ARTICLE

Teratogenic Exposures

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A consideration of teratogenic exposures includes not only an agent (chemical, radiation, biologic) but an exposure level and timing of exposure. There are criteria by which exposures are evaluated for a causal connection with an abnormal outcome. We here review some teratogenic exposures and discuss how they were initially described and confirmed. We have limited our discussion to some of the exposures for which a connection to structural malformations has been accepted in some quarters, and we indicate some exposures for which a causal association awaits confirmation. We recommend that counselors find a reliable and updatable source of information on exposures during pregnancy. © 2011 Wiley-Liss, Inc.

KEY WORDS: teratogenic exposures; angiotensin converting enzyme inhibitors; carbamzepine; diethylstilbestrol; ethanol; isotretinoin; lithium; methimazole; misoprostol; mycophenolate mofetil; penicillamine; phenytoin; rubella; thalidomide; toluene; valproic acid; varicella; warfarin; X-ray

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INTRODUCTION

Authors who propose to write a paper on teratogenic exposures owe their readers answers to some basic questions, questions that have been posed for decades and for which there are no entirely satisfying answers. First, what is a teratogenic exposure? Notice that we have avoided the term, "teratogen," which implies that a chemical or other agent might have some property of being teratogenic or non-teratogenic. We use the term, "teratogenic exposure" to include not only an agent but also exposure level (dose) and timing considerations. We are fearful of listing X-ray, for example, as a teratogen and having someone give poor advice to a woman who had a chest X-ray in early pregnancy.

When we write teratogenic exposure, we mean an exposure that increases the risk of an end point called, "teratogenicity," but what is included in teratogenicity? Certainly, we would include malformations that can be diagnosed on physical examination in a child, but other kinds of developmental toxicity, such as functional impairment, growth restriction, or impaired viability are also important.

This paper is an overview of selected exposures. If you are in the counseling business, you need a resource to provide more detailed and current information on a larger range of agents than we will discuss. We can recommend TERIS (http://depts.washington.edu/terisweb/teris/) and Reprotox® (www.reprotox.org). We both work for Reprotox®.

A final question: Who gets to decide what exposures are teratogenic? These decisions are made by the teratology community, but not everyone in the teratology community agrees about everything all the time. We use criteria similar to or derived from those articulated by Hill [1965], shown in Table I. Not all criteria need to be satisfied for an association to be considered causal, but the more criteria, the greater our comfort that we are dealing with causality.

It has been proposed that many human teratogenic exposures have been identified by "astute clinicians," essentially from observing cases of distinctive malformations associated with unusual exposures [Carey et al., 2009]. Our discussion of some teratogenic exposures would seem to confirm the impression that identification of teratogenicity arises from the reports of astute clinicians; however, a key part of this astute clinician model is that the initial observations are subsequently confirmed by other evidence. The clinicians who made the initial observations may or may not be astute, but they are certainly lucky in having their observations confirmed. We hear nothing about those observations of birth defect syndromes that went unconfirmed and have vanished from the literature.

In some cases, we are left with observations that have been inadequately confirmed but that still deserve some attention. We are in favor of counseling patients about exposures even if risk has not been confirmed. For example,

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TABLE I. Hill Criteria for Causation [Hill, 1965]

Strength of the association (the likelihood that the association is not due to chance, bias, or confounding)
Consistency of the association (the association is reproduced in different populations)
Specificity (uniqueness of the association both with respect to the exposure and with respect to outcome)
Temporal relationship (the putative cause comes before the effect)
Coherence (the association is compatible with related knowledge)
Biologic gradient (there is a dose–response effect)
Biologic plausibility (the association does not violate known principles)
Experiment (reducing the putative cause reduces the effect)
Analogy (evidence is similar to that for other cause–effect relationships)

recommending that women consider avoiding lithium during early pregnancy or that they consider fetal echocardiography if they have been exposed to lithium is appropriate counseling, even in the absence of certainty that lithium therapy increases the risk of Ebstein anomaly.

PHARMACEUTICAL PRODUCTS

Thalidomide

In 1957, a simple phthalimide derivative called thalidomide was marketed in Europe and elsewhere as a sedative/antiemetic at a dose of 50–150 mg/day. The drug was to become the most widely known cause of human birth defects in the world and one that changed the way exposures are evaluated for teratogenic potential. Thalidomide has little toxicity in adults, making it one of the few agents that is selectively toxic to the embryo. At a meeting in 1959, a German pediatrician presented a girl with phocomelia, an unusual limb reduction defect in which the hand or foot arises close to the shoulder or hip. An additional two children with similar findings were presented in September 1960. By November 1961, 34 congenital long bone malformations were reported, and William MacBride and Widukind Lenz independently made the association between these malformations and thalidomide. Secular trend analysis shows a clear parallel between sales of thalidomide and the appearance of characteristic limb malformations (Fig. 1).

Thalidomide therapy during pregnancy is associated with limb reduction defects, facial hemangiomata, esophageal and duodenal atresia, tetralogy of Fallot, renal agenesis, anomalies of the external ear, and cranial nerve abnormalities. The sensitive time period for the production of human thalidomide limb defects is 21–36 days from conception (Fig. 2). About 20% of pregnancies exposed during this period result in children with anomalies.

The most sensitive experimental animal models for thalidomide embryo toxicity appear to be the monkey and rabbit. Although it is often said that thalidomide is not teratogenic in rats, oral thalidomide causes resorptions in this species and intravenous administration of thalidomide to rats produces skeletal abnormalities involving the ribs, vertebra, hips, and tail [Schumacher et al. 1968a]. The increased sensitivity of rabbits compared to rats appears due at least in part to pharmacokinetic differences between the species [Schumacher et al., 1968b].

In 1998, Thalomid, a brand of thalidomide, was approved by the US Food and Drug Administration (FDA) for the treatment of erythema nodosum leprosum at a dose of 100–300 mg/day. FDA subsequently approved thalidomide for the treatment of multiple myeloma in 2006. Doses for multiple myeloma start at 200 mg/day. The prescribing and dispensing of thalidomide is strictly controlled in the US in an effort to prevent use by women who are pregnant [Zeldis et al., 1999].

ACE Inhibitors

Angiotensin converting enzyme (ACE) inhibitors are antihypertensives that inhibit the conversion of the biologically inactive angiotensin I to angiotensin II, a potent vasoconstrictor. During the second and third trimester of pregnancy, ACE inhibitors reduce fetal blood pressure and decrease renal function, which can cause oligohydramnios, intrauterine growth restriction, renal dysplasia, anuria, renal failure, hypocalvaria, and death [reviewed by Tabacova et al., 2003].

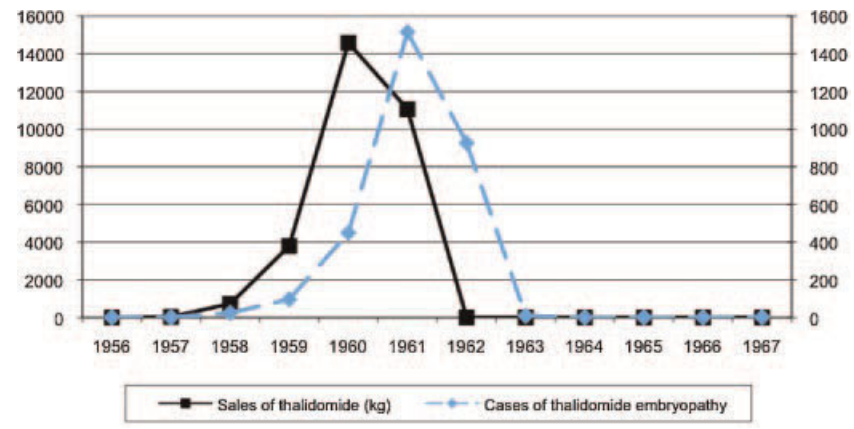

Figure 1. Sales of thalidomide and the appearance of the typical limb malformations in Germany. Drawn from data presented by Lenz [1988].

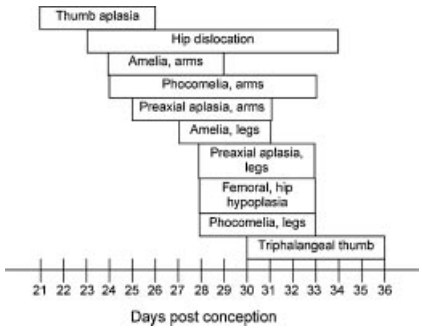

Figure 2. Sensitive periods for thalidomide associated limb defects.

Since 1992, the US Food and Drug Administration has required a warning regarding second and third trimester fetotoxic effects of all ACE inhibitors.

The first report of fetal adverse effects with the use of an ACE inhibitor was published in 1981. A woman took captopril in her 26th week of gestation. Oligohydramnios was noted in the 28th week and a cesarean section was performed in the 29th week. The child was anuric and hypotensive and died a week later. On autopsy, hemorrhagic foci were found in the renal cortex and medulla [Guignard et al., 1981].

The most common abnormalities due to ACE inhibitors are skull hypoplasia and renal dysfunction related to prolonged exposure rather than a first trimester insult. Fetal renal impairment can result in anuria and oligohyrdamnios, which can secondarily induce anomalies such as hypoplastic lungs, limb contractures, and craniofacial abnormalities [Buttar, 1997]. The hypocalvaria has been attributed to pressure on the skull from the uterus and decreased perfusion of the skull from fetal hypotension. Other reported cases include patent ductus arteriosus, IUGR and fetal death. There have been case reports of a reversal of oligohydramnios after discontinuation of ACE inhibitor therapy [e.g., Chisholm et al., 1997].

There is no unanimity on whether ACE inhibitor therapy during early pregnancy increases the risk of malformations. ACE inhibitors were reported to increase heart and central nervous system malformations after first trimester use in a study that used Tennessee Medicaid records to ascertain exposure and outcome [Cooper et al., 2006]. These malformations included seven cardiac septal defects, two patent ductus arteriosus, one spina bifida, one microcephaly, and two eye abnormalities. A record-linkage study from Finland, published in abstract, identified an increase in malformations after first trimester ACE inhibitor therapy, but the increase was explained by maternal diabetes mellitus [Malm et al., 2008]. A study from the Swedish Medical Birth Registry described an association between antihypertensive medication use during early pregnancy and cardiovascular defects in the offspring; however, there was no difference in the risk estimates for ACE inhibitors and beta blockers, and the association for ACE inhibitors was not statistically significant [Lennestål et al., 2009]. A teratology information service study from Israel and Italy found no increase in malformations in the offspring of 252 women exposed to ACE inhibitors or angiotensin-receptor blockers (ARBs) in the first trimester [Diav-Citrin et al., 2011].

ACE inhibitors are unusual in being considered as a group. Under ordinary circumstances, teratogenicity is unique to specific agents under specific conditions of exposure. Because ACE inhibition is considered central to the ACE inhibitor fetopathy, these drugs are considered to have similar potential for fetal harm. The assumption that interference with the renin-angiotensin system is central to the ACE fetopathy has been applied to ARBs and is supported by case reports of oligohydramnios, fetal skull hypoplasia, and fetal death with use of at least some ARBs during pregnancy [e.g., Saji et al., 2001].

Isotretinoin

Retinoids are vitamin A like chemicals that have an effect on epithelial cell differentiation. Systemic 13-*cis*-retinoic acid (isotreinoin) and topical all-*trans*-retinoic acid (tretinoin) are used in the treatment of severe cystic acne. Isotretinoin (Accutane®) was licensed in the US in 1982. Isotretionoin produces malformations of the central nervous system, limbs, cardiovascular system, and face in mice, rats, monkeys, and rabbits [Fantel et al., 1977; Goulding and Pratt, 1986; Nau, 2001]. These malformations are due at least in part to the inhibition of migration of cranial neural crest cells during early embryonic development.

Isotretinoin is less potent in mice than in humans due to a shorter half-life and decreased placental transfer. In addition, rodent maternal metabolism is through β-glucoronidation and not metabolism through 4-*oxo*-isotretinoin as is in rabbits, monkeys, and humans [Nau, 2001]. Kochhar and Penner [1987] speculated that 4-*oxo*-isotretinoin, which has a longer half-life than isotretinoin, might be a major contributor to teratogenesis in humans. They concluded that metabolism in the mother is an important determinant of embryotoxicity in a given species. Differences in maternal metabolism may be the reason that the teratogenic dose is 75–150 mg/kg in the mouse, 10 mg/kg in the rabbit, and 2.5–5 mg/kg in the human [Nau, 2001]. Another estimate of the teratogenic dose in humans is as low as 0.5–1.5 mg/kg/day [Adams and Lammer, 1993]. Human embryos may be more sensitive to isotretinoin than embryos of other species due to slow elimination of the drug and continuous isomerization to all-*trans*–retinoic acid [Nau, 2001].

The teratogenicity of therapeutic doses of isotretinoin was predicted based on experimental animal studies and the product was so labeled when it was first sold in the US in 1982. Case reports of malformed children born after maternal

isotretinoin therapy appeared in 1984 [De la Cruz et al., 1984; Stern et al., 1984]. Lammer et al. [1985] published the first systematic description of the embryopathy in humans. Among 154 isotretinoin-exposed pregnancies, 95 resulted in elective abortion, 12 in spontaneous abortion, 21 in infants without malformations, and 26 in infants with malformations. The relative risk of malformations was 25.6 (95% confidence interval 11.4–57.5). All malformed infants had a history of exposure to isotretinoin on or before 28 days of gestation. The four territories most consistently affected were cranium/face, heart, thymus, and central nervous system. Craniofacial abnormalities included small, low set ears, micrognathia, and flat depressed nasal bridge. Heart defects consisted of conotruncal malformations, and central nervous system abnormalities included hydrocephalus.

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Prenatal exposure to isotretinoin places a child at risk beyond only the structural abnormalities. Forty-seven percent of children exposed to isotretinoin in utero tested in the subnormal range for intelligence [Adams and Lammer, 1993]. There is a decrease in performance of visual-spatial processing tasks; overall males tend to be affected more than females [Adams, 2004].

Although prominent product labeling and a restrictive prescribing program have been in place, for some years, Bérard et al. [2007] found that the annual pregnancy incidence rate is 32.7/1,000 in women taking isotretinoin [2007]. In this study, 84% of women who became pregnant on isotretinoin terminated their pregnancies. Guidelines recommend discontinuing the medication 4 weeks prior to pregnancy, although pharmacokinetic considerations demonstrate that the drug is cleared from the body 10 days after the last dose.

There have been case reports of malformations after pregnancy exposure to topical tretinoin that suggested retinoid embryopathy to the reporting authors [e.g., Camera and Pregliasco, 1992; Lipson et al., 1993]. However, the low degree of systemic absorption and the available controlled studies, which include just over 400 exposed pregnancies, do not support the conclusion that topical tretinoin therapy increases the risk of malformations [Jick et al., 1993; Shapiro et al., 1997; Loureiro et al., 2005].

Etretinate and its metabolite acitetin are avoided during pregnancy due to case reports of malformations consistent with retinoid embryopathy associated with these medications. Etretinate has the disadvantage of very slow elimination, and there is a case report of an infant with retinoid-like defects conceived 1 year after discontinuation of maternal etretinate therapy [Lammer, 1988]. Acitretin is more rapidly excreted, but there is evidence that acitretin can be metabolized to etretinate. To our knowledge, there have been no reports of retinoid embryopathy in pregnancies conceived after discontinuation of acitretin therapy.

Methotrexate

Folic acid is a cofactor in the synthesis of thymidylate, a rate limiting step in DNA synthesis. Folic acid analogs may interfere with DNA synthesis and have found use in the treatment of ectopic pregnancy, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, and some malignancies. Among the earliest folic acid analogs were aminopterin and amethopterin, which is known more commonly as methotrexate (Fig. 3). Methotrexate developmental abnormalities have been produced in animal models including chickens, mice, rats, and rabbits [Skalko and Gold, 1974; Schmid, 1984; Zamenhof, 1985; DeSesso and Goeringer, 1992]. The most common malformations involve the central nervous system and palate.

Aminopterin interferes with early human fetal development, and this compound was used as an abortifacient in the 1940s and 1950s. Failed abortion after aminopterin sometimes resulted in fetal malformation [Thiersch and Phillips, 1950; Thiersch, 1952]. Subsequent reports also identified malformations in newborns surviving attempted aminopterin abortion [Meltzer, 1956; Warkany et al., 1959; Shaw and Steinbach, 1968]. In these case reports, the administration of aminopterin had been between 4 and 12 weeks gestation. The associated

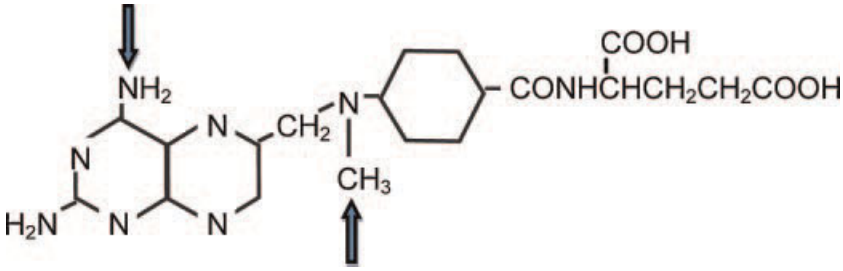

Figure 3. The structure of methotrexate. The arrows show the differences from folic acid, which consist of an amino group in place of a hydroxyl group and a methyl group in place of a hydrogen.

abnormalities included meningoencephalocele, hydrocephalus, anencephaly, cleft palate, absent parietal bones, incomplete skull ossification, and limb malformations.

Case reports of similar malformations after methotrexate have also appeared. Feldkamp and Carey [1993] presented a review of the case reports of malformations after methotrexate or aminopterin. They suggested a methotrexate dose of more than 10 mg/week is necessary to produce anomalies and that the sensitive period is 6–8 weeks postconception. Defects described as classic for methotrexate/aminopterin are clover-leaf skull with a large head, swept-back hair, low-set ears, prominent eyes, and wide nasal bridge.

The prevalence of malformations after methotrexate therapy during pregnancy is not known. Of particular interest is the prevalence of malformations after use methotrexate to terminate suspected ectopic pregnancy when an intrauterine pregnancy continues after therapy. There are case reports of malformations in surviving children [Adam et al., 2003; Chapa et al., 2003; Usta et al., 2007]. Some practitioners recommend folinic acid supplementation for women who continue their pregnancies after treatment with methotrexate and ultrasound examination to evaluate fetal anatomy.

It is not clear how long conception should be delayed after successful treatment of ectopic pregnancy with methotrexate, inasmuch as the drug may persist in the liver for months. There is a study showing no difference in outcome in pregnancies conceived less than 6 months compared to more than 6 months after methotrexate therapy; however, there were only 45 pregnancies in the less-than-6-month group [Svirsky et al., 2009].

Warfarin

In 1948, a potent, naturally occurring coumarin called warfarin was marketed as a rodenticide, killing rats and mice by inducing internal hemorrhage [reviewed by Wardrop and Keeling, 2008]. Soon after its success as a rodenticide, warfarin was adopted for use in clinical medicine. Advantages of warfarin were water solubility, oral bioavailability, and reversibility by the administration of vitamin K. A case report by Disaia [1966] presented a pregnancy exposed to warfarin therapy for a prosthetic heart valve. The infant was born with hypoplastic nose, optic atrophy, and mental retardation. Two years later, Kerber et al. [1968] proposed a relationship between vitamin K antagonist ingestion and characteristic fetal anomalies. Shaul and Hall [1977] reviewed the literature and reported on 14 mothers who ingested oral anticoagulants during pregnancy. All 14 children were born with a hypoplastic nose; many of them had stippled epiphyses and five had eye abnormalities.

Warfarin embryotoxicity is most likely between 6 and 9 weeks of gestation [Hall et al., 1980; Iturbe-Alessio et al., 1986], although Schaefer et al. [2006] did not see warfarin-related effects with exposures prior to 8 weeks gestation.

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Warfarin therapy during pregnancy has been associated with spontaneous abortion, stillbirth, nasal hypoplasia, stippled epiphyses, distal limb hypoplasia, and malformations of the central nervous system, eye, jaw, and urinary tract [Harrod and Sherrod, 1981; Oakley, 1983; Hall, 1989; Pauli and Haun, 1993; Schaefer et al., 2006]. The use of oral anticoagulants throughout pregnancy is associated with warfarin embryopathy in 6.4% (95% confidence interval, 4.6–8.9%) of livebirths [Chan et al., 2000]. Substituting heparin for warfarin between 6 and 12 weeks of gestation eliminated the risk of warfarin embryopathy, but it did not eliminate the risk of spontaneous abortions or stillbirths [Chan et al., 2000]. The poorest pregnancy outcomes were associated with a daily warfarin dose of more than 5 mg [Cotrufo et al., 2002].

After the first trimester, the fetus continues to be at risk for CNS defects likely caused by microhemorrhages in neuronal tissue due to low stores of vitamin K and low levels of vitamin K dependent procoagulant factors in the fetus, and neurological abnormalities in children and adults born to women who use warfarin during pregnancy have been reported [Hall et al., 1980; Cotrufo et al., 2002; Raghav and Reutens, 2007].

A rat model of the nasal hypoplasia and skeletal dysplasia of warfarin embryopathy was developed by treating rats postnatally with warfarin and using supplemental vitamin K1 to permit survival [Howe and Webster, 1992]. Extrahepatic vitamin K deficiency in this model was responsible for the induced abnormalities.

Phenytoin

Phenytoin is most commonly used as an antiepileptic medication. It suppresses abnormal brain activity by stabilizing voltage-gated sodium channels. Phenytoin is a treatment option in trigeminal neuralgia and some cardiac antiarrhythmias.

Exposure during pregnancy has been associated with a constellation of abnormalities sometimes called the fetal hydantoin syndrome (Table II). The prevalence of major malformations among the offspring of women taking phenytoin during pregnancy is about 10% [Meador et al., 2006]; minor malformations occur considerably more commonly. Polytherapy with anti-epileptic drugs is associated with a higher likelihood of fetal adverse effects than is monotherapy [Samren et al., 1999]. Use of phenytoin during pregnancy has been associated by case reports with a neuroectodermal tumors, specifically neuroblastomas, in the offspring [Satgé et al., 1998]. Without controlled studies, this association remains tentative at best.

TABLE II. Features of the Fetal Hydantoin Syndrome

Short nose
Low or broad nasal bridge
Epicanthic folds
Hypertelorism
Microcephaly
Abnormal ears
Wide mouth
Oral clefts
Hypoplasia of distal phalanges
Fingerlike thumbs
Short/webbed neck
Low hairline
Abnormal mental development
Abnormal motor development

The first association between phenytoin and malformations is credited to Janz and Fuchs [1964], but these investigators were focused on anticonvulsant therapy in general, not phenytoin. Janz and Fuchs polled women with epilepsy about malformations in their children and came up with a prevalence of 2.2% [reviewed by Kalter, 2003]. The term fetal hydantoin syndrome was coined by Hanson and Smith [1975], who described five children whose mothers received hydantoin anticonvulsants. The children were described as having "craniofacial anomalies, nail and digital hypoplasia, prenatal-onset growth deficiency, and mental deficiency."

There has been and remains a question of whether malformations associated with phenytoin are due to the medication itself, maternal epilepsy, or an underlying genetic disorder that gives rise to maternal epilepsy and fetal malformations. At present, most people favor a direct effect of the medication on embryo development, particularly due to the experimental animal support for a direct effect [reviewed by Finnell and Dansky, 1991]. One theory holds that sensitivity to phenytoin embryopathy is conferred by a decreased ability to detoxify an arene oxide intermediate of the drug [Buehler et al. 1990]. This detoxification ability is genetically determined and would be evidence of a gene-environment interaction.

Carbamazepine

Carbamazepine is an anticonvulsant drug used in treatment of bipolar disorder and trigeminal neuralgia. As is the case for phenytoin, Janz and Fuchs [1964] are credited with the first investigation of the possibility of teratogenicity with the use of antiepileptic drugs. Niebyl et al. [1979] reviewed the literature including 94 infants with some exposed to carbamazepine alone or in combination with other anticonvulsant drugs and suggested no evidence of teratogenicity. Indeed, for some years, carbamazepine was considered by many clinicians to be the anticonvulsant of choice in pregnancy.

The identification of the adverse developmental effects of carbamazepine therapy can be credited to Jones et al. [1989], who described a malformation syndrome in eight exposed children and confirmed in a prospective series that the syndrome occurred more often than expected by chance. They reported craniofacial defects in 11%, fingernail hypoplasia in 26%, and developmental delay in 20% of children from 35 prospectively enrolled pregnancies. The authors noted the similarity of these outcomes to the fetal hydantoin syndrome and proposed a common mechanism. The developmental delay noted by these and later authors has been questioned due to lack of adjustment for parental cognitive testing.

Two years after this report, the FDA's Franz Rosa [1991] published a communication based on his Michigan Medicaid data base in which maternal prescriptions were linked to subsequent insurance claims for malformation-related services in the offspring. Rosa proposed based on four children with spina bifida and a review of other reports that carbamazepine causes spina bifida in 1% of exposed pregnancies. Although this estimate has not been rigorously confirmed, the 1% figure remains enshrined in counseling practice. High doses of folic acid are often prescribed to pregnant women on carbamazepine in spite of the lack of evidence of benefit of doses above those usually recommended in pregnancy.

A study from the Hungarian Case–Control Surveillance of Congenital Abnormalities identified an association between carbamazepine exposure during pregnancy and posterior cleft palate (odds ratio 13.7, 95% confidence interval 3.9–47.5) [Puhó et al., 2007]. This surveillance project did not include adequate information on possibly confounding exposures to nicotine and ethanol.

Carbamazepine exposed infants have about a twofold greater risk of malformations than the general population with major malformation rates of about 2% [Diav-Citrin et al., 2001; Morrow et al., 2006], although some estimates of adverse neonatal outcome are up to 8% [Meador et al., 2006; Eroğlu et al., 2008]. A relationship between carbamazepine dose and malformation prevalence has been found, with a twofold increase in malformations in the offspring of women on daily doses of >1,000 compared to <400 mg [Morrow et al., 2006]. There appears to be a higher rate of malformation with carbamazepine in polytherapy compared to monotherapy.

Valproic Acid

Valproic acid is used as an anticonvulsant and in the treatment of bipolar disorder and migraine. Experimental animal studies have demonstrated an increase in malformations in multiple species [Binkerd et al., 1988; Hendrickx et al., 1988; Narotsky et al., 1994]. Indeed, it was based on experimental animal studies that the teratogenicity of valproic acid therapy was first considered. Brown et al. [1980] had noted that valproic acid therapy in pregnant mice produced exencephaly in the offspring at dose levels that were low compared to dose levels at which maternal toxicity was evident. They posed the question in a letter-to-the-editor of *The Lancet* as to whether there was clinical evidence of teratogenicity. In response, a group of clinicians wrote that they had treated 12 women during pregnancy with valproic acid, often in combination with phenytoin, and all the children were normal [Hiilesma et al., 1980].

It was not until 2 years later that, in an unrelated epidemiology study, valproic acid was associated with a 20-fold increase in lumbar meningomyelocele in human pregnancy [Bjerkedal et al., 1982; Robert and Guibaud, 1982]. Other abnormalities have been reported in the offspring of women being treated with valproic acid including atrial septal defect, cleft palate, hypospadias, craniosynostosis, radial aplasia, and developmental delay [Verloes et al., 1990; Ylagan and Budorick, 1992; Wyszynski et al., 2005; Jentink et al., 2010].

Large studies have produced estimates of the incidence of congenital malformations in children exposed to valproic acid during pregnancy ranging from 6 to nearly 18%. The prospective observational Neurodevelopmental Effects of Antiepileptic Drugs Study reported a birth defect rate of 17.7% among 69 babies with first trimester valproic acid exposure [Meador et al., 2006]. The frequency of major congenital anomalies in children exposed to valproate monotherapy was 9% in pooled data from five prospective European studies with an apparently higher incidence of malformations in children exposed to valproate plus other anticonvulsants [Samrén et al., 1997]. The Antiepileptic Drug Pregnancy Registry maintained at Massachusetts General Hospital reported 16 malformed children among 149 pregnancies (incidence 10.7%) exposed to monotherapy with valproic acid [Wyszynski et al., 2005]. The UK Epilepsy and Pregnancy Register reported 44 children with major malformations among 715 pregnancies exposed to valproate monotherapy, for an incidence of 6.2% [Morrow et al., 2006]. The Australian Pregnancy Registry identified 19 malformed children among 113 pregnancies exposed to valproic acid, giving an incidence of 16.8% [Vajda et al., 2006].

Higher dose levels of valproic acid therapy appear to be associated with a greater likelihood of teratogenicity, and 1,000 mg/day has been suggested as a threshold for adverse effects on morphological development. This dose level was also suggested as threshold for adverse effects of valproic acid therapy on offspring cognitive function [Meador et al., 2009]. Mean IQ scores in children exposed to higher dose levels were 6–9 points lower than those of children exposed to other anticonvulsants or to lower dose levels of valproic acid.

Other Anticonvulsants

There is some question about whether other anticonvulsant medications increase the risk of congenital malformations. Part of the uncertainty is based on the possibility that seizure disorders themselves impose an increased risk of abnormal development, although current thought has minimized this possibility. Much of the difficulty in studying the older anticonvulsant medications has been the frequent use of combination therapy. For example, there has been suspicion that phenobarbital therapy during pregnancy can increase the risk of malformations, but most use of phenobarbital for epilepsy was traditionally in combination with phenytoin. There have been case reports, however, of phenytoin-like malformations in children exposed during gestation only to phenobarbital, and a controlled study suggested that the prevalence of malformations with phenobarbital monotherapy was similar to that with other anticonvulsant monotherapy [Bertollini et al., 1987]. Current counseling practice identifies phenobarbital therapy as being associated with an increased risk of congenital malformations similar to those associated with phenytoin.

The newer anticonvulsant medications have been evaluated in various pregnancy registries with evidence of an increase in malformations for lamotrigine and topiramate. With respect to lamotrigine, some registries have not shown an increase in risk, but the antiepileptic drug registry at the Massachusetts General Hospital reported about a 10-fold increase in all nonsyndromic orofacial clefts and a 21-fold increase in isolated cleft palate [Holmes et al., 2008]. The comparator group for these estimates was based on historical experience in the hospital. For topiramate, increases in malformations and low birth weight have been suggested by two registries [Vajda et al., 2007; Hern-dández-Díaz et al., 2010]. In one of the registries, cleft lip appeared to be overrepresented among the malformations.

The Massachusetts General registry continues to monitor the outcome of pregnancies in which anticonvulsant medications have been used. To learn more about this registry or to enroll subjects, call 1-888-233-2334, or visit online, http://www.massgeneral.org/aed. Outside North America, the International Registry of Antiepileptic Drugs and Pregnancy can be reached at http://www.eurapinternational.org.

Penicillamine

Penicillamine is a heavy metal chelating agent used to treat Wilson disease, rheumatoid arthritis, and cystinuria. Penicillamine has also been used to chelate mercury, cadmium, and lead. Chelation of copper or zinc has been proposed as a mechanism by which penicillamine may interfere with normal embryo development, particularly with respect to connective tissue.

Penicillamine given in high doses to pregnant rats and mice has been associated with increases in connective tissue, skeletal, palate, and lung abnormalities in the offspring [Steffek et al., 1972; Merker et al., 1975; Irino et al., 1982; Keen et al., 1982, 1983; Kilbourn and Hess, 1982; Mark-Savage et al., 1983; Myint, 1984; Dubick et al., 1985]. In some of these studies, copper supplementation reduced the teratogenic effects of penicillamine.

A case report of an infant with lax skin, hyperflexibility of the joints, and poor wound healing born to a mother who had received high-dose penicillamine (2,000 mg/day) for cystinuria appeared in 1971 [Mjolnerod et al., 1971]. Other children with lax skin, inguinal hernias, and other connective tissue problems have been reported after therapy during pregnancy with penicillamine in doses from 900 to 1,500 mg/day [Solomon et al., 1977; Linares et al., 1979; Harpey et al., 1983; Rosa, 1986].

It is possible that fetal connective tissue abnormalities are related to abnormally low maternal or fetal tissue levels of copper or zinc. The offspring of

women with Wilson disease may not be at risk if maternal copper levels are reduced only to normal. This theory would predict that women treated with high doses of penicillamine and women treated for illnesses other than Wilson disease would be at particular high risk of giving birth to an affected child. There are, however, case reports that do not fit with this theory, including a normal infant born after maternal treatment with penicillamine 2,250 mg/day for cystinuria [Laver and Fairley, 1971] and an abnormal infant born to a woman treated for Wilson disease with penicillamine 900 mg/day [Solomon et al., 1977].

Abnormalities associated with pregnancy exposure to penicillamine appear to occur infrequently. Endres [1981] summarized the outcome of 87 pregnancies exposed to penicillamine, 46 of which were exposed throughout pregnancy. There were two children with connective tissue abnormalities. The lax skin reported in affected children may resolve with age [Linares et al., 1979]. It has been suggested that the use by pregnant women with Wilson disease of low doses (250 or 500 mg/day) of penicillamine might offer protection from penicillamine-associated birth defects while permitting adequate control of the underlying illness [Marecek and Graf, 1976]. This proposal was based on eight cases under the authors' care and has not been subjected to rigorous confirmation.

Misoprostol

Misoprostol is a synthetic prostaglandin E_1 analogue that is used for the prevention of gastric ulcers associated with nonsteroidal anti-inflammatory drugs, to empty the uterus in incomplete miscarriage and early voluntary abortion, to ripen the cervix in preparation for labor, and in the treatment of postpartum hemorrhage.

Use of misoprostol as an abortifacient fails in 10% of cases [Song, 2000]. This risk of failure may be particularly high when misoprostol is used as a single agent instead of in combination with mifepristone or methotrexate [Golderg et al., 2001]. The risk of misoprostol exposure of early pregnancies is highest in countries where abortion is illegal or not widely available. In Brazil, for example, the use of misoprostol is not monitored by health professionals and frequently results in the birth of children after exposure to misoprostol in the first trimester [Philip et al., 2002].

In 1991, the first cases of fetal anomalies associated with use of misoprostol were reported from Brazil [Fonesca et al., 1991; Schonhofer, 1991]. Fonesca et al. [1991] described the association of skull malformations with the use of 400–600 μg misoprostol in the first trimester of pregnancy. The infants described were born with frontal and/or temporal defect of the cranium, exposing the dura matter and the underlying cerebrum.

In one series, the most common anomalies associated with use of misoprostol in pregnancy involved the lower limbs and included clubfoot, meromelia, and joint constriction [Philip et al., 2002]. There were also anomalies of cranial nerves III–XII with the majority of anomalies associated with cranial nerve VI, followed by V and XII. Many of the cranial nerve anomalies resembled the Möbius syndrome, with loss of cranial motor nerve function resulting in facial bilateral paralysis.

Another series of 42 infants born with congenital anomalies after exposure to misoprostol during gestation reported that the most common dose of misoprostol used was 800 μg with a range of 200–16,000 μg and that all exposures were in the first trimester [Gonzalez et al., 1998]. The most common anomalies were clubfoot with abnormalities of cranial nerves V–VII. Other anomalies included arthrogryposis, terminal transverse limb defects, and constriction bands.

The proposed mechanism of these anomalies is interruption of normal vascular development [Bavnick and Weaver, 1986; Vargas et al., 2000]. Most misoprostol exposures in pregnancy occur between 5 and 8 weeks after the last menstrual period [Gonzalez et al., 1998; Philip et al., 2002], a sensitive time for limb development.

A review of four studies comprising 4,899 cases of congenital anomalies compared to 5,742 normal controls evaluated the risk of fetal malformations in relation to misoprostol exposure [da Silva Dal Pizzol et al., 2006]. Increased risks related to misoprostol use were found for Möbius syndrome (OR 25.31, 95% confidence interval 11.11–57.66) and terminal transverse limb defects (OR 11.86, 95% confidence interval 4.86–28.90).

Among offspring of 120 women who used misoprostol in an attempt to induce abortion, an association was found between misoprostol use and total congenital anomalies (OR = 2.64; 95%CI: 1.03–6.75) [da Silva Dal Pizzol et al., 2008]. The anomalies identified in this study included meningomyelocele, microcephaly, clubfoot, syndactyly, and fingernail defects. The reported incidence of all anomalies in misoprostol-exposed fetuses was 4.24%. Infants were evaluated only after delivery, leading to possible under-reporting of Möbius syndrome and other central nervous system abnormalities, which may not be apparent until months later.

Diethylstilbestrol

Diethylstilbestrol (DES) is a synthetic nonsteroidal estrogen. This compound was used as a pharmaceutical from around 1938 until 1971 in the US and in Europe until 1978 in an attempt to prevent miscarriage, premature delivery, and other pregnancy complications. Doses varied but typically started at 5 mg/day early in pregnancy with a steady increase to 150 mg/day at term.

In 1971, Herbst et al. reported eight cases of vaginal adenocarcinoma in young women [Herbst et al., 1971]. The authors had seen seven of the patients, aged 15–22 years, at the Vincent Memorial Hospital in Boston between 1966 and 1969. Vaginal carcinoma is very rare in women in this age group, and vaginal carcinoma in any age group is virtually always squamous, not glandular, so seeing this many cases of vaginal adenocarcinoma in a short period of time raised the suspicion that a new causal factor was at play. The authors performed a case-control study, comparing historical aspects of the pregnancies of the eight patients they had identified with 32

controls matched for date of birth (within 5 days) and hospital service (ward or private). They found that seven of the eight patients had been exposed during pregnancy to diethylstilbestrol given for a maternal history of miscarriage and/or bleeding in the current pregnancy. None of the control patients had been exposed to diethylstilbestrol.

This first paper was remarkable in being not only the first case series but also the first controlled study of the association. Moreover, the authors offered the theory in this first paper, a theory that is still in vogue, that the adenocarcinoma was due to adenosis (the presence of glandular elements in the vaginal epithelium) in the diethylstilbestrol-exposed vagina that was at risk for malignant transformation. Subsequent work by Herbst and coworkers led to an estimate that 1 in 1,000 women with intrauterine exposure to diethylstilbestrol would develop adenocarcinoma and that about two-thirds of women who developed adenocarcinoma would have a history of maternal treatment during pregnancy with diethylstilbesterol or another estrogen [Melnick et al., 1987].

Diethylstilbestrol exposure during pregnancy also results in abnormalities of the uterus in more than two-thirds of female offspring; these abnormalities including hypoplasia and irregularity of the cavity, a T-shaped cavity, and constriction bands [reviewed by Goldberg and Falcone, 1999]. The uterine abnormalities are associated with infertility and preterm delivery. Abnormalities of the cervix include collars, hoods, and septae. The risk of female genital tract abnormalities is highest with exposure prior to 15 weeks gestation (44%), intermediate at 15–22 weeks (22%), and lowest after 23 weeks gestation (5%) [Jefferies et al., 1984]. Male offspring have been found to have an increased risk of cryptorchidism, epididymal cyst, and orchitis, with stronger associations when exposure is before 11 weeks gestation [Palmer et al., 2009].

Lithium

Lithium therapy is often considered to increase the risk of an unusual cardiac defect called Ebstein anomaly, in which the tricuspid valve is displaced into the right ventricle, but the evidence is contradictory. The first connection between lithium therapy and Ebstein anomaly was published by Nora et al. [1974]. These investigators obtained teratology-oriented histories from 733 women. Two women in the group had taken lithium during pregnancy and both gave birth to children with Ebstein anomaly.

Based on suspicions raised by experimental animal studies, a Register of Lithium Babies was started in Denmark in 1969 and was soon expanded to include input from Canada, the US, and elsewhere. An early report from this registry indicated that there were nine malformed infants among 118 exposed pregnancies [Schou et al., 1973]. The authors cautioned that due to the retrospective nature of the reporting, the registry might over-represent abnormal pregnancy outcomes. Not long thereafter, a publication from this registry reported an analysis based on 143 pregnancies in the registry [Weinstein and Goldfield, 1975]. There were four instances of Ebstein anomaly. The authors concluded that the proportion of malformations that was cardiac and the proportion of cardiac malformations that was Ebstein anomaly exceeded what would be expected based on general population rates. The registry would go on to add an additional two cases of Ebstein anomaly (from 225 exposed pregnancies) before it closed in 1979.

The question remained, however, whether the publicity generated by the registry served to attract serious defects in general and Ebstein anomaly cases in particular. A multicenter teratology information service study followed 138 pregnancies that included first trimester exposure to lithium [Jacobson et al., 1992]. There was no increase in birth defects as a group; however, one case of Ebstein anomaly was found among the exposed fetuses based on antenatal fetal echocardiography.

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Other observations suggested that lithium exposure may not be an important causal factor in Ebstein anomaly. A short communication presented 25 Swedish and 15 French cases of Ebstein anomaly with no maternal history of lithium use during pregnancy [Källén, 1988]. A case–control study from the Birth Defects Monitoring Program did not identify any maternal lithium exposure during pregnancy for 34 children with confirmed Ebstein anomaly [Edmonds and Oakley, 1990]. A Canadian case–control study of Ebstein anomaly also found no cases in which there was maternal exposure to lithium during pregnancy [Zalzstein et al., 1990]. Based on the sample size, it was suggested that the upper limit for any increase in risk would be 28-fold, or about 0.14%.

The interpretation of the cases from the Register of Lithium Babies was based in part on the presumed prevalence of Ebstein anomaly of 1 in 20,000 births. More recent reports suggest that Ebstein anomaly can go undiagnosed until adulthood and may be associated with few symptoms [Rosas et al., 2000]. Inasmuch as most lithium-exposed fetuses and infants now are recommended to undergo echocardiography, ascertainment of Ebstein anomaly and other cardiac defects can be expected to be virtually complete in these pregnancies while unexposed children with Ebstein anomaly may go undiagnosed until adulthood. This propensity to diagnose heart defects in lithium-exposed fetuses and newborns may contribute to the impression that there is a causal relationship between the use of

lithium during pregnancy and cardiac defects in the offspring.

It is ironic that the experimental animal studies, which started the suspicions about lithium during pregnancy almost 50 years ago, can now be cited as reasons to doubt a causal connection with cardiac anomalies. Lithium exposure of pregnant laboratory mice and rats increases malformations only with very high exposure levels, often given intraperitoneally [Szabo, 1970; Wright et al., 1971; Smithberg and Dixit, 1982; Marathe and Thomas, 1986; Jurand, 1988]. Other studies in rodents, rabbits, and six monkeys have failed to show an increase in malformations with lithium exposure during pregnancy [Johansen, 1971; Gralla and McIlhenny, 1972; Hoberman et al., 1990]. The report by Gralla and McIlhenny [1972] is brief but confirms that pregnant animals attained serum lithium concentrations within or above the human therapeutic range. The study by Hoberman et al. [1990] was a standard developmental study reported from an experienced laboratory. No experimental animal study, even using extreme treatment conditions, has shown an increase in cardiovascular malformations.

Current counseling practice includes the advice that there may be an increase in Ebstein anomaly after exposure to lithium. Exposed women are routinely offered fetal echocardiography. If there is a risk of Ebstein anomaly associated with lithium, it appears to be well under 1%. Counselors can advise their clients that the chance of identifying a cardiovascular anomaly using fetal or neonatal echocardiography is greater than the likelihood that any identified abnormality is due to lithium. After counseling, women who elect to continue lithium therapy during their pregnancies should be supported in their decisions. Hypotonia, kidney, or thyroid impairment can occur in exposed neonates, and consideration can be given during counseling to the nonmalforming effects of this medication.

Methimazole

Methimazole is an antithyroid agent that has a reputation for causing a punched out lesion of the scalp called aplasia cutis. The first report of this association appeared in 1972 [Milham and Elledge, 1972]. This letter-to-the-editor of *Teratology* read in part, "In the 6-month period October 1970–March 1971, 11 cases of newborn scalp defects were ascertained in Washington State by birth-certificate report and physician questionnaire. The lesions were single, circular, punched-out, ulcerlike midline defects of the scalp at the vertex or in the occipital area. Query of the mothers revealed that two of the 11 had taken methimazole. . . during pregnancy for hyperthyroidism. A third mother had taken thyroid hormone during her pregnancy for treatment of hypothyroidism." These authors suggested that the defect might be associated with antithyroid drugs or other factors associated with thyroid dysfunction.

In 1985, one of the original authors published a report of nine cases of scalp defect, including those he had previously published, associated with maternal therapy with methimazole or carbimazole, which is metabolized to methimazole [Milham, 1985]. There followed other case reports of congenital anomalies in children born to women on methimazole therapy [reviewed by Diav-Citrin and Ornoy, 2002]. Among the malformations, choanal and gastrointestinal atresias were given particular prominence by report authors.

Controlled studies, however, have mostly failed to confirm that children with intrauterine exposure to methimazole have an increased risk of aplasia cutis or other malformations [Momotani et al., 1984; Van Dijke et al., 1987; Wing et al., 1994; Di Gianantonio et al., 2001]. One of these papers equivocated in their conclusions, because they found one infant with choanal atresia and a second infant with esophageal atresia among 241 pregnancy outcomes after maternal exposure to methimazole or carbimazole [Di Gianantonio et al., 2001].

The exceptional controlled study was a case-control study of choanal atresia that identified a statistically significant association with methimazole therapy with an odds ratio of 17.75, 95% confidence interval 3.49–121.40, based on 10 exposed cases [Barbero et al., 2008]. These authors postulated that the association with choanal atresia was due to the underlying maternal hyperthyroidism rather than to methiazole therapy. They based this conclusion in part on the study of Momotani et al. [1984], which found an increase in malformations associated with untreated maternal hyperthyroidism, and in part on their belief that the genesis of choanal atresia is shortly after 9–10 embryonic weeks of development. This timing would call into question some of the case reports in the literature as well as at least one of their cases, in which exposure did not occur until 7 months of pregnancy. Barbero et al. further suggested that the lack of reports of choanal atresia with propylthiouracil therapy might be due to the greater effectiveness of propythiouracil in protecting the embryo from exposure to excess triiodothyronine.

The prevailing wisdom until recently had been to recommend propylthiouracil for hyperthyroid pregnant women due in part to the presumption that therapy with this drug had less teratogenic liability that methimazole therapy. Reports of severe and even fatal hepatic dysfunction associated with propylthiouracil therapy have resulted in reconsideration of treatment during pregnancy. One commentary pointed out that the incidence of aplasia cutis in children exposed antenatally to methimazole (0.03%) has never been shown to be greater than that in the general population and that choanal atresia may be associated with the maternal disease rather than the treatment [Cooper and Rivkees, 2009]. These authors suggested that given the uncertainty about malformations with methimazole, it would be reasonable to treat hyperthyroid women with propylthiouracil during the first trimester and then to switch the methimazole to decrease the likelihood of maternal hepatic failure.

Mycophenolate

Mycophenolate mofetil and mycophenolate sodium are used in immunosuppression regimens. Mycophenolate

therapy was suspected of being teratogenic based entirely on case reports. There are now controlled studies that support the teratogenicity of this therapy, although not with unanimity.

The mycophenolate story hit the streets in 2006 with a paper from the National Transplant Pregnancy Registry that reported on 26 mycophenolate-exposed pregnancies born to 18 women [Sifontis et al., 2006]. There were 15 1ive born children of whom four had malformations. One child had hypoplastic nails and shortened fifth fingers. The other three malformed children had microtia, and two of these children also had cleft lip and palate.

Following that report, several case reports and case series appeared describing mycophenolate-exposed pregnancies resulting in a variety of different abnormalities (Table III). It is not clear that this entire array of abnormalities constitutes a mycophenolate embryopathy. The abnormalities that appear to be the most characteristic of effects of this drug are ear abnormalities, facial clefts, and perhaps conotruncal heart defects [Carey et al., 2009].

Denominator-based reports do not give a clear picture of the presence of a mycophenolate embryopathy or its prevalence. Adverse event reports summarized in the product labeling indicates that of 77 pregnancies reportedly exposed to mycophenolate, 25 spontaneously aborted, and 14 resulted in a malformed infant or fetus. Six of the 14 malformed offspring had ear abnormalities. As the labeling points out, spontaneous adverse event reporting does not give reliable prevalence rates, because adverse outcomes may be disproportionately reported compared to normal outcomes. An abstract from the European Network of Teratology Information Services reported that malformations occurred in 8 of 50 prospectively ascertained pregnancies after mycophenolate exposure, and that the miscarriage rate (excluding voluntary abortions) was 35% [Hoeltzenbein et al., 2010]. The malformations included microtia, tracheoesophageal fistula, hydronephrosis, and atrial septal defect.

TABLE III. Malformations From Case Reports of Pregnancy Exposures to Mycophenolate During Pregnancy

Ear malformations
Microtia
Atretic or absent external auditory canals
Anotia
Absent internal auditory structures
Preauricular pit
Conductive hearing loss
Low set ears
Ocular malformations
Hypertelorism
Coloboma
Microphthalmia
Cataracts
Orofacial malformations
Cleft lip and/or palate
Micrognathia
Nasal bifid anomaly or other dysplasia
Central incisor
Cardiovascular malformations
Ventricular septal defect
Atrial septal defect
Anterior aorta
Double-outlet right ventricle
Pulmonary valve stenonosis
Anterior aorta and interventricular communication
Digit anomalies
Hypoplastic nails
Shortened fifth finger
Polydactyly
Thumb anomalies
Overlapping fingers
Urogenital malformations
Pelvic ectopic kidney
Kidney asymmetry
Hydronephrosis
Tethered foreskin
Bilateral inguinal hernia
Gastrointestinal malformations
Intestinal malrotation
Tracheo-estophageal fistula or atresia
Brain, spine and skeletal abnormalities
Agenesis of the corpus callosum
Immature white matter with focal necrosis
Trigonocephaly
Hydrocephaly
Sacral dimple
Vertebral body anomalies
Rib fusion
Other diagnoses
Polyhydramnios
Intrauterine growth restriction
Umbilical hernia
Short webbed neck, facial coarseness
Non-immune hydrops
Diaphragmatic hernia

From REPROTOX [2011].

On the other hand, an Iranian report on 61 pregnancies in 53 renal-transplant patients reported no difference in outcome between pregnancies exposed to mycophenolate and pregnancies exposed to azathioprine [Ghafari and Sanadgol, 2008]. There are few details in the paper, but of the 53 women, 38 were exposed to mycophenolate, cyclosporine A, and prednisone and the other 15 were exposed to the same regimen with azathioprine in place of mycophenolate. There were two infants with malformations, including clubfoot and hemangioma (exposure not specified). A group of North American teratology information services reported outcomes of 10 pregnancies exposed to mycophenolate; there were four miscarriages, one voluntary abortion, and five normal births [Klieger-Grossmann et al., 2010].

Experimental animal studies do not support the putative malformation syndrome of ear abnormalities and facial clefts. These studies, unpublished but summarized in FDA documents, showed malformations in rats and rabbits at exposure levels that did not produce maternal toxicity. The malformations consisted of agnathia, anophthalmia, and hydrocephaly in rats, and failure of closure of the thoracic wall, renal agenesis or ectopia, and umbilical and diaphragmatic hernia in rabbits. Although rare human case reports included agnathia and diaphragmatic hernia, the animal models do not show what has been described in humans as the mycophenolate embryopathy.

Until more detailed denominator-based data are available, it is not possible to counsel on the rate at which a mycophenolate embryopathy occurs. It appears prudent all the same to avoid pregnancy exposures to this medication.

RECREATIONAL DRUGS

Ethanol

Ethanol is one of the oldest recreational drugs. The reputation of ethanol abuse as a teratogenic exposure likely dates to ancient Greece, where drinking was prohibited on the eve of a wedding for fear of conceiving a damaged child [Haggard and Jellinek, cited by Streissguth, 1978]. In 1899, Sullivan published a study of alcoholic women who were inmates in a Liverpool jail. He reported an increase in both morbidity and mortality in infants of those alcoholic women [cited by Streissguth, 1978].

The first report of what is now known as fetal alcohol syndrome was published by Lemoine, a French physician, and his coworkers in 1968 [Lemoine et al., 1968; translated and reprinted as Lemoine et al., 2003]. Dr. Lemoine recounted the observations in 127 children, 112 of whom had alcoholic mothers (sometimes with alcoholic fathers) and 15 of whom had only alcoholic fathers. This report makes particular mention of the distinctive facies and deficient growth in these children. This report was not widely appreciated, and it was not until 1973 that Jones et al. put fetal alcohol syndrome on the map based on a report of eight affected children [Jones et al., 1973]. Dr. Lemoine recounted the story some years later, observing wryly that his 127 cases had not made much of a splash and that he was grateful for the eight American cases that brought recognition to the problem [Lemoine, 2003].

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Commonly encountered effects of fetal alcohol syndrome are prenatal and postnatal growth deficiency (97%), microcephaly (93%), and mental deficiency (89%) [Hanson et al., 1976]. Anatomical evaluation of the brain demonstrates microcephaly, hydrocephaly, cerebral dysgenesis, corpus callosum anomalies, and cerebelar anomalies [Roebuck et al., 1998]. Other features include short palpebral fissures, a long smooth philtrum, thin upper lip, joint anomalies, and cardiac septal defects [Hanson et al., 1976; Clarren, 1981; Jones, 1986].

The incidence of fetal alcohol syndrome among the offspring of alcoholic women has been estimated as anywhere from 4.3% [Abel, 1995] to 40% [Jones, 1986]. Alcohol consumption during pregnancy has also been associated with an increase risk of other adverse outcomes. Florey et al. [1992] reported that consumption of more than 120 g of alcohol per week was associated with spontaneous abortion (odds ratio 2.3, 95% confidence interval 1.1–4.5). An association between second trimester pregnancy loss and consumption of more than 3 drinks/day has also been reported (relative risk 3.5, 95% confidence interval 1.8–7.0) [Harlap and Shiono, 1980]. Women who drink >5 drinks per week compared to women who drink <1 drink per week are at increased risk of delivering a stillborn baby (relative risk 2.96, 95% confidence interval 1.37–6.41) [Kesmodel et al., 2002]. Binge drinking three or more times during a pregnancy was associated with stillbirth (hazard ratio 1.56, 95% confidence interval 1.01–2.4) [Strandberg-Larsen et al., 2008].

Among the issues that limit the assessment of outcomes in women with

presumed light to moderate alcohol intake are self-reporting of use, variability of drinking patterns, quantification and strength of the alcohol consumed, diet, and smoking status [Wallpole et al., 1990]. Although it can be assumed that there is an intake of ethanol during pregnancy that is too low to cause adverse effects on the offspring, we do not know what that intake might be. Maternal intake as low as three drinks/week has been associated with an increase in intrauterine growth restriction [Windham et al., 1995]. For this reason, current counseling practice is to recommend that pregnant women avoiding drinking alcohol entirely.

Toluene Abuse

Recreational inhalation of toluene by pregnant women has been associated with microcephaly, mental retardation, and dysmorphic features similar to those in fetal alcohol syndrome. The first report of the association was published by Toutant and Lippmann [1979] who noted small body size, microcephaly, a flat nasal bridge, hypoplastic mandible, short palpebral fissures, mildly low-set ears, sacral dimple, sloping forehead, and uncoordinated arm movements in a child born to a woman who abused toluene and ethanol. The mother presented with ataxia, tremor, sensory deficits, memory impairment, and poor intellectual functioning attributed to her toluene addiction.

Other case reports followed. The first denominator-based report of any size was published by Wilkins-Haug and Gabow [1991]. Ten toluene-abusing women were systematically identified and their 21 toluene-exposed pregnancies were evaluated. Preterm delivery occurred in 86%, perinatal death in 14%, and intrauterine growth restriction in 72%, more often than expected in the general population. Fetal alcohol syndrome-like features were noted in three of the children, but it is not clear how carefully the other children were evaluated for dysmorphic features. Pearson et al. [1994] reported that half of children born to toluene-abusing women were growth-restricted, two-thirds had microcephaly, 80% had developmental delay, and nearly 90% had dysmorphic features similar to fetal alcohol syndrome or had other minor anomalies. These authors believed they could distinguish toluene from ethanol effects: children affected by toluene were more likely to be premature and to have micrognathia, abnormal ears, narrow bifrontal diameter, abnormal scalp hair patterning, nail hypoplasia, downturned mouth corners, large anterior fontanel, and abnormal muscle tone; children affected by ethanol were more likely to have prenatal microcephaly, thin upper lip, smooth philtrum, small nose, and altered palmar creases.

In experimental animal studies, inhalation exposure or gavage treatment with toluene increase the incidence of abnormal embryo development only at very high exposure levels intended to model human recreational use. The most consistent effects at these high exposure levels are reductions in fetal body weight and viability [Gospe et al., 1994, 1996; Bowen et al., 2005, 2009]. Among the structural alterations that have been described in various mouse and rat studies are cleft palate, short or missing digits, missing limbs, misshapen scapula, missing and supernumerary vertebrae and ribs, fused digits, cryptorchidism, displaced abdominal organs, microgastria or gastromegaly, distended/hypoplastic bladder, and small atria. These abnormalities are not suggestive of the findings in children born to toluene-abusing women, and an experimental animal model mimicking all the features of toluene embryopathy has not been developed.

Toluene abuse has been estimated to involve inhalation of at least 800 ppm and usually in excess of 10,000 ppm [Bowen et al., 2005]. Women who abuse toluene commonly have renal tubular acidosis and in some cases, their offspring have associated transient acidosis and electrolyte abnormalities [Goodwin, 1988]. It is not known whether the acidosis or electrolyte abnormalities contribute to any of the adverse effects on fetal development associated with toluene abuse. Moreover, many women who report toluene abuse also report abuse of other substances. These other exposures or other factors associated with the abusers' lifestyles may be at play in the effects on the offspring. The identification of toluene abuse as a teratogenic exposure appears to require the abuse component as much as the toluene component. It has been estimated that occupational exposure to toluene (<100 ppm) does not pose a significant fetal risk [Wilkins-Haug, 1997].

PHYSICAL AGENTS

X-Ray

X-rays are a class of electromagnetic radiation with a characteristically short wavelength used in both diagnostic imaging and in therapy. These electromagnetic waves are energetic enough to detach electrons from their orbits, resulting in ionization, and the ionization results in tissue damage.

During the early 1920s, case reports suggested an association between decreased infant head size and mental retardation in children born to women exposed to 60 rad (cGy) ionizing radiation during pregnancy [reviewed by Miller, 2004]. Small head size was reported with doses as low as 20 rad. Data from the atomic bombing of Hiroshima and Nagasaki identified the period of greatest susceptibility to the fetus as between 8 and 15 weeks of gestation, with no demonstrated risk at less than 8 weeks [Hal, 1991].

Severe intellectual disability from ionizing radiation occurs in about 40% of offspring after exposure to 100 rad and 60% of offspring after exposure to 150 rad [Hal, 1991]. In a well-known analysis, Otake and Schull [1984] suggested that any dose of radiation between 8 and 15 weeks of gestation could increase the risk of mental retardation and microcephaly by an estimated 0.4% per rad [ICRP, 1986]. The Otake and Schull analysis was based on a small number of patients with varying and uncontrolled sources of radiation and is not easily comparable to the filtered radiation used in diagnostic radiology. Contemporary thought, however, holds that there is a threshold exposure level

below which there is no increase in the risk of microcephaly and mental retardation; that level is placed at ~20 rad, a threshold supported by experimental animal studies [Brent, 1989, 2006]. The threshold for counseling purposes is often placed at 5 rad (5,000 mrad) to provide a margin of safety. Diagnostic studies do not result in this level of embryofetal exposure (Fig. 4), and most pregnant women with a history of diagnostic X-ray exposure do not have an increase in risk of bearing a child with congenital malformations over that of the general population.

Intrauterine X-ray exposure may increase the risk of childhood malignancy including leukemia [Harvey et al., 1985]. It has been estimated that 1/2,000 (0.05%) children exposed to x-ray pelvimetry will develop leukemia compared to a baseline risk of 1/3,000 (0.03%) [Brent, 2006]. This increase is equivalent to an additional case of childhood leukemia for every 6,000 exposed fetuses.

INFECTIONS

Rubella

In 1941, congenital cataract was associated with rubella virus infection during pregnancy by Norman Gregg, an Australian ophthalmologist. The story of Gregg's discovery was reviewed by Webster [1998]. Gregg had seen 13 infants with bilateral cataracts during the previous year and collected 65 additional cases from coworkers in Australia. A definite history of rubella infection was obtained from 68 of the 78 mothers. Many of these children had difficulty feeding, suggesting congenital heart disease. By the time of Gregg's paper, 15 of the children had died with autopsy confirmation of heart defects. The congenital rubella syndrome was considered to have been accepted when Wesselhoeft published his detailed review of reports by Gregg and a number of others indicating that of 573 pregnancies with rubella infection, there were 521 abnormal and 52 normal babies for an attack rate of about 90% [Wesselhoeft, 1947].

Although maternal infection with rubella virus can affect any fetal organ, most congenital anomalies affect the eyes, heart, brain, and ears. Deafness is the most common consequence, but cardiac disease and mental retardation also occur frequently. In addition, the newborn may exhibit poor growth, thrombocytopenia, and encephalitis [Menser et al., 1967; Webster, 1998; Forrest et al., 2002]. If the infection occurs in the first 12 weeks of gestation about 80% of fetuses will be born with congenital anomalies. Between 12 and 16 weeks some 50% of fetuses will be affected [Miller et al., 1982; Webster, 1998]. After 17 weeks the risk of congenital defects is significantly less. With infection after16 or 17 weeks the most common finding is deafness; all other anomalies occur with infection in the first trimester.

In 1966, Parkman et al. developed the first live attenuated rubella vaccine [Parkman et al., 1966]; the vaccine was available in the US in 1969 [Parkman, 1999]. Thereafter, the incidence of congenital rubella has significantly decreased. Although live vaccines are not recommended for administration during pregnancy, there have been no reports of adverse pregnancy outcome attributed to rubella vaccine. The Centers for Disease Control and Prevention summarized reports on 210 women who received the vaccine in the first trimester. These women delivered 212 healthy infants [The Centers for Disease Control, 1989].

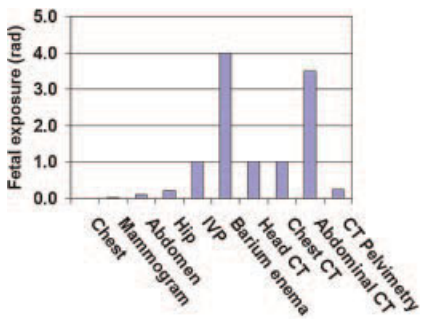

Figure 4. Exposure of the conceptus from diagnostic x-ray studies. Drawn from data in American College of Obstetricians and Gynecologists [2004].

Varicella

Vareicella-zoster virus is responsible for both chickenpox and herpes zoster (shingles). More than 80% of children have chickenpox by the time they reach 10 years of age. Some women who are seronegative can reach childbearing age and have a primary infection during their pregnancy. Varicella complicates 0.5–0.7/1,000 pregnancies [Sever and White, 1968]. Maternal effects can range from a chickenpox rash to a more severe viral pneumonia.

After the association between rubella infection and congenital malformations was recognized, there was interest in identifying the potential effects of other viral infections on pregnancy outcome. The first published report of a pregnancy complicated by varicella was presented in 1945 [Conte et al., 1945]. The child was described as normal. The first case report of a child with abnormalities after maternal varicella followed 2 years later [Laforet and Lynch, 1947]. The woman delivered the child at term after a diagnosis of varicella at 8 weeks gestation. She had had a viral exanthem and a fever of 102 F lasting 2 weeks. The child had an undescended left testicle, atrophied right leg with anomalous digits, cortical atrophy, hydrocephalus, and a relaxed anus.

Transmission of varicella zoster virus to the fetus occurs in 25% of primary maternal infections, half of which will be symptomatic [Paryani and Arvin, 1986; Pastaszak et al., 1994]. Infection may result in skin scarring and organ necrosis. Features of

TABLE IV. Maternal Infections Associated With Developmental Toxicity

Infection	Effects	Prevalence of effects after infection	Sensitive period	Comments
Cytomegalovirus (CMV; a DNA herpesvirus)	Jaundice, petichiae, thrombocytopenia, hepatosplenomegaly, growth restriction, non-immune hydrops	24% sensorineural hearing loss; 32% CNS sequelae	First trimester	Primary infection: 5–18 % children experience serious sequelae (especially first half of pregnancy)
	Long term: developmental delay, seizures, sensorineural hearing loss	2.5% sensorineural hearing loss; 15% CNS sequelae	Second trimester	Most common congenital infection Leading cause of sensorineural hearing loss 0.7–4% primary CMV infection rate among pregnant women in US Risk of transmission to the fetus is 30–40%
Varicella zoster virus (VZV; a DNA herpesvirus)	Spontaneous abortion, intrauterine fetal demise, hydrops, polyhydramnios	0.4%	<13 weeks	Respiratory droplets
	Varicella embryopathy: limb hypoplasia, scars, malformed appendages, muscular atrophy, microcephaly, cortical atrophy, cataracts, chorioretinitis, microophthalmia, psychomotor retardation	2%	13–20 weeks	Neonatal VZV has 20–30% mortality rate
Rubella (an RNA virus)	Sensorineural hearing loss, growth retardation, miscarriage, stillbirth, heart defects, cataracts, glaucoma, retinitis, microcephaly, micropthalmia, intrauterine growth restriction, cerebral palsy, mental retardation	67%	<12 weeks	Transmission by respiratory droplets
		35%	13–16 weeks	Seen mostly in pregnancies in women born outside the US Infection <12 weeks associated with greater severity of fetal effects Fetal defects rare with infection after 16 weeks
Parvovirus B19 (a DNA virus)	Fetal death, hydrops, spontaneous abortion	19%	1–12 weeks	Respiratory secretions
		15%	13–20 weeks	Fetal infection in 33% of maternal infections
		6%	>20 weeks	Fetal death 11% with infection <20 weeks
Toxoplasmosis (a protozoan)	Mental retardation, chorioretinitis, periventricular calcifications, seizures, ventriculomegaly, chorioretinitis, hepatosplenomegaly, fever, ascites, rash	Congenital toxoplasmosis occurs in 1/8,000 pregnancies	All trimesters can be affected	Cat feces
		Transmission rate		Infected meat
		10–15%	1st trimester	Congenital toxoplasmosis is rare with chronic maternal infection
		25%	2nd trimester	
		60%	3rd trimester	

(*Continued*)

TABLE IV. (*Continued*)

Infection	Effects	Prevalence of effects after infection	Sensitive period	Comments
Syphilis (Treponema palladium; a spirochete)	Early congenital syphilis: hepatosplenomegaly, hydrops, intrauterine growth restriction, osteochondritis, jaundice, anemia, skin lesions, rhinitis, CNS involvement, chorioretinitis	8.8 cases/100,000 pregnancies		
	Early latent syphilis: stillbirths, miscarriage, preterm delivery	Early latent: 20% prematurity, 10% stillbirths, 4% neonatal death, 40% congenital syphilis, 20% normal		
	Late congenital syphilis: Hutchinson's teeth, deafness, mental retardation, hydrocephalus, palsies, frontal bossing, saddle nose, saber shin, protuberant mandible	Late latent: 9% prematurity, 10% stillbirths, 1% neonatal death, 10% congenital syphilis, 70% normal		
Listeria (a gram positive bacterium)	Late miscarriage, stillbirth, preterm delivery	50% perinatal mortality 10% mortality among live born infants		Food borne: luncheon meats, soft cheeses, smoked seafood Flu like symptoms Symptoms of food poisoning Septicemia, pneumonia, meningitis in the mother
Measles (an RNA virus)	Spontaneous abortion, preterm delivery	20–60%		Respiratory droplets Pregnant women are 2 times more likely to be hospitalized, 3 times more likely to have pneumonia, 6 times likely to die from complications than nonpregnant women No increased risk of malformations There has been an association of measles exposure at birth and Hodgkin's disease in children
Herpes simplex (HSV; a DNA herpesvirus)	Skin vesicles, scarring, microcephaly, hydranencephaly, disseminated infection	50–60% mortality with disseminated infection	At delivery	Maternal fetal transmission during delivery
	Questionable intrauterine growth restriction with third trimester infection	15% mortality with encephalitis		Most often from primary infections rather than recurrences
		Sequelae in 50% of survivors		Fetal HSV infection in 1/200,000 deliveries Neonatal HSV in 1/3,500 deliveries Risk of neonatal HSV after primary infection 50%, after recurrent infection 0–3% 70% of neonatal herpes is caused by HSV-2

Hitchcock et al. [1999], Gabbe et al. [2007], and DeCherney et al. [2007].

congenital varicella syndrome include scarring in a dermatomal pattern, cataract, microphthalmia, chorioretinitis, microcephaly, mental retardation, and dysfunction of the bowel or bladder sphincter [Pastaszak et al., 1994].

Peak susceptibility to varicella embryopathy occurs with infection between 8 and 20 weeks gestation when the virus is most likely to damage neural tissue [Enders, 1984; Alkalay et al., 1987]. Women who contract varicella

in the first 20 weeks of gestation have about a 1.2% risk of a child with varicella embryopathy [Enders et al., 1994; Jones et al., 1994; Pastaszak et al., 1994]. Varicella infection prior to 13 weeks gestation is associated with embryopathy considerably less often, and maternal zoster appears to entail little if any risk for the fetus [Enders et al., 1994].

Other Infections

Other infectious agents may be responsible for developmental toxicity in exposed pregnancies. These exposures are summarized in Table IV.

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