Teratogenic Hearing Loss

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John T. Jacobson*

Abstract

Congenital hearing loss continues to be a devastating and disabling affliction in our society. In an effort to promote early recognition and treatment of hearing impairment in children, the Joint Committee on Infant Hearing has established a series of risk factors that place a newborn or infant at risk for hearing loss. These factors have been selected based on either genetic evidence of inherited familial hearing loss, acquired hearing loss from either known or unknown causative agents, or multifactorial inheritance that combines genetic and non-genetic factors. Included in these risk factors are exposures to environmental agents that possess the potential to adversely affect the developing auditory system. In this article, the principal environmental teratogens and their potential impact upon the auditory system will be reviewed.

Key Words: Congenital hearing loss, environmental agents, risk factors for hearing loss, teratogenesis

The Joint Committee on Infant Hearing (JCIH, 1991) recognized a series of risk factors that place a newborn or infant at risk for hearing loss (see Table 1). Each factor has been carefully selected based on either genetic evidence of inherited familial hearing loss, acquired hearing loss from either known or unknown causative agents, or multifactorial inheritance that combines genetic and non-genetic environmental factors. Of the JCIH risk factors, at least two (congenital infection and ototoxic drugs) can be considered teratogenic agents, since they can lead to hearing loss as a primary or secondary result of a physical or functional abnormality within the embryonic or fetal environment during pregnancy. Other risk factors such as craniofacial anomalies that include hearing loss may also occur due to exposure to a teratogenic agent.

Advanced genetic technology and clinical investigations have demonstrated that congenital defects are considerably more frequent than once thought. The overall prevalence of congenital defects ranges between 1 and 3 percent, depending on the definition. However, these figures refer to disorders that are generally recognizable at birth, such as malformations or syndromes. More subtle defects such as mental retardation and congenital deafness without syndromic association are therefore less likely to be reported. The purpose of this article is to briefly introduce the area of teratology and discuss the ototoxic teratogenic agents that have potentially deleterious effects on the human auditory system.

EMBRYOLOGIC CONSIDERATIONS

The embryo is extremely susceptible to teratogenesis from the third to ninth week of gestation because it is during this period that the fetal organs are formed out of the germ cell layers (Robbins et al, 1984). An auditory (otic) placode first appears in the 3-week-old embryo on the lateral surface of the head and eventually invaginates to form an otic cyst. At 5 weeks, this otic cyst differentiates to form a wide dorsal (vestibular) part and a more slender ventral (cochlear) part. At 6 weeks, the dorsal portion forms two pouches: a dorsal pouch (horizontal and posterior semicircular canal) and a lateral pouch (lateral semicircular canal). During week 7, the vestibule divides into a dorsal utricle and a ventral saccule. By 12 weeks, the semicircular canals and utricle are well developed and the
Table 1 High-Risk Criteria for Infant Hearing Loss*

<table>
<thead>
<tr>
<th>Risk Criteria: Neonates (birth–28 days)</th>
<th>Risk Criteria: Infants (29 days–2 years)</th>
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</thead>
<tbody>
<tr>
<td>The risk factors that identify those neonates who are at risk for sensorineural hearing impairment include the following:</td>
<td>The factors that identify those infants who are at risk for sensorineural hearing impairment include the following:</td>
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<tr>
<td>• Family history of congenital or delayed-onset childhood sensorineural impairment.</td>
<td>• Parent/caregiver concern regarding hearing, speech, language, and/or developmental delay.</td>
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<td>• Congenital infection known or suspected to be associated with sensorineural hearing impairment such as toxoplasmosis, syphilis, rubella, cytomegalovirus, and herpes.</td>
<td>• Bacterial meningitis.</td>
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<td>• Craniofacial anomalies including morphologic abnormalities of the pinna and ear canal, absent philtrum, low hairline, etc.</td>
<td>• Neonatal risk factors that may be associated with progressive sensorineural hearing loss (e.g., cytomegalovirus, prolonged mechanical ventilation, and inherited disorders).</td>
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<td>• Birth weight less than 1500 gms (3.3 lbs).</td>
<td>• Head trauma, especially with either longitudinal or transverse fracture of the temporal bone.</td>
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<td>• Hyperbilirubinemia at a level exceeding indication for exchange transfusion.</td>
<td>• Stigmata or other findings associated with syndromes known to include sensorineural hearing loss (e.g., Waardenburg or Usher syndrome).</td>
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<td>• Ototoxic medications including but not limited to the aminoglycosides used for more than 5 days (e.g., gentamicin, tobramycin, kanamycin, streptomycin) and loop diuretics used in combination with aminoglycosides.</td>
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<tr>
<td>• Bacterial meningitis.</td>
<td>• Children with neurodegenerative disorders such as neurofibromatosis, myoclonic epilepsy, Werdnig-Hoffman disease, Tay-Sach’s disease, infantile Gaucher's disease, Nieman-Pick disease, any metachromatic leukodystrophy, or any infantile demyelinating neuropathy.</td>
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<td>• Severe depression at birth, which may include infants with Apgar scores of 0–3 at 5 minutes, those who fail to initiate spontaneous respiration by 10 minutes, or those with hypotonia persisting to 2 hours of age.</td>
<td>• Childhood infectious diseases known to be associated with sensorineural hearing loss (e.g., mumps, measles).</td>
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<tr>
<td>• Prolonged mechanical ventilation for a duration ≥ 10 days (e.g., persistent pulmonary hypertension).</td>
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<tr>
<td>• Stigmata or other findings associated with a syndrome known to include sensorineural hearing loss (e.g., Waardenburg or Usher syndrome).</td>
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*Adapted with permission from Joint Committee on Infant Hearing, 1991.

Cochlear duct has developed its two-and-one-half turns. Elements of the cochlear duct continue to achieve finer differentiation into the second trimester.

We see then that the vestibular labyrinth, semicircular canals, and utricle (pars superior) develop before the auditory labyrinth, saccule, and cochlea (pars inferior). It has been stated that the older a structure is phylogenetically, the more resistant it is to either developmental or acquired disease. One would therefore anticipate a relative predisposition for teratogenic agents to affect developing structures within the pars inferior more so than those of the pars superior.

TERATOLOGY

Teratology is the area of medical science dedicated to the study of environmental factors contributing to abnormal prenatal growth and development (Smithells, 1980). When present in the fetal environment, a teratogenic agent may cause birth defects that include developmental, learning, and behavioral disorders and, potentially, fetal death (Gorlin et al, 1990). Table 2 lists the common causes and their percentage contribution to the occurrence of human congenital anomalies, of which perhaps as many as 65 percent are of unknown etiology (Brent, 1986). Approximately 20 percent of all congenital anomalies result from gene mutations, whereas another 5 percent manifest from chromosomal aberrations (Shepard, 1989). Of the remaining identified anomalies, less than 10 percent are known to be due to a teratogenic agent (Wilson, 1977).

Interest in the subject of teratology awaited recognition of the successive tragedies of the rubella epidemic in the early 1960s (Cooper, 1968) and thalidomide in the 1970s (Teff and Munro, 1976). The succeeding decades have seen a dramatic growth of clinical and epidemiologic investigations into the problem of environmental teratogenesis. To date, there have been over 1500 teratogenic agents identified that have produced congenital anomalies in experimental animals. Health care agencies have moved to erect barriers against the introduction of potentially teratogenic agents into the pregnant population. With an increasing awareness of the hazards of environmental teratogenic exposure, certain generalizations have
begun to emerge that help us to characterize and recognize such agents. The severity of congenital infant morbidity and prenatal susceptibility to a teratogenic agent during fetal development is extremely variable. Gorlin and colleagues (1990) have described four factors that account for the wide range of expression encountered among patients who are adversely affected by prenatal exposure to environmental agents. They are:

1. Dosage of the agent. In general, the greater the exposure to a teratogenic agent, the more likely an effect is to occur, and the more likely the effect will be severe.

2. Developmental timing of the exposure. Most target tissues have relatively specific periods of susceptibility during which they are vulnerable to damage by a particular mechanism. Thus, the stage of embryonic fetal development at which exposure to a teratogen occurs may be of critical importance in determining outcome.

3. Genetic host susceptibility. Humans vary widely in their genetic control of drug metabolism, resistance to infection, and other biochemical and molecular processes. Therefore, some individuals may be at strikingly greater risk from a given exposure than the population as a whole. Furthermore, during pregnancy, the susceptibility of two different individuals, mother and fetus, must be considered.

4. Interactions with other environmental factors. It is common during pregnancy for exposures to more than one agent to occur. The interrelationship of these contributing factors and their potential role in the development of congenital defects is reflected in the extreme variability of demonstrable birth anomalies. It is obvious then that prediction of possible teratogenic-induced birth defects is a difficult task at best.

ENVIRONMENTAL TERATOGEN

Teratogenic agents may be broadly grouped into four categories: (1) infectious agents, (2) drugs and chemical agents, (3) physical agents, and (4) maternal metabolic and genetic factors. Table 3 lists the various major teratogenic agent categories and their subsets. It should be noted that only a handful of agents have been directly implicated in congenital hearing loss and other craniofacial abnormalities (Table 4). However, the effects of teratogenic agents on the auditory system, while variable, can be potentially devastating. A complete discussion of any one of these agents is beyond the scope of this publication. Furthermore, the reader is cautioned that considerable debate still exists regarding the relative contribution of these offending agents to the development of human birth defects. The following discussion is presented as a general guide to teratogenic agents and their possible impact upon the auditory system. The reader is encouraged to consult standard medical references for a more thorough discussion of individual agents. Finally, it is extremely important to avoid “categorizing” any one particular type or degree of hearing loss with a teratogenic agent. For example, direct association of an audiometric configuration to an infant exposed to a teratogenic agent may be misleading, given the variability of penetrance and expression.

INFECTIONOUS AGENTS

Viral Infections

By far, the majority of infections in pregnant women involve the upper respiratory and gastrointestinal tract. As a rule, these infections
Table 3  Teratogenic Agents in Humans*

<table>
<thead>
<tr>
<th>Physical Agents</th>
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<tbody>
<tr>
<td>Radiation (e.g., atomic, radiiodine, therapeutic)</td>
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<tr>
<td>Hyperthermia</td>
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<tr>
<td>Mechanical factors (e.g., oligohydramnios)</td>
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Infectious Agents

<table>
<thead>
<tr>
<th>Viruses</th>
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<tbody>
<tr>
<td>Cytomegalovirus</td>
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<tr>
<td>Herpes virus</td>
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<tr>
<td>Parvovirus B-19</td>
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<tr>
<td>Rubella</td>
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<tr>
<td>Bacteria</td>
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<td>Syphilis</td>
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<tr>
<td>Mycoplasma</td>
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<tr>
<td>Parasites</td>
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<td>Toxoplasmosis</td>
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Maternal Metabolic and Genetic Factors

<table>
<thead>
<tr>
<th>Alcohol</th>
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<tbody>
<tr>
<td>Cretinism</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>Folic acid deficiency</td>
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<tr>
<td>Hyperthermia</td>
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<tr>
<td>Nutritional disturbances</td>
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<tr>
<td>Phenylketonuria</td>
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<tr>
<td>Rheumatic heart disease and congenital heart block</td>
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<tr>
<td>Virilizing tumors</td>
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</table>

Drugs and Environmental Chemicals

<table>
<thead>
<tr>
<th>Aminopterin and methylaminopterin</th>
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<tr>
<td>Androgenic hormones</td>
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<tr>
<td>Busulfan</td>
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<td>Chlorobiphenyls</td>
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<tr>
<td>Coumarin anticoagulants</td>
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<tr>
<td>Cyclophosphamide</td>
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<tr>
<td>Diethylstilbestrol</td>
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<tr>
<td>Diphenylhydantoin and trimethadione</td>
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<tr>
<td>Lithium</td>
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<tr>
<td>Mercury</td>
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<tr>
<td>Methimazole</td>
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<tr>
<td>Penicillamine</td>
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<tr>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Thalidomide</td>
</tr>
<tr>
<td>Trimethadione</td>
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<td>Valproic acid</td>
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*Adapted with permission from Shepard, 1989.

remain localized and have no apparent effect upon the developing fetus. Occasionally, infectious agents do gain access to the blood stream, leading to transplacental infection of the fetus. Many of these potentially teratogenic infectious agents go unrecognized due to a relative paucity of clinical symptoms in the host. Examples include rubella and cytomegalovirus (CMV) infections, which often go undetected in the pregnant mother. Serologic methods are often not helpful in diagnosing maternal-fetal infection unless the patient is examined during the acute phase of the illness when a rising antibody titer is elicited. Retrospective analysis can only determine whether an infection has taken place, not the time of its occurrence.

Rubella

Maternal rubella infection within the first 3 months of pregnancy poses a serious risk to the developing fetus. Risk figures for congenital rubella have been reported as high as 50 percent for the first month and 10 to 15 percent for the third month, with significant risk extending up to the sixteenth week. Common mani-
festations include heart disorders, low birth weight, mental retardation, visual loss, and sensorineural hearing impairment (Hanshaw and Dridgeon, 1978). It is estimated that as a result of the last epidemic of rubella in the United States in the 1960s, over 25,000 infants were born with congenital rubella. The incidence of rubella has dramatically decreased since the introduction of the rubella vaccine; however, there are still approximately 50 infants per year born with congenital rubella syndrome and hearing loss.

Hearing loss is the most common of all the rubella-associated defects, occurring in 50 percent of surviving infants afflicted in the first trimester (Davis, 1983). The prevalence of hearing loss decreases to less than 20 percent when maternal rubella is contracted during the second or third trimester. Hearing defects often occur in the absence of other diagnostic findings. Most of these children tend to have bilateral sensorineural hearing loss that may be asymmetric and progressive in one-quarter of the children with the syndrome (Bordley and Alford, 1970). Audiograms typically demonstrate a flat or gradually sloping severe to profound sensorineural loss (Fraser, 1976; Anvar et al, 1984). In addition to inner ear defects, central auditory processing disorders with associated speech delay may occur due to cerebral involvement (Ames et al, 1971). The middle ear is usually spared.

Temporal bone findings in patients with congenital rubella typically reveal cochleosaccular degeneration with collapse of Reissner's membrane and the saccular wall. The vestibular apparatus is generally unaffected. It is important to note that despite substantial evidence implicating the rubella virus in congenital deafness, the virus itself has not been isolated from the inner ear of any affected individuals.

In general, rubella vaccination offers adequate protection against the disease. Bottiger (1979) reportedly found no cases of rubella infection in appropriately immunized women, whereas 15 percent of nonvaccinated women had contracted the disease. In contrast to rubella vaccination, the value of passive immunization with immunoglobulin remains doubtful.

**Cytomegalovirus**

CMV, a virus of the herpes group, is the leading cause of fetal viral infection in the US, and accounts for over 4000 cases of sensorineural hearing loss per year (Reynolds et al, 1974). The infection is most often asymptomatic in the mother. Because of difficulties in determining the time of maternal infection, it is unclear which stage of intrauterine development is most susceptible to CMV infection.

Approximately 3 percent of pregnant women and 1 to 2 percent of newborns demonstrate evidence of CMV infection (Hanshaw, 1971). Clinical manifestations include microcephaly, mental retardation, hepatosplenomegaly, and deafness. Over 97 percent of congenitally infected infants show no sign of disease in the neonatal period. However, there is a growing body of evidence to suggest that a number of infants, asymptomatic at birth, will eventually develop neurologic abnormalities that become apparent in later life. In fact, 10 to 15 percent of infected children will eventually demonstrate adverse sequelae such as mental retardation, coordination disturbances, and hearing loss (Reynolds, 1974; Stagno et al, 1977a). The prevalence of sensorineural hearing loss in infants who are symptomatic at birth may be as great as 50 percent (Pass et al, 1980; Hanshaw, 1982). The diagnosis of congenital CMV infection cannot be made on clinical grounds alone and must be based on isolation of the virus from fresh urine or tissue during the first week of life. Alternatively, a variety of serologic tests are available to detect CMV antibody to document the presence of infection. Owing to the limited period during which proper diagnosis can be made, it is likely that many cases of congenital deafness today classified as of unknown etiology can be ascribed to congenital CMV infection. There is no consistent pattern or degree of severity of hearing loss in infants with CMV infection. Hearing loss may be symmetric with primarily high-frequency impairment (Pappas, 1985). Asymmetric or unilateral hearing loss has also been reported (Stagno et al, 1977a). The incidence of hearing loss in congenital CMV has been reported as high as 40 percent in surviving neonates (Davis, 1981). In contrast, Johnson and colleagues (1986) evaluated 40 premature infants having perinatal-acquired CMV. In this group, only one infant (3.75%) was reported to demonstrate high-frequency sensorineural hearing loss. The prevalence of hearing loss did not differ from a matched control group, and the authors suggested that significant sensorineural hearing loss may not be identified in premature infants through the age of 3 years. Pappas (1985) recommends careful audiometric follow-up in children with asymmetric hearing since progressive hearing loss is
prevalent in this group. This degenerative process may be due to reactivation of viral disease following a period of latent infection (Dahle et al, 1974), which may last throughout the first decade of life (Hanshaw, 1971).

Temporal bone histopathology in infants with CMV infection reveals infected epithelial cells within the cochlea, saccule, utricle, and semicircular canals (Meyers and Stool, 1968). Hydrops of the cochlea and saccule have also been observed (Davis and Johnson, 1983). Vestibular pathology may occur as a result of infection of the vestibular apparatus (Davis et al, 1977).

There is presently no safe method for vaccination against CMV infection. Furthermore, naturally acquired infection may not produce a significant protective effect. Primary prevention of CMV infection thus consists mainly of avoidance of exposure during pregnancy.

Other Viral Infections

Numerous other viral infections including polio virus, varicella, measles, and mumps have been implicated as potentially teratogenic agents. However, a direct causal relationship between viral infection and associated congenital defects remains largely unproven. Careful epidemiologic studies are necessary before the role of any of these viral agents in the development of congenital defects, including hearing loss, can be firmly established.

Bacterial Infections

While a host of bacterial agents are capable of infecting the fetus antenatally, only syphilis is thought to have a significant teratogenic potential.

Syphilis

In 1958, Hutchinson described the classic triad of congenital syphilis: notched incisor teeth, interstitial keratitis, and sensorineural hearing loss. Congenital syphilis may manifest either as secondary syphilis in the first 2 years of life or as tertiary syphilis between ages 8 to 20 years. There may be a substantial time period between the onset of ocular disease and the onset of hearing loss.

Syphilitic infection of the labyrinth or acoustic nerve may result in sudden, progressive, or fluctuating sensorineural hearing loss. In secondary syphilis, early acquired hearing loss is common and is typically sudden, bilateral, and progressive. Delayed acquired hearing loss is usually associated with luetic labyrinthitis occurring during the tertiary stage of syphilis. Auditory deficits tend to manifest as a severe, bilateral, and progressive sensory loss. Speech recognition deteriorates in concert with decreases in auditory sensitivity. Middle ear mobility is unaffected, although acoustic reflex patterns reflect bilateral sensorineural pathology. Early-onset syphilitic hearing loss has the potential for reversibility with early detection and prompt treatment with high-dose intravenous penicillin and oral steroids. In more advanced cases, however, hearing loss is generally permanent (Balkany and Dans, 1978; Pillsbury and Shea, 1979).

Cochlear histopathology includes atrophy of the organ of Corti along with degeneration of the fibers of the cochlear nerve (Karmody, 1966). Antenatal or perinatal diagnosis can be made by serologic testing or pathologic examination for identification of the organism. All women should be screened for syphilis during pregnancy since prompt treatment may be curative and prevent the serious sequelae of intrauterine infection.

Parasites

Toxoplasmosis

Toxoplasmosis is caused by the protozoan parasite Toxoplasma gondii, and the infection is usually asymptomatic in the mother. The incidence of intrauterine toxoplasmosis averages one case per 750 deliveries in the US. Infection during the first trimester appears most likely to lead to an enhanced risk of severe fetal consequences, whereas later infections in pregnancy appear to result in clinically asymptomatic disease.

Congenital toxoplasmosis commonly manifests with central nervous system involvement including microcephaly, intracranial calcification, mental retardation, and seizures. In addition, ocular disease, including cataracts, chorioretinitis, and microphthalmia, is seen.

In children with more subtle disease in the newborn period, long-term follow-up has revealed a high incidence of sensorineural deafness that is usually severe and bilateral (Alford et al, 1974). In some instances, serologic testing among deaf individuals has supported a direct causal relationship between congenital toxoplasmosis infection and hearing loss. Temporal bone studies, however, have failed to isolate the putative
organism within the auditory system. Vaccination against toxoplasmosis is not presently available. Therefore, preventative measures consist of avoidance of infection during pregnancy. Methods for prevention include avoiding ingestion of the oocysts contained in raw meat and eggs or exposure to infected materials such as cat feces.

**DRUGS AND CHEMICAL AGENTS**

It has been reported that, on average, women receive three or more medications, both prescribed and nonprescribed, during pregnancy (Nora et al., 1967). The mechanisms by which drugs and chemical agents produce birth defects remain largely unknown, and, in many instances, their association with risk to the developing fetus is conjectural at best. Proposed mechanisms include cell death, alteration of cellular growth, and derangement of morphogenetic processes.

**Nonprescription Drugs**

**Thalidomide**

The most tragic evidence of drug-induced birth defects occurred in the 1960s when European drug manufacturers released thalidomide as an over-the-counter sedative preparation. It has been estimated that between 1958 and 1963, over 10,000 children were damaged by this drug worldwide (Swinyard, 1978). Thalidomide was rather convincingly shown to be teratogenic when taken even in a single dose during the susceptible period of fetal development (days 20 to 35). A variety of defects were produced including phocomelia, esophageal atresia, renal agenesis, facial hemangiomas, and external ear anomalies. In 1963, Mihlke and Partsch described a syndrome associated with thalidomide use that consisted of anomalies of the ears and paralysis of the facial and abducens nerves. Thalidomide has been shown to produce abnormal cochlear development, and, in these instances, severe sensorineural hearing loss is a common outcome.

**Ethyl Alcohol**

Ethyl alcohol continues to be one of the most abused drugs that is consumed throughout the world. It is estimated that approximately 2 per 1000 children suffer from fetal alcohol syndrome (FAS). Epidemiologic studies indicate that almost 1 out of every 30 pregnant women abuse alcohol and that approximately 6 percent of their children demonstrate clinical features of FAS. Initially coined by Jones and Smith (1973), FAS describes a series of irreversible congenital anomalies observed in the offspring of alcoholic mothers. FAS is recognized as the leading cause of mental retardation in the western world, exceeding disorders such as Down syndrome and cerebral palsy.

With the progressive rise of maternal alcohol abuse, the prevalence of FAS has become a major universal health concern. However, FAS has not been a well-recognized clinical entity, and there remains a wide variance in the reported incidence of this syndrome. This variance is likely due to the reluctance of mothers to admit to substance abuse and the fact that congenital severity appears related to the amount and period of chronic consumption (Little and Streissguth, 1981). Furthermore, recognition of the syndrome may not occur at birth, and typical congenital facial characteristics are not always recognized.

The actual reported prevalence of FAS ranges between 1:500 to 1:2500 term pregnancies (Streissguth et al., 1980; Sokol, 1981; Smith, 1982), with apparent regional concentrations (Little and Streissguth, 1981). This higher incidence (e.g., Sweden, 1:600) may be attributed to the nature of the health care systems and tracking methods. As many as one half of all infants born to chronic alcoholics may present with some diagnostic feature of FAS.

The exact amount of alcohol necessary to produce fetal damage has not been well documented; however, many studies suggest that consumption of two or more drinks per day during pregnancy is associated with an increased risk of fetal insult. Furthermore, fetal susceptibility to ethyl alcohol appears to occur throughout the majority of intrauterine life with the degree of malformation related to the amount of alcohol consumption.

The exact mechanism of teratogenesis seen with ethyl alcohol use during pregnancy remains uncertain. Alcohol has been shown to adversely affect cellular metabolism both directly as well as through its metabolites. Additionally, malnutrition and vitamin deficiency commonly seen in alcoholics likely contribute to adverse fetal outcome.

Prenatal use of ethyl alcohol can result in a wide spectrum of fetal abnormalities. The FAS includes dysmorphic facial features along with a series of neurologic, behavioral, and other physical anomalies. Typically, infants are
born with craniofacial dysmorphogenesis. Characteristics include microcephaly, short palpebral fissures, hypoplastic philtrum, thinned upper lip, ptosis, low nasal bridge, epicantal folds, micrognathia, and midface hypoplasia (Jung, 1989). Other structural, otolaryngologic deficits include cleft palate and pinna abnormalities (Jones and Smith, 1973; Toutant and Lippmann, 1980; Smith, 1982). Posterior rotation of the auricle as well as a poorly formed concha may be evident.

Although ethanol has been reported to be ototoxic (Gieldanowski, 1965; Morizono and Sikora, 1981; Church, 1987), there is little agreement with regard to its effects on the developing auditory system. Church (1987) and Church and Gerkin (1988) reported the results of 14 children with FAS. Thirteen children (93%) had clinically significant histories of bilateral recurrent serous otitis media and four children (29%) had concurrent permanent bilateral sensory hearing loss. This reported high incidence of middle ear effusion confirms earlier cited evidence (Johnson et al, 1981; Streissguth et al, 1985). The presence of cleft lip and palate may account for this high rate of occurrence. In 1980, Toutant and Lippmann found hearing loss in one of six siblings with FAS; however, the specific type of hearing disorder was not reported.

Audiologic and otologic management of FAS demands early recognition and therapeutic treatment, including that of recurrent serous otitis media. Because speech and language disorders have been reported (Isoub et al, 1981), appropriate referral is also an important consideration in the overall FAS management.

Prescription Drugs

Aminoglycosides

There have been numerous reports describing the potential deleterious effects of aminoglycosides on the developing auditory system. Aminoglycosides infiltrate the perilymph and endolymph of the inner ear, resulting in higher local concentrations of the drug than typically seen in the peripheral blood. Since aminoglycosides are administered intramuscularly or intravenously and excreted through the kidneys, the degree of ototoxic danger appears to be primarily related to the blood level of the drug and its duration in the circulation. Aminoglycosides may be toxic to both the neuroepithelium of the vestibular system, as well as the sensory hair cells of the cochlea.

Transplacental transfer of aminoglycoside antibiotics has been well demonstrated in humans (Neinstein et al, 1976). The majority of reports considered women with tuberculosis who were treated with streptomycin or dihydrostreptomycin. For example, in a study by Conway and Burt (1965), streptomycin was shown to cross the placenta, resulting in labyrinthine damage and high-frequency hearing loss in the fetus. Of note, when auditory changes were reported in the offspring of mothers who received aminoglycoside antibiotics, the ototoxicity occurred independently of ototoxicity in the mother.

Intrauterine ototoxicity has also been reported for newer aminoglycosides, including kanamycin and gentamicin. Most of these studies, however, are retrospective and lack data describing duration of therapy and serum levels of drugs employed. Furthermore, combinations of aminoglycosides and diuretics such as furosemide or ethacrynic acid demonstrate synergism with regard to ototoxicity. The treatment of a pregnant woman with aminoglycosides may subject the developing fetus to the risk of ototoxicity similar to that seen in adults and children. However, a true postnatal teratogenic effect on the developing fetal auditory system remains to be proven.

The reported incidence of hearing loss associated with aminoglycoside antibiotics ranges from 10 to 16 percent (Quick, 1986; Lerner and Matz, 1980). The affects of aminoglycosides on the auditory system typically include bilateral, symmetrical, high-frequency sensorineural hearing loss. Typical reductions in speech recognition are demonstrated with a concomitant decrease in pure-tone sensitivity. Middle ear mobility is normal, although acoustic reflex patterns are consistent with sensory hearing loss. The degree of severity and the audiometric configuration are typically related to the type of drug, its dosage, and duration in the system and drug interaction.

Chloroquine

Chloroquine, an antimalarial drug, has been associated with an increased risk of auditory and optic abnormalities. Deafness from direct VIIIth nerve damage has been reported. However, the overall risk when standard doses are used during pregnancy appears to be relatively low.
PHYSICAL AGENTS

A variety of physical agents have been implicated as being potentially teratogenic to the fetus. The most notable agents include radiation and thermal energy.

Concern over potential teratogenic effects of high-dose radiation arose from experimental observations of the offspring of survivors of nuclear explosions during World War II. Abnormalities including growth retardation, central nervous system damage, and ocular defects were noted. It is thought that even low-dose radiation associated with natural exposure may contribute to an enhanced rate of embryonic mutations. Concern over the carcinogenic potential of intrauterine radiation exposure also appears valid.

Prolonged exposure of the fetus to high thermal environmental temperatures such as during bathing or sauna has been questioned as being potentially teratogenic. Animal studies support the notion that heat may act as a teratogen during initial stages of neural tube development. However, similar evidence of a direct teratogenic effect in man is lacking (Edwards, 1977).

At the present time, evidence is inadequate to invoke a direct causal relationship between intrauterine exposure to thermal or radiation energy and auditory disabilities in the newborn. However, it would appear prudent to avoid either prolonged thermal exposure or inadvertent radiation exposure during the first trimester of pregnancy.

MATERNAL METABOLIC AND GENETIC FACTORS

Although not strictly environmental, metabolic and/or genetic factors within the mother may alter the fetal intrauterine environment. Examples include diabetes mellitus, maternal myotonic dystrophy, and maternal phenylketonuria. While not directly implicated in auditory malformation, there is sufficient evidence to suggest that intrauterine exposure to maternal alterations in these and other metabolic/genetic factors can lead to fetal wastage along with a variety of abnormalities including microcephaly, neural tube defects, and mental retardation. In addition, the data suggest that control of these factors, particularly in the first few weeks of pregnancy, may be associated with a somewhat lower risk of fetal malformations (Shepard, 1989).

TERATOGIC HEARING LOSS: GENERAL CONSIDERATIONS

Considerable debate still exists regarding the role of environmental agents in the development of birth defects in our population. However, it is becoming abundantly clear that genetic factors alone cannot account for the alarming number of fetal abnormalities identified. With these observations comes an increasing emphasis on identification and prevention of teratogenic exposures.

The primary means of prevention of birth defects from teratogenic exposures is the elimination of the potential teratogen from the prenatal environment. Toward this end, it is incumbent upon all medical professionals to be aware of the teratogenic potential of a multitude of environmental agents and offer appropriate counseling and treatment alternatives, particularly during the early months of pregnancy.

The evaluation and treatment of a child suspected of having been exposed to a potentially teratogenic agent begins with a high index of suspicion. A careful review of the prenatal history should be performed along with an in-depth examination to search for abnormalities known to be associated with teratogenic exposure. A careful otologic examination, as well as objective electrophysiologic testing to accurately determine the extent and type of hearing loss is indicated. If hearing loss is discovered, prompt medical or surgical intervention is warranted. Appropriate amplification is critical to the intellectual, social, and emotional development of these children. Parents must also be educated to inform them as to their role in the rehabilitation of the hearing-impaired child.

CONCLUSION

In view of the large number of drugs, infections, and physical agents that the fetus may be exposed to in utero, it is remarkable that so few have thus far proven to be teratogenic. Perhaps this merely reflects our present inability to recognize the complicated relationships between various exogenous agents and their clinical consequences. Until complete characterization of such agents is available, emphasis should be placed on strict avoidance of potentially hazardous agents whenever possible during pregnancy.
REFERENCES


