condition is compatible with pregnancy, effects are similar to those following administration of high or low doses of the hormone. Hypo- and hyperthyroidism may increase the risk of abortion. Cushing's disease, pituitary tumors, hypothalamic tumors and androgen-producing tumors do not appear to increase the risk of abortion, but may contribute to infertility.	Quality of available information: good. Receptor-mediated exposures to high levels of hormone.
Nutritional deprivation	Central nervous system anomalies; intrauterine growth restriction; increased morbidity. In some instances of teratogenesis, abnormal nutrition may be the final common mechanism. Severe malnutrition can contribute to pregnancy loss at any stage of pregnancy.	Quality of available information: fair to good. The high mitotic rate of the fetus in general and the central nervous system in particular is very sensitive to severe alterations in nutrient supply.
Phenylketonuria	Mental retardation; microcephaly; intrauterine growth retardation. Documented significant increased risk of abortion. The risk is greatest in pregnant women who were not treated for their phenylketonuria.	Quality of available information: good. Very high levels of phenylalanine interfere with embryonic cell metabolism.
Mechanical problems	Birth defects such as club feet, limb reduction defects, aplasia cutis, cranial asymmetry, external ear malformations, midline closure defects, cleft palate and muscle aplasia. Submucosal and intramural myomata, amniotic bands, multiple implantations, bifid uterus or infantile uterus which contribute to mechanical problems do not result in early abortions.	Quality of available information: good. Physical constraint can result in distortion and a reduction in blood supply and is more frequent in pregnancies with multiple conceptuses, abnormal uterus, amniotic abnormalities and oligohydramnios.
Methyl mercury	Minamata disease: cerebral palsy, microcephaly, mental retardation, blindness, cerebellar hypoplasia. Does not appear to decrease fertility unless the mother becomes clinically ill from methyl mercury poisoning. At low exposures the teratogenic effect predominates and there are few human data to indicate the risk of abortion.	Quality of available information: good. Organic mercurials accumulate in lipid tissue causing cell death due to inhibition of cellular enzymes, especially sulphydryl enzymes. Since most cases result from accidental environmental exposure, risk estimation is usually retrospective.
Methylene blue	Hemolytic anemia and jaundice in neonatal period after exposure late in pregnancy. There may be a small risk for intestinal atresia but this is not yet clear. No indication of increased risk of abortion.	Quality of available information: poor to fair. Used to mark amniotic cavity during amniocentesis.
Misoprostol	Misoprostol is a synthetic prostaglandin analog that has been used by millions of women for illegal abortion. A low incidence of vascular disruptive phenomenon, such as limb reduction defects and Moebius syndrome, has been reported.	Quality of available information: fair. Classical animal teratology studies would not be helpful in discovering these effects, because vascular disruptive effects occur after the period of early organogenesis.
Mycophenolate mofetil	This drug is a highly efficient immunosuppressant used to prevent organ rejection after organ transplantation. The agent, which blocks purine synthesis in lymphocytes, raised definite concern when congenital defects were reported to the National Transplantation Pregnancy Registry: three infants all exposed through the first trimester exhibited congenital malformations, two with cleft lip with cleft palate, and all three with microtia; one of the infants had a diaphragmatic defect, a malformation seen in rats and rabbits treated with mycophenolate mofetil.	Quality of the data: fair. Investigators raise concerns regarding teratogenicity.
Oxazolindione-2,4-diones (trimethadione, paramethadione)	Fetal trimethadione syndrome: V-shaped eye brows, low-set ears with anteriorly folded helix, high-arched palate, irregular teeth, CNS anomalies, severe developmental delay. Wide variation in reported risk. Characteristic facial features are documented only with chronic exposure. The abortifacient potential has not been adequately studied, but appears to be minimal.	Quality of available information: good to excellent. Anticonvulsants; affects cell membrane permeability. Actual mechanism of action has not been determined.
D-Penicillamine	Cutis laxa, hyperflexibility of joints. Condition appears to be reversible and the risk is low. There are no human data on the risk of abortion.	Quality of available information: fair to good. Copper chelating agent; produces

Table 1 (continued)

Developmental toxicant	Reported effects or associations and estimated risks	Comments ^a
Polychlorinated biphenyls	Cola-colored babies; pigmentation of gums, nails and groin; hypoplastic deformed nails; intrauterine growth retardation; abnormal skull calcification. Although abortion can be induced at high exposures, most human exposures from environmental contamination are unlikely to increase the risk of abortion.	copper deficiency inhibiting collagen synthesis and maturation. Quality of available information: good. Environmental contaminants; polychlorinated biphenyls and frequently occurring contaminants are cytotoxic. Body residues in exposed women can affect pigmentation in offspring for up to 4 years after exposure.
Progestins	Masculinization of female embryo exposed to high doses of some testosterone-derived progestins and may interact with progesterone receptors in the liver and brain later in gestation. The dose of progestins present in modern oral contraceptives presents no masculinization or feminization risks. All progestins present no risk for non-genital malformations. Many synthetic progestins and natural progesterone have been used to treat luteal phase deficiency, embryos implanted via in-vitro fertilization, threatened abortion or bleeding in pregnancy with variable results. Conversely, synthetic progestins that interfere with progesterone function may cause early pregnancy loss; RU-486 (mifepristone) is presently used specifically for this purpose.	Quality of available information: good. Stimulates or interferes with sex steroid receptor-containing tissue.
Radioactive isotopes	Tissue- and organ-specific damage is dependent on the radioisotope element and distribution, i.e. ¹³¹ I administered to a pregnant woman can cause fetal thyroid hypoplasia after the 8th week of development. Radioisotopes used for diagnosis present no risk for inducing abortion because the dose to the embryo and implantation site is too low. There may be unusual circumstances wherein isotopes are introduced into the abdominal cavity in a pregnant woman for the treatment of malignancy. If the resulting dose to the embryo or fetus is substantial, the risk for abortion is increased.	Quality of available information: good to excellent. Higher doses of radioisotopes can produce cell death and mitotic delay. Effect is dependent on dose, distribution, metabolism, and specificity of localization.
Radiation (external irradiation)	Microcephaly; mental retardation; eye anomalies; intrauterine growth retardation; visceral malformations. Teratogenic risk depends on dose and stage of exposure. Exposures from diagnostic procedures present no increased risk of abortion, growth retardation or malformation. No measurable risk with exposures for ≤ 5 rad (≤ 5 mGy) of X-rays at any stage of pregnancy. In contrast, exposure of the pregnant uterus to therapeutic doses of ionizing radiation significantly increases the risk of aborting the embryo; the fetus is more resistant.	Quality of available information: good to excellent. Diagnostic and therapeutic agents; produce cell death and mitotic delay.
Retinoids, systemic (isotretinoin, tretinate)	Increased risk of central nervous system, cardio-aortic, ear and clefting defects. Microtia, anotia, thymic aplasia and other branchial arch, aortic arch abnormalities and certain congenital heart malformations. Exposed embryos are at greater risk for abortion. This is plausible since many of the malformations, such as neural tube defects, are associated with an increased risk of abortion.	Quality of available information: fair. Used in treatment of chronic dermatoses. Retinoids can cause direct cytotoxicity and alter programmed cell death; affect many cell types but neural crest cells are particularly sensitive.
Retinoids, topical (tretinoin)	Epidemiological studies, animal studies and absorption studies in humans do not suggest a teratogenic risk. Regardless of the risks associated with systemically administered retinoids, topical retinoids present little or no risk for intrauterine growth retardation, teratogenesis or abortion because they are minimally absorbed and only a small percentage of skin is exposed.	Quality of available information: poor. Topical administration of tretinoin in animals in therapeutic doses is not teratogenic, although massive exposures can produce maternal toxicity and reproductive effects. More importantly, topical administration in humans results in non-measurable blood levels.
Smoking and nicotine	Placental lesions; intrauterine growth retardation; increased postnatal morbidity and mortality. While there have been some studies reporting increases in anatomical malformations, most studies do not report an association. There is no syndrome associated with maternal smoking. Maternal or placental complications can result in fetal death. Exposures to nicotine and tobacco smoke are a significant risk for pregnancy loss in the first and second trimester.	Quality of available information: good to excellent. While tobacco smoke contains many components, nicotine can result in vascular spasm vasculitis which has resulted in a higher incidence of placental pathology.
Sonography (ultrasound)	No confirmed detrimental effects resulting from medical sonography. The levels and types of medical sonography that have been used in the past have no measurable risks. The present clinical use of diagnostic ultrasound presents no increased risk of abortion.	Quality of available information: good to excellent. It appears that if the embryonic temperature never exceeds 39 °C, there is no measurable risk.
Streptomycin	Streptomycin and a group of ototoxic drugs can affect the eighth nerve and interfere with hearing; it is a relatively low risk phenomenon. There are not enough data to estimate the abortigenic potential of streptomycin. Because the deleterious effect of streptomycin is limited to the eighth nerve, it is unlikely to affect the incidence of abortion.	Quality of available information: fair to good. Long-duration maternal therapy during pregnancy is associated with hearing deficiency in offspring.
Tetracycline	Bone staining and tooth staining can occur with therapeutic doses. Persistent high doses can cause hypoplastic tooth enamel. No other congenital malformations are at increased risk. The usual therapeutic doses present no increased risk of abortion to the embryo or fetus.	Quality of available information: good. Antibiotic; effects seen only if exposure is late in the first or during second or third trimester, since tetracyclines have to interact with calcified tissue.
Thalidomide	Limb reduction defects (preaxial preferential effects, phocomelia), facial hemangioma, esophageal or duodenal atresia, anomalies of external ears, eyes, kidneys, and heart, increased incidence of neonatal and infant mortality. The thalidomide syndrome, although characteristic and recognizable, can be mimicked by some genetic diseases. Although there are fewer data pertaining to its abortigenic potential, there appears to be an increased risk of abortion.	Quality of available information: good to excellent. Sedative–hypnotic agent. The etiology of thalidomide teratogenesis has not been definitively determined.

(continued on next page)

Table 1 (continued)

Developmental toxicant	Reported effects or associations and estimated risks	Comments ^a
Thyroid: iodides, radioiodine, antithyroid drugs (propylthiouracil), iodine deficiency	Fetal hypothyroidism or goiter with variable neurologic and aural damage. Maternal hypothyroidism is associated with an increase in infertility and abortion. Maternal intake of ≥ 12 mg of iodide per day increases the risk of fetal goiter.	Quality of available information: good. Fetopathic effect of endemic iodine deficiency occurs early in development. Fetopathic effect of iodides, antithyroid drugs and radio iodine involves metabolic block, decreased thyroid hormone synthesis and gland development.
Toluene	Intrauterine growth retardation; craniofacial anomalies; microcephaly. It is likely that high exposures from abuse or intoxication increase the risk of teratogenesis and abortion. Occupational exposures should present no increase in the teratogenic or abortifacient risk. The magnitude of the increased risk for teratogenesis and abortion in abusers is not known because the exposure in abusers is too variable.	Quality of available information: poor to fair. Neurotoxicity is produced in adults who abuse toluene; a similar effect may occur in the fetus.
Valproic acid	Malformations are primarily neural tube defects and facial dysmorphism. The facial characteristics associated with this drug are not diagnostic. Small head size and developmental delay have been reported with high doses. The risk for spina bifida is about 1% but the risk for facial dysmorphism may be greater. Because therapeutic exposures increase the incidence of neural tube defects, one would expect a slight increase in the incidence of abortion.	Quality of available information: good. Anticonvulsant; little is known about the teratogenic action of valproic acid.
Vitamin A	The same malformations that have been reported with the retinoids have been reported with very high doses of vitamin A (retinol). Exposures $< 10,000$ IU present no risk to the fetus. Vitamin A in its recommended dose presents no increased risk for abortion.	Quality of available information: good. High concentrations of retinoic acid are cytotoxic; it may interact with DNA to delay differentiation and/or inhibit protein synthesis.
Vitamin D	Large doses given in vitamin D prophylaxis are possibly involved in the etiology of supravalvular aortic stenosis, elfin faces, and mental retardation. There are no data on the abortifacient effect of vitamin D.	Quality of available information: poor. Mechanism is likely to involve a disruption of cell calcium regulation with excessive doses.

^a Quality of available information is modified from TERIS [22].

them on the options available, but not on which option to select. On the contrary, in one survey, up to 6% of all physicians would recommend medical termination of pregnancy for women who had undergone a single CT at 6 weeks of gestation and 27% of all physicians surveyed were uncertain if they would recommend a medical termination of pregnancy (Box 2) [29]. In case of a toxicological exposure, the counselor should attempt to establish a good understanding of the exposure in question and its timing. A list of information required to provide high quality counseling to those exposed is listed in Boxes 1 and 3. The pervasive problem is that many physicians and counselors tell the patient or family what to do. In many instances the counselor (i) has no expertise concerning the risks of an exposure, or (ii) the counselor knows the risks, but he/she does not take the time to educate the patient about the risks.

6. Counseling: What are the reproductive or developmental concerns of pregnant women and/or family members concerning the risk of alleged or suspected toxicological exposures during pregnancy or before pregnancy? Role of the counselor

These concerns include (i) birth defects (congenital malformations), (ii) pregnancy loss (miscarriage or spontaneous abortion), (iii) growth retardation, (iv) prematurity, (v) neurobehavioral effects (decreased IQ, small head size, convulsive disorders, autism, attention deficit hyperactivity disorder) and cancer. All of these effects except for cancer and mutations in the F_1 generation are deterministic effects (threshold effects, tissue reaction effects) (Table 5). The term 'tissue reaction' effects is a new term adopted because it conveys the concept that these effects involve exposure to tissues indicating that many cells have to be affected, which explains why there is a threshold below which there is no increased risk (Table 5).

Mutagens have the potential to induce cancer or genetic effects by altering one cell, and therefore theoretically do not have a threshold [20–44]. Recent discussions of the universal application

of the linear-no-threshold hypothesis (LNTH) indicate that there is disagreement as to whether the LNTH is applicable at very low exposures to environmental toxicants and with protracted toxicant exposures (Table 5) [35–37].

7. The role of the counselor

The classical approach for the evaluation of risks from in-utero environmental exposures is to review the available epidemiological studies and appropriate animal models, and to evaluate these data from the standpoint of biologic plausibility or biologic common sense (Box 4) [26]. In order to perform an analysis outlined in Box 4, the drug, chemical or physical agent has to have been distributed or sold for a period of years so that epidemiological data, animal toxicology data and in-vitro studies are available for analysis.

7.1. Evaluating the allegation of teratogenicity

When confronted with the question of the teratogenicity of certain environmental agents, the question can be posed from various vantage points:

1. Evaluating the risk of reproductive toxicity of an environmental agent.
2. Evaluating the suggestion that an environmental agent was responsible for an individual child's birth defect or other reproductive effects.
3. Evaluating the cause of congenital malformations in a particular child or a group of children.
4. Determining whether to publish a case report of a patient or a cluster of patients with a particular congenital malformation or a constellation of congenital malformations that may be associated with an environmental agent [38].

If one wishes to answer the generic question, 'Is a particular environmental drug, chemical or physical agent a reproductive toxicant?', then a formal approach is recommended that includes a

Box 2

Responsibilities of the counselor.

1. Questions submitted by patients or contacts regarding environmental toxicant exposures should never be described as silly, dumb or unnecessary. Every response should attempt to dignify the question as appropriate. However, the counselor should provide scientific explanations as to why the contact's concerns are or are not substantiated by the available facts. The counselor is an educator.
2. It is difficult for many counselors to comprehend the anguish, heartache, fear and concern in the hearts and minds of the contacts when they are concerned about the health of their fetus from exposures to environmental toxicants. The degree of fear is related to the mental state of the contact as well as the type and magnitude of the exposure to the environmental toxicant.
3. Many counselors do not understand that their professional goal should be to educate the contact about the reproductive or developmental risks that may result from a particular environmental exposure, not to advise them what decision they should select.
4. Many novice counselors do not realize that it is their responsibility to provide the contacts with the background risk that they face, even when there are no increased risks from the exposure. The contacts are requested to keep the counselor informed. Do they have any more questions? Please keep in touch, send a picture. The consultation is signed with 'Warm regards'. It should be made clear to the contact that the counselor has functioned as an educator. The counselor does not advise contacts on what decision to select, only the options that are available. Yet, many contacts thank the counselor for telling them what to do, even though they have not been advised on which available option to select.
5. It is important to permanently save a written record of the statements of the contact and the counselor.
6. Each consultation that definitively determined that their reproductive or developmental risks are not increased ends with this statement:

'Your risk for birth defects or miscarriage is not increased above the background risks that all healthy pregnant women face. The background risks for pregnant women with no personal or family history of reproductive or developmental problems is 3% for birth defects and 15% for miscarriage. All pregnant women face these risks, many of which we cannot yet prevent.'

We wish them good luck with their pregnancy and to keep in touch. If the contact asks about the risks of mental retardation, cancer or other effects, these background risks are discussed also. The answers are directed specifically to their questions.

If the contact is concerned about cancer in her offspring from either preconception or postconception exposures, it is most important to educate the contact regarding the high background incidence of cancer in the population. Potentially lethal cancers occur in 23% of the population, which dwarfs the incidence of environmentally induced cancer. It is important to point out that the spontaneous occurrence of cancer, which increases with age due to mutation that occurs in the dividing somatic cells, is the most important etiology of human cancer.

Box 3

Minimum information required to provide adequate counseling to women or couples regarding concerns about the risks of environmental toxicant exposures before or during the pregnancy.^a

1. Is the contact pregnant, possibly pregnant or planning to become pregnant?
2. If the contact is pregnant, does she know the date she became pregnant? Does she know the date of the first day of her last menstrual period?
3. Does she know the date of conception from other sources: an ultrasound that timed the pregnancy or a date when intercourse took place that is consistent with other information about timing?
4. Are there historical pregnancy risks (birth defects, miscarriage, etc.) for the mother or the family – for example, a history of miscarriages, birth defects, infertility or serious illnesses in the contact, spouse, or parents or siblings?
5. Does the contact know the name of the environmental toxicant to which she or her spouse was exposed? Is it a drug, chemical or physical agent (such as radiation or heat)? What was the amount and length of the exposure before or during pregnancy? Provide the dates and amount (dose) of the exposure. The Environmental Protection Agency (EPA) has prepared toxicological evaluations of chemicals using animal studies and now high-throughput in-vitro studies. The EPA may even have estimated a reference dose exposure, which is an exposure that has no deterministic reproductive effects.
6. Has the woman or couple sought advice from another counselor about the developmental risks of this exposure? Please provide details of the response.
7. The needs of the person seeking counseling are the only operative issues to be considered.

^aAdapted from Brent [23].

five-part evaluation as described in Box 4 [26]. This formal approach is utilized only when a drug or chemical has been utilized and sold for a period of many years and, during that time, studies on epidemiology, animals and pharmacokinetics have been performed [30–37].

If, on the other hand, one is concerned about the reproductive effects of an environmental agent in an individual patient, the question may sometimes be answered without the benefit of epidemiological studies, dosimetry or animal studies, utilizing the basic principles of teratology, reproductive toxicology and genetics. Key factors in such an evaluation are having an experienced clinician who is knowledgeable about the genocopies that can mimic environmental teratogens, who is aware of the importance of dose or exposure and who is aware of the basic principles of developmental biology and teratology. A clinician trained and experienced in these fields may have a decisive role in utilizing the principles of teratology (Box 1) and biological plausibility in evaluating the allegation that a particular environmental agent was responsible for a child's congenital malformations [10,28,38–40,42,44,45,52].

7.2. Counselors must have knowledge of known or possible reproductive toxins

Reproductive and developmental counselors should have been educated and prepared to discuss background risks of birth defects and the broad subject of the etiology of developmental birth defects

Table 2
Etiology of human congenital malformations.^a

Suspected cause	Percent of total
Unknown	65
Polygenic	
Multifactorial (gene–environment interactions)	
Spontaneous errors of development	
Synergistic interactions of teratogens	
Genetic	15–25
Autosomal and sex-linked inherited genetic disease	
Cytogenetic (chromosomal abnormalities)	
New mutations	
Environmental (total)	10
Maternal conditions: alcoholism; diabetes; endocrinopathies; phenylketonuria; smoking and nicotine; starvation; nutritional deficits	4
Infectious agents: rubella, toxoplasmosis, syphilis, herpes simplex, cytomegalovirus, varicella-zoster, Venezuelan equine encephalitis, parvovirus B19	3
Mechanical problems (deformations): amniotic band constrictions; umbilical cord constraint; disparity in uterine size and uterine contents	1–2
Chemicals, prescription drugs, high-dose ionizing radiation, hyperthermia	2

^a Source: Brent [9].

and reproductive problems (Tables 2 and 3). Counselors must have knowledge of known or possible reproductive toxins and be familiar with how the medial literature dealing with teratogens can be accessed [22,46–55].

Table 1 provides a list of known or alleged reproductive toxin or teratogenic agents. The TERIS and OTIS websites are more up-to-date, as is the genetic website of the National Library of Medicine (OMIM).

Each counselor may have many consultations in their files; however, it is not the purpose of this publication to provide numerous examples. On the Health Physics website, Ask the Expert (ATE), there are more than 60 prototype questions. NCRP 174, published in 2013 [52], has an appendix with scores of consultation questions and answers that pertain to the preconception and postconception risks of ionizing radiation, ultrasound, non-ionizing electromagnetic fields, CT scans and magnetic resonance imaging.

A few examples of responses to contacts exposed to environmental toxicants are presented below. A preconception and post-conception toxicant exposure is discussed, as well as a contact who

Table 3
Reproductive risks per million recognized pregnancies.^a

Reproductive risks	Frequency
Immunologically and clinically diagnosed spontaneous abortions per million conceptions (<20% has lethal malformations or chromosome abnormalities that cause abortion before the first month of gestation).	350 000
Clinically recognized spontaneous abortions per million clinically recognized pregnancies. Spontaneous abortion after the first missed menstrual period.	150 000
Genetic diseases per million births	110 000
Multifactorial or polygenic genetic environmental interactions)	90 000
Dominantly inherited disease	10 000
Autosomal and sex-linked genetic disease	1200
Cytogenetic (chromosomal abnormalities)	5000
New mutations in the developing ova or sperm prior to conception	3000
Major malformations (genetic, unknown, environmental)	30 000
Prematurity (Ireland: 55 000; USA: 124 000)	69 000
Fetal growth restriction	30 000
Stillbirths (>20 weeks; wide range in prevalence because of variables contributed by cultures, socio-economic factors, race, prenatal medical care)	4000–20 900
Infertility	7% of couples

^a Source: Brent [9].

Box 4

Evaluation of potential for developmental toxicity in the human: evidence of a possible causal relationship.^a

- Epidemiological studies

Controlled epidemiological studies consistently demonstrate an increased incidence of a particular spectrum of embryonic and/or fetal effects in exposed human populations.

- Secular trend data

Secular trends demonstrate a positive relationship between the changing exposures to a common environmental agent in human populations and the incidence of a particular embryonic and/or fetal effect.

- Animal developmental toxicity studies

An animal model can be developed which mimics the human developmental effect at clinically comparable exposures. Since mimicry may not occur in all animal species, animal models are more likely to be developed once there is good evidence for the embryotoxic effects reported in the human. Developmental toxicity studies in animals are indicative of a potential hazard in general rather than the potential for a specific adverse effect on the fetus when there are no human data on which to base the animal experiments.

- Dose–response relationship

Developmental toxicity in humans increases with dose (exposure) and the developmental toxicity in animals occurs at a dose that is pharmacokinetically (quantitatively) equivalent to the human exposure.

- Biological plausibility

The mechanisms of developmental toxicity are understood and the effects are biologically plausible.

^aModified from Brent et al. [25], Brent [26,27], and Shepard [28].

is concerned about the etiology of the child's birth defects. Another frequently asked question pertains as to whether a cluster of similar birth defects in a small geographic area is due to an environmental toxicant.

(1) Preconception exposure: The father or the mother in the family may have been exposed to a toxicological exposure before the pregnancy has occurred. One of the future parents could have been treated with radiation therapy or chemotherapy for cancer that they survived; or one of the parents had multiple diagnostic X-rays as a child or adolescent. The family is concerned about the genetic effects of prior alleged toxicological mutagenic exposures at home or at work. Of the thousands of consultations we have received, about 20% are from future parents concerned about preconception toxicological exposures. Some of the exposures have occurred many years before they contemplated having a family.

Genetic studies of the offspring of patients exposed to mutagenic agents are largely negative. However, we know that mutations have been produced, but the risk of viable offspring with an

Table 4

Survey of obstetricians and family physicians from Ontario, Canada, on medical termination of pregnancy in women who underwent radiography or computed tomography (CT) during early pregnancy.^a

Medical termination of pregnancy recommended	Percentage of respondents			
	Family physicians (n = 208)		Obstetricians (n = 65)	
	Radiography	CT	Radiography	CT
Yes	1	6	0	5
Not sure	25	39	6	25
No	74	55	94	70

^a Source: Ratnapalan et al. [29].

increased incidence of new mutations or cancer is so low that you would need very large populations of exposed individuals to demonstrate the increased risk.

There is no convincing direct evidence of germline mutation seen as heritable disease in the offspring of humans and attributable to ionizing radiation and mutagenic chemicals and drugs, yet these mutagens clearly induce mutations in microbes and somatic cells of rodents and humans, and in offspring of exposed mice. It would be unwise to ignore the possibility of human germ-cell mutations, especially since progress in human genetics may be able to address these issues in the future. Preconception exposure of the ovaries or testes to toxicological agents or low exposure to mutagenic drugs or chemicals is a very low risk phenomenon, especially for exposures from diagnostic radiological procedures. There is no risk for sterility. Since the vulnerable irradiated ova will have been ovulated in two menstrual cycles (2 months) and the irradiated sperm replaced in two spermatogenesis cycles (4 months), it is best that the family wait that period of time before attempting conception. If pregnancy occurs during these windows of time, the environmental toxicant mutagenic risks are miniscule (Box 3) compared with spontaneous risk of germ cell mutations. There are numerous published studies on the offspring of parents who have been exposed to high dose radiation, chemotherapy and other toxicological agents that are proven mutagens; if the exposure is high enough, infertility may result. However, if fertility is intact, the offspring do not manifest an increase in cancer or hereditary diseases [31,34,56–77]. One additional consideration is that many deleterious mutations (spontaneous or as a result of preconception toxicity exposure) would not be expressed as effects in the offspring because they are lethal to the developing ova or sperm or to the very young developing embryo because of defective ova or sperm, a result that has been described as biological filtration [9,42].

Down syndrome has been extensively studied as a possible consequence of diagnostic X-ray procedures but an association has not been established [83]. Some medical studies have been plagued by differential recall bias between mothers of affected and normal

children, as well as publication bias in not reporting negative findings [84].

Studies of cancer survivors are particularly important because they are numerous and, most importantly, because the timing and dose of their exposure to radiation (and potentially mutagenic chemicals) is accurately documented. The rates of genetic defects in offspring of survivors and of sibling controls were not statistically significant [34,56,59–69,72–82]. In a population of Danish children born after their parent's treatment with radiation, the risk of congenital malformation was increased but was not statistically significant [risk ratio: 1.2 (95% confidence interval: 0.9–1.8; n = 36)] [85] and there was no evidence of a correlation between birth defects and gonadal dose, reconstructed on individual patient treatment records (mean doses were 1.3 Gy to ovaries and 0.5 Gy to testes) [34,79]. These data suggest that the agents and doses to which these individuals have been exposed do not induce transmissible mutations in human spermatogonial stem cells and resting oocytes at a frequency high enough to be detected over the background of spontaneous mutations (Table 3).

(2) The spouse is pregnant or considering pregnancy and is concerned about medications that she has been prescribed or is taking, chemicals in the workplace, whether she should have an X-ray suggested by her physician, concern about the power lines near her home, the microwave oven in her kitchen, or numerous frightening messages on the Internet. The most common concern is whether their child may be born with birth defects. Miscarriage and mental retardation are next on their list, or whether their future child is at increased risk for developing cancer.

If the family is concerned about medications prescribed for the pregnant spouse or other environmental exposures that have been extensively studied, the counselor may be able to determine whether there extensive toxicological data have been published and are available to the counselor. Table 1 lists about 60 environmental toxicants that have been studied to determine their ability to affect the developing embryo/fetus or that are alleged to have affected the developing embryo/fetus. If the concern is about a chemical exposure, the family may not know the name of the chemical or the exposure, which makes it difficult or impossible to provide an adequate risk assessment. Several websites may be of assistance (CDC, OMIM, TERIS; see Box 5).

After obtaining the toxicological information, the following process should be initiated as suggested in Boxes 2 and 3.

(3) Since the risk of birth defects is 3% and miscarriage occurs in 15% of pregnancies in women after the first missed menstrual period, the family may contact the counselor to explain the etiology of the developmental or reproductive problem in their child (Box 3, Table 2).

Determining the etiology of birth defects or miscarriage in an individual infant or pregnancy can be a difficult task, especially if the description of the malformation is provided to the counselor by the parent or the family physician. Second, this task could be very

Table 5

Stochastic and threshold dose–response relationships of diseases produced by environmental agents.

Phenomenon	Pathology	Site	Diseases	Risk	Definition
Stochastic (LNTH ^a)	Damage to a single cell may result in disease	DNA (genes and chromosomes)	Cancer, germ cell mutation	Some risk exists at all dosages; at low doses, risk may be less than spontaneous risk	The incidence of the disease increases but the severity and nature of the disease remain the same
Threshold (deterministic effect) (tissue reaction effect)	Multicellular injury	Multiple, variable etiology, affecting many cell and organ processes	Malformation, growth retardation, death, toxicity, etc.	No increased risk below the threshold dose	Both the severity and incidence of the disease increases with dose

LNTH, linear no-threshold hypothesis.

^a Modified from Brent [9].

Box 5 Websites.

CDC – Centers for Disease Control

www.cdc.gov/pregnancy.2009

OMIM – Online Mendelian Inheritance of Man

<http://www3.ncbi.nlm.nih.gov/omim>

Human Genome Project

www.geomics.energy.gov

TERIS – Teratogen Information System

<http://apps.medical.washington.edu/teris/teris1a.aspx>

(you need an ID and password, which can be obtained from your university library or hospital if they have a subscription). Shepard TH. *Catalogue of teratogenic agents*. 8th ed. Baltimore: Johns Hopkins University Press; 1995 (now on the TERIS website).

Health Physics Society

http://hps.org/documents/risk_ps010-2.pdf

OTIS – Organization of Teratology Information Specialists

www.mothersbaby.org

time consuming for an individual counselor. It is probably more appropriate to refer the family to a good genetic or dysmorphology clinic.

(4) Determining whether to publish a case report of a patient or a cluster of patients with a particular congenital malformation or a constellation of congenital malformations that may be associated with an exposure to an environmental agent [38].

Clinical evaluation of a child with congenital malformations by an experienced and well-trained physician who is familiar with the fields of developmental biology, teratology, epidemiology, and genetics may be a simple or complex task. Too often, the entire emphasis is placed on epidemiological data that may be meager or insufficient for a rational conclusion when clinical findings that are readily available can provide definitive answers with regard to the etiology of a child's malformations or the merits of an environmental etiology. Robert W. Miller [10] coined the term 'the alert physician' because he observed that discoveries of toxic environmental situations or agents were made by observant clinicians. A review article by Brent [36] indicated that most new teratogens were discovered by alert counselors, physicians or scientists, not by epidemiological investigations. Epidemiological investigations could be initiated in order to confirm the alert scientist's presumptive findings. Shepard emphasized that, if the teratogenic syndrome observed in a group of toxicant-exposed patients was rare and unique, the finding was worth pursuing because the toxicant may be a new teratogen [28].

The editor of the *American Journal of Medical Genetics* requested a teratologist to determine whether a submitted article should be published since several pregnant women had been exposed to misoprostol and the offspring had malformations that could be produced by a vascular disruptive agent. The reviewer recommended that the article should be published in order to stimulate further research concerning this drug's potential teratogenicity and to alert health care workers about the fact that misoprostol might be a new teratogen [38]. A clinician trained and experienced in these fields can have a decisive role in utilizing the principles of teratology (Box 4) and biological plausibility in evaluating the allegation that a particular environmental agent was responsible for a child's congenital malformations [9,28,38–40,42,44,45]. Two

excellent publications that discuss the utilization of teratology principles and biologic plausibility have been published by Graham et al. [45] and Carey et al. [44].

8. Conclusion

During the past century and especially since the end of World War II, there have been many advances and discoveries in the fields of teratology, developmental biology, genetics, radiology, obstetrics, reproductive toxicology and many other fields, improving the care and diagnosis of children with birth defects. In the early years of the twentieth century, medical education improved in the USA through the efforts of the Carnegie Foundation and Abraham Flexner. However, there were no educational programs for training professionals on how to deal with environmental toxicants and their risks or on dealing with patients or families who were concerned about these risks. It was George Engle who introduced the biopsychosocial model of health care, which taught that one should not ignore the patient's environmental and social defenses because these determine how the patient will respond to the care program. If the patient or contact does not sense that the counselor is compassionate or empathetic, the care program will falter. Engle and Rogers legitimized counseling. Rogers put the final stamp on this philosophy by indicating that the counselor's task was to convince the contact that the contact's best interests were the counselor's highest priority (unconditional positive regard) [4].

The Teratology Society was chartered in 1961 and was the first group of clinicians and scientists who were interested in birth defects. An offspring of the Teratology Society, OTIS, was more interested in counseling but never developed a program that certified counselors. Genetics became a board-certified specialty that did certify counselors. Similar birth defect organizations were formed in Europe, Japan and Australia.

The review includes a summary of the drugs, chemicals and physical agents that have been documented to result in congenital malformations and reproductive effects when pregnant women are exposed during pregnancy. The principles of teratology were also summarized and emphasize that: (i) no teratogenic agent can be described qualitatively as a teratogen, since a teratogenic exposure must include not only the agent, but also the dose and the time in pregnancy when the exposure occurs; (ii) even agents that have been demonstrated to result in malformations cannot produce every type of malformation; (iii) known teratogens can be presumptively identified by the spectrum of malformations they produce; (iv) it is easier to exclude an agent as a cause of birth defects than to definitively conclude that it was responsible for birth defects; (v) when evaluating the risk of exposures, the dose is a crucial component in determining the risk; (vi) teratogenic agents follow a toxicological dose–response curve – this means that each teratogen has a threshold dose, below which there is no risk of teratogenesis, no matter when in pregnancy the exposure occurred; (vii) the evaluation of a child with congenital malformations cannot be adequately performed unless it is approached with the same scholarship and detail as is any other complicated medical problem; (viii) each physician must recognize the consequences of providing erroneous reproductive risks to pregnant women exposed to drugs and chemicals during pregnancy or alleging that a child's malformations are due to an environmental agent without performing a complete and scholarly evaluation.

When a counselor responds to a parent's inquiry ('What caused my child's birth defect?'), the physician should respond in the same scholarly manner that would be utilized in performing a differential diagnosis for any clinical problem. Physicians have a protocol for evaluating complex clinical problems. If a mother of a malformed infant had some type of exposure during pregnancy, such as a

diagnostic radiological examination or medication during pregnancy, the consulting physician should not support or suggest the possibility of a causal relationship before performing a complete evaluation. Likewise, if a pregnant woman who had not yet delivered had some type of exposure during pregnancy, the consulting physician should not support or suggest the possibility that the fetus is at increased risk before performing a complete evaluation. Only a small percentage of birth defects are due to prescribed drugs, chemicals and physical agents.

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