Medical genetics: 1. Clinical teratology in the age of genomics

Janine E. Polifka, J.M. Friedman

Abstract

Teratogenic exposures are those that can cause an embryo or fetus to develop abnormally. Several factors determine whether an agent is teratogenic, including the gestational timing of the exposure, as well as the dose, route and nature of the agent itself. We review the general concepts of teratogenesis, as well as known genetic susceptibilities to teratogenic effects, with a special focus on antiepileptic drugs. We discuss general principles of risk counselling and risk reduction, and we describe several long-known teratogens, as well as several exposures recognized only recently to have teratogenic potential.

Case

A 27-year-old woman with epilepsy and her husband are planning to have a child but are concerned that their baby may be harmed by the mother's epilepsy or its treatment during pregnancy. The woman is otherwise healthy, and her seizures are well controlled with oral divalproex, 900 mg per day. What information should the couple be given? What course of action should be recommended?

Teratology is the study of abnormal prenatal development. A teratogenic exposure is one that can cause an embryo or fetus to develop abnormally. Teratogenic exposures can affect prenatal development by altering gene expression, programmed cell death (apoptosis), cell migration or proliferation, histogenesis, synthesis or function of proteins or nucleic acids, or the supply of energy sources. Some teratogenic exposures act directly on the embryo, whereas others act through intermediates produced by maternal metabolism.

The nature of an agent is an important factor in determining whether an exposure will damage a developing embryo, and certain chemicals such as thalidomide and isotretinoin do have a greater teratogenic potential than others. Nevertheless, it is inappropriate to classify some agents as teratogenic and others as not teratogenic, because teratogenicity depends on the gestational timing and on the dose and route of exposure, as well as on the nature of the agent itself. The presence of other concurrent exposures and the biological susceptibility of the mother and fetus are also important factors that determine whether or not an exposure will be teratogenic. For example, the occasional use of one or 2 ASA tablets during early pregnancy is unlikely to be harmful to the embryo or fetus; however, taking ASA during this period of time may not be safe if the dose is so great that it causes coma in the mother.

One of the most important factors affecting safety is the stage of pregnancy during which an exposure occurs. During the first 2 weeks after conception, toxic exposures are unlikely to cause malformations, because the cells of the conceptus are pluripotent at this stage. Cells that are killed by an exposure can be replaced by other cells. However, if too many cells are damaged or die, the embryo will not survive. The first 2 weeks after conception are sometimes referred to as the "all-or-none" period, because toxic exposures during this time usually kill the embryo or produce no permanent effect if the embryo survives.[1] However, some mutagenic treatments during the preimplantation period produce malformations in rodent experiments, so the "all-or-none" rule does not always hold.[2]

Organogenesis (18–60 days post conception in humans) is the time during which the embryo is most sensitive to many teratogenic exposures and when most structural anomalies are produced. The fetal period is marked by rapid growth and matu-

Review

Synthèse

Dr. Polifka is with the Department of Pediatrics, University of Washington, Seattle, Wash. Dr. Friedman is with the Department of Medical Genetics, University of British Columbia, Vancouver, BC

This article has been peer reviewed.

CMAJ 2002;167(3):265-73

ß See related articles pages 253, 256, 259 and 275

Series editor: *Dr. Judith Hall, Professor of Pediatrics and Medical Genetics, Department of Pediatrics, Children's and Women's Health Centre of British Columbia, Vancouver, BC*

ration as well as active cell growth, proliferation and migration, particularly in the central nervous system. Teratogenic exposures during this period may cause fetal growth retardation, death or central nervous system dysfunction that may not be apparent until later childhood. Some treatments with long-recognized teratogenic potential and the stage of pregnancy during which they exert their effects are summarized in Table 1. Several treatments that have only been recognized as having teratogenic potential in the last few years are listed in Table 2.[3–21] Many of these teratogenic effects have been recognized in humans not because of their frequency of occurrence but because of the characteristic pattern of anomalies that is produced in exposed children. Fig. 1 shows a child who has minor facial anomalies consistent with methimazole embryopathy (see Table 2 for details of this syndrome).

Dose is a critical feature of any teratogenic exposure. Exposures are teratogenic only when they exceed a threshold dose.[22] This means that for every exposure there is a level below which damage to the embryo does not occur. As the dose increases above the threshold, the frequency and severity of teratogenic effects also increase. Almost any agent can have adverse effects on the developing embryo if given in a dose that is high enough to produce maternal toxicity. Chronic exposures usually have a greater potential to cause teratogenic effects than acute exposures at similar doses. For example, typical fetal alcohol syndrome will not occur in the child of a woman who only got drunk once during pregnancy, even if it was in the first trimester, but the risk increases substantially if the mother consumes large amounts of alcohol throughout gestation. Route of exposure also affects the dose received by the embryo. Dermal exposures that do not produce substantial systemic absorption are unlikely to cause adverse effects in the embryo.

Genetic susceptibility to teratogenic effects

Both maternal and fetal genotypes can affect placental

Table 1: Drugs long recognized to have teratogenic effects in humans at therapeutic doses (continued on facing page)

Drug	Maternal condition	Most susceptible period, post conception	Nature of adverse effect
ACE inhibitors: benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril	Hypertension	Second or third trimester (13th wk–term)	Oligohydramnios, intrauterine growth retardation, neonatal renal failure, hypotension, pulmonary hypoplasia, hypocalvaria, joint contractures, death
Amiodarone	Thyroid disorder	10 wk–term	Neonatal thyroid dysfunction or goitre
Aminopterin (≥ 1–3 mg/d)	Cancer	Organogenesis (18–60 d)	CNS, limb and skeletal defects
Antiepileptic drugs: carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, trimethadione, valproic acid	Epilepsy	Organogenesis (18–60 d)	CNS, cardiac, eye, gastrointestinal and genitourinary defects, facial dysmorphism and digital hypoplasia, growth retardation
Coumarin derivatives: dicumarol, warfarin	Thromboembolic disorders	For CNS defects: unknown; for other defects: second part of first trimester (6–9 wk)	Nasal hypoplasia, stippled epiphyses, vertebral abnormalities, CNS and ocular defects, cutaneous hematomas, intracranial hemorrhage, growth retardation, stillbirth
Cyclophosphamide	Cancer, transplant rejection	Organogenesis (18–60 d)	Skeletal and ocular defects, cleft palate
Danazol (≥ 200 mg/d)	Endometriosis, fibrocystic breast disease, hereditary angioedema	Unknown	Virilization of external genitalia in female fetuses
Diethylstilbestrol (1.5–150 mg/d)	Ovarian insufficiency, postcoital contraception	First and second trimesters (1–24 wk)	Vaginal/cervical carcinoma in females and genital tract abnormalities in males and females
Indomethacin	Fever, inflammation, premature labour, hydramnios	Second or third trimester (13th wk–term)	Oligohydramnios, anuria, premature closure of the ductus arteriosus, necrotizing enterocolitis
Lithium	Mental illness	Organogenesis (18–60 d)	Cardiac defects, particularly Ebstein's anomaly of the tricuspid valve

Table 1 continued

Drug	Maternal condition	Most susceptible period, post conception	Nature of adverse effect
Methotrexate (≥ 12.5 mg/wk)	Cancer, rheumatic disease	Organogenesis (18–60 d)	Large fontanelles, abnormal head shape, craniosynostosis, ocular and skeletal defects
Methylene blue (Intra-amniotic injection)	Twin pregnancy (as an aid to amniocentesis)	Second trimester when amniocentesis is generally performed	Jejunal atresia
Penicillamine	Cystinuria, rheumatoid arthritis	Unknown	Connective tissue abnormalities resembling cutis laxa with loose skin, hernias, loose joints, flat face, small jaw
Quinine (≥ 2 g/d)	Leg cramps, malaria	First–third trimesters (1 wk–term)	Deafness, abortion
Radioiodine (296–8325 MBq)	Thyroid carcinoma, thyroid disorder	End of first–third trimester (10 wk–term)	Fetal hypothyroidism and goitre
Retinoids (oral): acitretin, eretinate, isotretinoin	Dermatologic disease	Organogenesis (18–60 d)	CNS and ear defects, microagnathia, cleft lip/palate, cardiac and great vessel defects, thymic abnormalities, eye anomalies, limb defects
Tetracycline derivatives: chlortetracycline, demeclocycline, doxycycline, methacycline, minocycline, oxytetracycline, tetracycline	Infection	Second or third trimester (13th wk–term)	Staining of primary dentition
Thalidomide	Insomnia, oropharyngeal and esophageal ulcers associated with AIDS, immuno-pathologic disease, graft-versus-host disease	Organogenesis (27–40 d)	Limb reduction, cardiac, urogenital, renal, orofacial, ocular and gastrointestinal defects, cranial nerve anomalies, microtia

Note: CNS = central nervous system.

transport, absorption, metabolism, distribution and receptor binding of an agent, influencing its teratogenicity. Such gene–teratogen interactions may explain why the range of effects seen after identical exposures can be so broad. The extent to which teratogenic effects depend on the fetal or maternal genotype is much more easily determined in experimental animals than in humans; however, there is evidence of differences in genetic susceptibility within human populations that result in greater damage from a teratogenic exposure in one individual than in another.[23,24] Some examples of the interplay between genetic variants in humans and the development of congenital anomalies follow.

Cigarette smoking

The association of cigarette smoking by pregnant women with low birth weight and preterm delivery of their infants is well recognized.[25–29] Although maternal smoking during pregnancy is associated with low birth weight regardless of maternal genotype, greater reductions in birth weight have been found among infants whose mothers smoked and had certain variants of the *CYP1A1* gene.[29] These variants influence the activity of enzymes involved in the metabolism of some of the chemicals found in cigarette smoke.[29,30]

Children of women who smoke during pregnancy have also been found to have orofacial clefts, limb reduction defects, congenital foot deformities, urinary tract abnormalities, craniosynostosis and other congenital anomalies 1.5–2 times more frequently than expected in some studies.[31–37] Other studies suggest that maternal smoking poses a higher risk of producing oral clefts in infants of women who carry genetic variants involved in the metabolism of cigarette smoke.[38–40] Further research is needed to define the interaction of genetic predisposition, maternal smoking and birth defects.

Alcohol

Excessive maternal drinking during pregnancy has been associated with a wide spectrum of birth defects in children.

Table 2: Recently recognized teratogenic exposures in humans

Exposure	Indication for treatment	Most susceptible period, post conception	Risk in embryo or fetus	Comments	References
Fluconazole (chronic, parenteral doses, 400–800 mg/d)	Mycotic infection	First trimester (1–12 wk)	Four children have been described with a similar and rare pattern of congenital anomalies. The features seen in these children are brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis and congenital heart disease	1) Risk appears to be more likely with high-dose, chronic, parenteral use 2) A single, oral dose of fluconazole (150–200 mg) is unlikely to pose a substantial teratogenic risk	3–5 6,7
Methimazole (usual therapeutic doses)	Hyperthyroidism	First trimester (1–12 wk)	Aplasia cutis congenita, skull hypoplasia, dystrophic nails and supernumerary nipples. Three children exhibited a characteristic pattern of malformations including facial dysmorphism, scalp defects, severely hypoplastic nipples, choanal atresia, esophageal atresia, psychomotor delay and growth retardation	1) Risk of fetal goitre or congenital anomalies is minimal to small 2) Untreated or inadequately treated maternal hyperthyroidism during pregnancy may lead to life-threatening complications of thyrotoxicosis and an increased risk of fetal death 3) Fetal hypothyroidism and goitre are unlikely to be caused by methimazole treatment before about 10 wk after conception when the fetal thyroid begins to function	8–12
		Second–third trimesters (10 wk–term)	Infants of women who are treated for Graves' disease during pregnancy with methimazole are at increased risk of hyperthyroidism due to placental transfer of thyroid-stimulating immunoglobulins as well as of hypothyroidism and goitre due to the medication		
Misoprostol (usual therapeutic oral doses)	Peptic ulcer disease, cervical ripening, pregnancy termination	First–second trimesters (1–24 wk)	Moebius anomaly, terminal transverse limb reduction defects, arthrogryposis multiplex congenita and talipes equinovarus	1) The risk of congenital anomalies resulting from vascular disruptions has been associated with unsuccessful attempts to induce abortion early in pregnancy 2) No consistent adverse effect has been observed in newborns of women who were given misoprostol for cervical ripening and induction of labour near term	13–18
Trimethoprim (usual therapeutic doses)	Bacterial infection, *pneumocystis carinii* pneumonia	First trimester (1–12 wk)	Neural tube defects, oral clefts, hypospadias and cardiovascular defects	The absolute risk of neural tube defects in infants of women treated with trimethoprim during the first 2 months of pregnancy is about 1%	19–21

The most severe manifestation is fetal alcohol syndrome, which typically occurs among children whose mothers abuse alcohol in large amounts daily. Features of fetal alcohol syndrome include growth retardation, microcephaly, mental retardation, neurobehavioural deficits and facial dysmorphism.[41] Lower levels of maternal alcohol consumption during pregnancy are associated with less severe neurodevelopmental anomalies in children.[42] The finding that concordance for alcohol-related birth defects is higher among monozygotic twins than among dizygotic twins born to women who drink during pregnancy supports the importance of genetic factors in determining susceptibility to fetal alcohol syndrome.[43]

Ethanol is metabolized by alcohol dehydrogenase (ADH) and cytochrome P4502E1 (CYP2E1) to acetaldehyde, which is then oxidized to acetate by aldehyde dehydrogenase (ALDH). Genetic variants of each of these enzymes occur.[44] A protective role for one particular variant at the *ADH2* locus has been demonstrated for both their offspring's neurobehavioural development and intrauterine growth in a prospective study of African American women who drank during pregnancy.[45]

Antiepileptic drugs

Maternal treatment with most antiepileptic drugs (AEDs) has been associated with an increased risk of congenital anomalies in the offspring. These anomalies include central nervous system, cardiovascular, genitourinary and gastrointestinal defects (see Table 3).[46–62] An anticonvulsant embryopathy that includes growth retardation, developmental delay, midface hypoplasia and distal digital hypoplasia has been observed among the children of women treated with several different AEDs.[63–65] The features of this syndrome may vary somewhat with the different AEDs, but it does not occur among the children of women with epilepsy who are not treated with an AED during pregnancy.[56,65] In addition, neural tube defects occur in 1%–2% of infants whose mothers were treated with valproic acid and 0.5%–1.7% of infants whose mothers were treated with carbamazepine during pregnancy.[21,51,66–68]

The overall risk of congenital anomalies among the infants of epileptic mothers treated with AEDs during pregnancy is 2–3 times higher than the "baseline" risk that attends every pregnancy, which has been estimated to be between 3% and 5%.[1,63–65] The extent to which this increased risk of congenital anomalies can be attributed to genetic factors, severity of maternal epilepsy, AEDs or a combination of these factors has been difficult to ascertain. The risk of congenital anomalies is even greater in those infants whose mothers must take more than one AED concomitantly during pregnancy.[51,69–70] Although the real magnitude of this increased risk is unknown, investigators in one study found that women with epilepsy who took only one AED during pregnancy had a 3% risk of giving birth to an infant with congenital anomalies compared with a 2% risk in untreated women with epilepsy.[69] This risk increased to 5% in women who took 2 AEDs during pregnancy, 10% when 3 AEDs were taken and 20% when as many as 4 AEDs were taken. The combination of valproic acid, carbamazepine and phenobarbital, in particular, may be more teratogenic than other combinations of AEDs.[51]

The teratogenic risk associated with the use of AEDs during pregnancy for indications other than epilepsy may be different. In addition, the information available about the new AEDs, such as felbamate, lamotrigine, gabapentin, oxcarbazepine, tiagabine, topiramate or vigabatrin, is too limited at the present time to determine whether or not the therapeutic use of these medications during pregnancy poses a greater or smaller teratogenic risk.

Maternal seizures during the first trimester of pregnancy are also associated with an increased risk of congenital anomalies in the children. In one study, congenital anomalies were found in 12% of infants of AED-treated mothers who experienced seizures in the first trimester of pregnancy compared with only 4% of infants whose AED-treated mothers did not have seizures.[71] Seizures during pregnancy have also been associated with higher fetal (30%–50%) and maternal mortality rates.[72]

Women who are treated with AEDs and give birth to an infant with congenital anomalies are at increased risk of

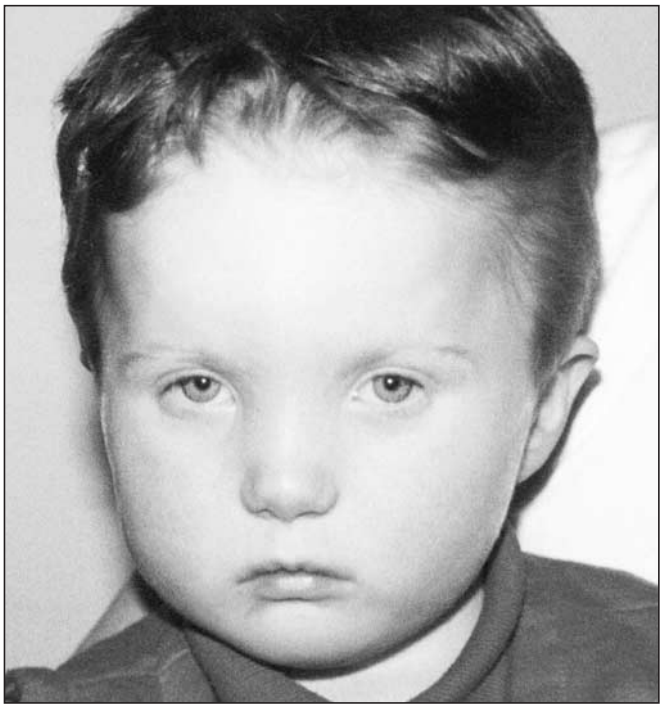

Fig. 1: Minor facial anomalies in a 3-year-old boy whose mother was treated with carbimazole (a prodrug that is completely metabolized to methimazole) for the treatment of Graves' disease during pregnancy (picture provided by Drs. L.C. Wilson, B.A. Kerr, R. Wilkinson, C. Fossard and D. Donnai). Reprinted with permission from Wiley-Liss, Inc. (*Am J Med Genet* 1998;75:220-2).

having another affected child in subsequent pregnancies.[73] A number of AEDs are metabolized through an epoxide hydrolase pathway,[74] and significantly lower levels of epoxide hydrolase activity have been found in children with fetal hydantoin syndrome than in unaffected children born to women with epilepsy who were treated with phenytoin during pregnancy.[75] It has also been suggested that genetic differences in folate metabolism may account for the increased risk of congenital anomalies, particularly neural tube defects, in the children of women with epilepsy treated with AEDs. In one study, epileptic mothers of children who were diagnosed with fetal anticonvulsant syndrome were more likely than epileptic mothers of unaffected children to be homozygous for the C677T variant of the *MTHFR* gene.[76]

Women with epilepsy who are planning a pregnancy should be advised to take 4–5 mg of folic acid per day at least 3 months before conception and throughout pregnancy.[72] They should be told about their increased risk of giving birth to an infant with congenital anomalies if they continue AED therapy while they are pregnant. They should also be informed of the potential maternal and fetal risks associated with discontinuation of AEDs and the recurrence of seizures during pregnancy. If AED withdrawal is attempted, it should be completed at least 6 months before conception, because the risk of seizure recurrence is greatest during the first 6 months of AED withdrawal.[72] If treatment cannot be discontinued, then the patient's physician should prescribe the AED that best controls the patient's seizures at the lowest effective dose. The use of a single agent is preferable to using multiple AEDs.

Women with epilepsy who become pregnant while being treated should be advised of their increased risk of giving birth to an infant with congenital anomalies. AED therapy should not be discontinued, because the frequency of seizures may increase. Prenatal diagnostic tests, such as serum alpha-fetoprotein screening at 15–22 weeks and ultrasonography at 18–22 weeks of pregnancy, should be offered, and amniocentesis for amniotic alpha-fetoprotein and acetylcholinesterase measurement at 16–20 weeks should be considered if appropriate.[72] Serum concentrations of the AED should be monitored regularly to help avoid toxic and subtherapeutic treatment.[77]

Many of the commonly used AEDs can decrease fetal vitamin K–dependent coagulation factors (II, VII, IX and X) and cause early hemorrhagic disease of the newborn.[72,78] It

Table 3: Teratogenic effects of some antiepileptic drugs (AEDs)

Drug	Dose	Most susceptible period, post conception	Nature of risk	References
Carbamazepine	Therapeutic, chronic	Organogenesis (18–60 d)	Facial dysmorphism similar to that seen with oxazolidine-2,4-diones, spina bifida, hypoplasia of distal phalanges, growth and developmental delay	46,47
Clonazepam	Therapeutic, chronic	Organogenesis (18–60 d)	Congenital anomalies have been reported in 13% of infants whose mothers took clonazepam during pregnancy in combination with other AEDs. No recurrent pattern of anomalies was observed. Congenital anomalies among infants whose mothers took clonazepam during pregnancy have also been described in anecdotal reports, although not in sufficient detail to determine whether there is a recurrent pattern. Typical craniofacial or digital features of anticonvulsant embryopathy were described in 8 infants whose mothers took clonazepam in combination with primidone in one study	48–51
Oxazolidine-2,4-diones (trimethadione, paramethadione)	Therapeutic, chronic	Organogenesis (18–60 d)	Growth retardation, microcephaly, cleft lip and/or palate, and unusual facies with v-shaped eyebrows, broad nasal bridge, epicanthal folds and anteverted nostrils. Mental retardation and cardiovascular, genitourinary and gastrointestinal anomalies also occur	52
Phenobarbital	Therapeutic, chronic	Organogenesis (18–60 d)	Facial clefting, congenital heart defects, facial dysmorphism and nail hypoplasia similar to that seen with oxazolidine-2,4-diones, neonatal withdrawal, learning deficits, mental retardation	53,54
Phenytoin/ fosphenytoin	Therapeutic, chronic	Organogenesis (18–60 d)	Fetal hydantoin syndrome: hypoplasia of nails and distal phalanges, ocular hypertelorism, flat nasal bridge, cleft lip/palate, congenital heart disease, microcephaly, developmental delay	55,56
Primidone	Therapeutic, chronic	Organogenesis (18–60 d)	Hirsute forehead, thick nasal root, facial dysmorphism and nail hypoplasia similar to that seen with oxazolidine-2,4-diones, congenital heart disease, developmental delay	46
Valproic acid	Therapeutic, chronic	Organogenesis (18–60 d)	Brachycephaly with a high forehead, shallow orbits, ocular hypertelorism, small nose and mouth, low-set ears, long overlapping fingers and toes, hyperconvex fingernails, septo-optic dysplasia, cleft palate/lip, limb defects, growth retardation, microcephaly, spina bifida, urogenital and respiratory tract anomalies, craniosynostosis, developmental delay, autism	46,57–62

is therefore recommended that women who are treated with AEDs receive oral supplementation with vitamin K, 10 mg/d, at least one month before their delivery.[72,77]

Teratogen risk counselling

Counselling for possible teratogenic risks should be provided by physicians or other health care professionals who have training and experience in clinical teratology. Difficult or complex cases should be referred to the appropriate specialists (see the Additional resources box at the end of this article). When estimating a patient's teratogenic risk, the counsellor must determine whether a pregnant woman's exposure significantly increases her risk of giving birth to an infant with major malformations or mental retardation, or both, above the risk expected without such exposure. This "baseline" risk that attends every pregnancy is usually quoted as 3%–5%,[1] but the baseline risk may be higher because of a woman's age, medical or family history, or other exposures.

In order to determine a woman's teratogenic risk, the counsellor must take a thorough medical and family history. The nature, dose, route, duration and gestational timing of the exposure of concern should be documented, as well as the reason for the exposure. It is important to include information regarding the woman's exposure to other agents, such as herbal products, tobacco, alcohol and other "recreational" drugs. Many women have more than one exposure during pregnancy.

Several attempts have been made to provide lists of agents that are "safe" or "unsafe" in pregnancy.[79,80] Although it is tempting to rely on these lists, they have serious limitations and can result in the mismanagement of pregnancies.[81] This is because agents cannot be classified as teratogens or nonteratogens without consideration of the dose, route, duration and gestational timing of the treatment. In addition, the likelihood that a particular treatment will cause fetal damage may also depend on concomitant exposure to other agents, the maternal illness that is being treated, and both maternal and fetal susceptibility. Moreover, the level of risk (or, alternatively, the amount of assurance of safety) that is acceptable varies from patient to patient. If a physician is contemplating initiating treatment in a pregnant woman, the benefit of the therapy to her and her fetus and the availability of safe and effective alternatives are also important issues. In addition, a list of "safe" drugs implies that the agents on the list have been tested in humans for the full range of potential developmental toxicities, including fetal death, structural malformations and functional deficits. Very few drug treatments have been evaluated to this extent.

Once the magnitude of teratogenic risk has been estimated, the counsellor must communicate this risk to the patient in a manner that enables her to make informed decisions regarding future exposures and further management of the pregnancy. Pregnant patients at high risk should be advised about prenatal diagnosis for possible teratogen-induced abnormalities, but many such anomalies are not detectable by detailed ultrasonography and few can be identified by amniocentesis.

A woman who requires treatment for a chronic disease such as epilepsy, diabetes or a psychiatric illness will often benefit from planning her pregnancies in consultation with her physician, who can discuss the risks and advantages of changing the treatment to one that is safer for the embryo and fetus. The feasibility of stopping treatment, completing certain aspects of the treatment before becoming pregnant or deferring part of the treatment until after pregnancy is completed can also be considered.

Modern genetics and clinical teratology

Genetic variants have been identified in more than 20 human drug-metabolizing enzymes that may produce significant alteration in clinical responses to drug treatment. These genetic variants often exhibit different frequencies in different populations. New genomic technology has enabled scientists to scan the entire human genome for genetic variants that may affect drug metabolism or activity, and many more are likely to be found in the next few years.[82–84]

Genetic variations that result in a deficiency of enzymes essential for the elimination of drugs or chemicals would be expected to increase the teratogenicity of these agents in at-risk individuals. On the other hand, people who lack the genetic susceptibility to the teratogenic effects of a particular treatment may be able to use that treatment safely even if it is likely to be teratogenic in most cases. Pharmacogenetics should prove useful in helping clinical teratologists understand how genetic variants influence teratogenic processes in humans, estimate teratogenic risk in individual patients and target intervention strategies to reduce the risk of birth defects.[85] More research is needed to identify genetic variants that predict susceptibility to teratogenic effects, so that harmful exposures can be prevented and more effective therapy provided to pregnant women and their babies.[82,83,86]

The case revisited

The couple described at the beginning of this article were counselled regarding their increased risk of having an infant with a major malformation or mental retardation because of the woman's epilepsy and AED treatment. The importance of seizure control and the risks of adverse maternal and fetal effects associated with seizures during pregnancy were also discussed. After consulting with her neurologist, the patient decided that she would continue treatment with divalproex when she became pregnant. She immediately began to take 5 mg of supplemental folic acid per day. To avoid high peaks of valproic acid plasma concentrations, her divalproex was given in divided doses

throughout the day instead of once a day. Three months later, the patient became pregnant. Plasma concentrations of valproic acid were monitored every month. The patient had serum alpha-fetoprotein screening at 15 weeks of pregnancy, targeted ultrasonography and fetal echocardiography at 18 weeks' gestation and amniocentesis for alpha-fetoprotein and acetylcholinesterase measurement at 20 weeks. All tests were normal. The patient began taking a 10-mg oral vitamin K supplement every day a month before her expected date of delivery. She delivered a healthy infant at term after completing an otherwise uneventful pregnancy.

Competing interests: None declared.

Contributors: Dr. Janine E. Polifka contributed to the substance of the manuscript, drafted the article and gave approval of the version to be published. Dr. J.M. Friedman contributed to the substance of the manuscript, revised it critically for important intellectual content and gave final approval of the version to be published.

References

1. Brent RL. Utilization of developmental basic science principles in the evaluation of reproductive risks from pre- and postconception environmental radiation exposures.*Teratology* 1999;59:182-204.
2. Rutledge JC, Generoso WM. Malformations in pregastrulation developmental toxicology. In: Korach KS, editor. *Reproductive and developmental toxicology*. New York: Marcel Dekker; 1998. p. 73-86.
3. Lee BE, Feinberg M, Abraham JJ, Murthy ARK. Congenital malformations in an infant born to a woman treated with fluconazole. *Pediatr Infect Dis J* 1992;11(12):1062-4.
4. Pursley TJ, Blomquist JK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis* 1996;22:336-40.
5. Aleck KA, Bartley DL. Multiple malformation syndrome following fluconazole use in pregnancy: report of an additional patient. *Am J Med Genet* 1997;72:253-6.
6. Mastroiacovo P, Mazzone T, Botto LD, Serafini MA, Finardi A, Caramelli L, et al. Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. *Am J Obstet Gynecol* 1996;175:1645-50.
7. Jick SS. Pregnancy outcomes after maternal exposure to fluconazole. *Pharmacotherapy* 1999;19(2):221-2.
8. Burrow GN. Thyroid function and hyperfunction during gestation. *Endocr Rev* 1993;14(2):194-202.
9. Mestman JH, Goodwin TM, Montoro MM. Thyroid disorders of pregnancy. *Endocrinol Metab Clin North Am* 1995;24(1):41-71.
10. Ecker JL, Musci TJ. Treatment of thyroid disease in pregnancy. *Obstet Gynecol Clin North Am* 1997;24(3):575-89.
11. Mestman JH. Hyperthyroidism in pregnancy. *Clin Obstet Gynecol* 1997;40(1): 45-64.
12. Momotani N, Yoshimura Noh J, Ishikawa N, Ito K. Effects of propylthiouracil and methimazole on fetal thyroid status in mothers with Graves' hyperthyroidism. *J Clin Endocrinol Metab* 1997;82:3633-6.
13. Fonseca W, Alencar AJC, Mota FSB, Coelho HLL. Misoprostol and congenital malformations. *Lancet* 1991;338:56.
14. Gonzalez CH, Vargas FR, Perez ABA, Kim CA, Brunoni D, Marques-Dias MJ, et al. Limb deficiency with or without Mobius sequence in seven Brazilian children associated with misoprostol use in the first trimester of pregnancy. *Am J Med Genet* 1993;47:59-64.
15. Gonzalez CH, Marques-Dias MJ, Kim CA, Sugayama SM, Da Paz JA, Huson SM, et al. Congenital abnormalities in Brazilian children associated with misoprostol misuse in first trimester of pregnancy. *Lancet* 1998;351:1624-7.
16. Castilla EE, Orioli IM. Teratogenicity of misoprostol: data from the Latin-American Collaborative Study of Congenital Malformations (ECLAMC). *Am J Med Genet* 1994;51:161-2.
17. Genest DR, Richardson A, Rosenblatt M, Holmes L. Limb defects and omphalocele in a 17 week fetus following first trimester misoprostol exposure. *Teratology* 1994;49(5):418.
18. Vargas FR, Brunoni D, Gonzalez C, Kim C, Meloni V, Conte A, et al. Investigation of the teratogenic potential of misoprostol [abstract]. *Teratology* 1997;55:104.
19. Czeizel A. A case-control analysis of the teratogenic effects of co-trimoxazole. *Reprod Toxicol* 1990;4(4):305-13.
20. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med* 2000; 343:1608-14.
21. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *Am J Epidemiol* 2001;153(10):961-8.
22. Brent RL. The application of the principles of toxicology and teratology in evaluating the risks of new drugs for treatment of drug addiction in women of reproductive age. *NIDA Res Monogr* 1995;149:130-84.
23. Hall JL, Harris MJ, Juriloff DM. Effect of multifactorial genetic liability to exencephaly on the teratogenic effect of valproic acid in mice. *Teratology* 1997;55(5):306-13.
24. Finnell RH, Gelineau-vanWaes J, Eudy JD, Rosenquist TH. Molecular basis of environmentally induced birth defects. *Annu Rev Pharmacol Toxicol* 2002;42:181-208.
25. Werler MM. Teratogen update: smoking and reproductive outcomes. *Teratology* 1997;55:382-8.
26. Lindley AA, Becker S, Gray RH, Herman AA. Effect of continuing or stopping smoking during pregnancy on infant birth weight, crown-heel length, head circumference, ponderal index, and brain: body weight ratio. *Am J Epidemiol* 2000;152(2):219-25.
27. England LJ, Kendrick JS, Gargiulio PM, Zahniser SC, Hannon WH. Measures of maternal tobacco exposure and infant birth weight at term. *Am J Epidemiol* 2001;153:954-60.
28. Woods SE, Raju U. Maternal smoking and the risk of congenital birth defects: a cohort study. *J Am Board Fam Pract* 2001;14(5):330-4.
29. Wang X, Zuckerman B, Pearson C, Kaufman G, Chen C, Wang G, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. *JAMA* 2002;287:195-202.
30. Carmella SG, Borukhova A, Akerkar SA, Hecht SS. Analysis of human urine for pyridine-N-oxide metabolites of 4-(methyl nitrosamino)-1-(3-pyridyl)-1-butanone, a tobacco-specific lung carcinogen. *Cancer Epidemiol Biomarkers Prev* 1997;6(2):113-20.
31. Chung KC, Kowalski CP, Kim HM, Buchman SR. Maternal cigarette smoking during pregnancy and the risk of having a child with cleft lip/palate. *Plast Reconstr Surg* 2000;105(2):485-91.
32. Croen LA, Shaw GM, Lammer EJ. Risk factors for cytogenetically normal holoprosencephaly in California: a population-based case-control study. *Am J Med Genet* 2000;90:320-5.
33. Friedman JM, Polifka JE. *Teratogenic effects of drugs: a resource for clinicians*. 2nd ed. Baltimore: Johns Hopkins University Press; 2000. p. 143-8.
34. Honein MA, Paulozzi LJ, Moore CA. Family history, maternal smoking, and clubfoot: an indication of a gene-environment interaction. *Am J Epidemiol* 2000;152(7):658-65.
35. Källen K. Multiple malformations and maternal smoking. *Paediatr Perinat Epidemiol* 2000;14:227-33.
36. Kallen K. The impact of maternal smoking during pregnancy on delivery outcome. *Eur J Public Health* 2001;11(3):329-33.
37. Lorente C, Cordier S, Goujard J, Aymé S, Bianchi F, Calzolari E, et al. Tobacco and alcohol use during pregnancy and risk of oral clefts. *Am J Public Health* 2000;90(3):415-9.
38. Hwang SJ, Beaty TH, Panny SR, Street NA, Joseph JM, Gordon S, et al. Association study of transforming growth factor alpha (TFGα) *Taq* I polymorphism and oral clefts: indication of gene-environment interaction in a population-based sample of infants with birth defects. *Am J Epidemiol* 1995; 141:629-36.
39. Shaw GM, Wasserman CR, Lammer EJ, O'Malley CD, Murray JC, Basart AM, et al. Orofacial clefts, parental cigarette smoking, and transforming growth factor-alpha gene variants. *Am J Hum Genet* 1996;58:551-61.
40. Romitti PA, Lidral AC, Munger RG, Daack-Hirsh S, Burns TL, Murray JC. Candidate genes for nonsyndromic cleft lip and palate and maternal cigarette smoking and alcohol consumption: evaluation of genotype-environment interactions from a population based case-control study of orofacial clefts. *Teratology* 1999;59:39-50.
41. Sokol RJ, Clarren SK. Guidelines for use of terminology describing the impact of prenatal alcohol on the offspring. *Alcohol Clin Exp Res* 1989;13(4):597-8.
42. Larroque B, Kaminski M. Prenatal alcohol exposure and development at preschool age: main results of a French study. *Alcohol Clin Exp Res* 1998;22(2):295-303.
43. Streissguth AP, Dehaene P. Fetal alcohol syndrome in twins of alcoholic mothers: concordance of diagnosis and IQ. *Am J Med Genet* 1993;47:857-61.
44. McCarver DG. ADH2 and CYP2E1 genetic polymorphisms: risk factors for alcohol-related birth defects. *Drug Metab Dispos* 2001;29(4 Pt 2):562-5.
45. McCarver DG, Thomasson HR, Martier SS, Sokol RJ, Li TK. Alcohol dehydrogenase-2*3 allele protects against alcohol-related birth defects among African Americans. *J Pharmacol Exp Ther* 1997;283(3):1095-101.
46. Yerby MS, Devinsky O. Epilepsy and pregnancy. *Adv Neurol* 1994;64:45-63.
47. Eller DP, Patterson CA, Webb GW. Maternal and fetal implications of anticonvulsive therapy during pregnancy. *Obstet Gynecol Clin North Am* 1997;24(3):523-34.
48. Dieterich E, Steveling A, Lukas A, Seyfeddinipur N, Spranger J. Congenital anomalies in children of epileptic mothers and fathers. *Neuropediatrics* 1980;11(3):274-83.
49. Ornoy A, Arnon J, Shechtman S, Moerman L, Lukashova I. Is benzodi-

azepine use during pregnancy really teratogenic? *Reprod Toxicol* 1998; 12(5):511-5.
50. Samren EB, van Duijn CM, Koch S, Hiilesmaa VK, Klepel H, Bardy AH, et al. Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. *Epilepsia* 1997;38(9):981-90.
51. Samren EB, van Duijn CM, Christiaens GCM, Hofman A, Lindhout D. Antiepileptic drug regimens and major congenital abnormalities in the offspring. *Ann Neurol* 1999;46(5):739-46.
52. Dansky LV, Finnell RH. Parental epilepsy, anticonvulsant drugs, and reproductive outcome. Epidemiologic and experimental findings spanning three decades; 2: Human studies. *Reprod Toxicol* 1991;5(4):301-35.
53. Waters CH, Belai Y, Gott PS, Shen P, De Giorgio CM. Outcomes of pregnancy associated with antiepileptic drugs. *Arch Neurol* 1994;51:250-3.
54. Koch S, Jager-Roman E, Losche G, Nau H, Rating D, Helge H. Antiepileptic drug treatment in pregnancy: drug side effects in the neonate and neurological outcome. *Acta Paediatr* 1996;84:739-46.
55. Hanson JW. Teratogen update: fetal hydantoin effects. *Teratology* 1986; 3:349-53.
56. Nulman I, Scolnik D, Chitayat D, Farkas LD, Koren G. Findings in children exposed in utero to phenytoin and carbamazepine monotherapy: independent effects of epilepsy and medications. *Am J Med Genet* 1997;68:18-24.
57. Jager-Roman E, Deichl A, Jakob S, Hartmann AM, Koch S, Rating D, et al. Fetal growth, major malformations, and minor anomalies in infants born to women receiving valproic acid. *J Pediatr* 1986;108:997-1004.
58. Rodriguez-Pinilla E, Arroyo I, Fondevilla J, Garcia MJ, Martinez-Frias ML. Prenatal exposure to valproic acid during pregnancy and limb deficiencies: a case-control study. *Am J Med Genet* 2000;90(5):376-81.
59. Iqbal MM, Sohhan T, Mahmud SZ. The effects of lithium, valproic acid, and carbamazepine during pregnancy and lactation. *J Clin Toxicol Clin Toxicol* 2001;39(4):381-92.
60. Lajeunie E, Barcik U, Thorne JA, Ghouzzi VE, Bourgeois M, Renier D. Craniosynostosis and fetal exposure to sodium valproate. *J Neurosurg* 2001; 95:778-82.
61. McMahon CL, Braddock SR. Septo-optic dysplasia as a manifestation of valproic acid embryopathy. *Teratology* 2001;64:83-6.
62. Williams G, King J, Cunningham M, Stephan M, Kerr B, Hersh JH. Fetal valproate syndrome and autism: additional evidence of an association. *Develop Med Child Neurol* 2001;43:202-6.
63. Jick SS, Terris BZ. Anticonvulsants and congenital malformations. *Pharmacotherapy* 1997;17(3):561-4.
64. Sabers A, a'Rogvi-Hansen B, Dam M, Fischer-Rasmussen W, Gram L, Hansen M, et al. Pregnancy and epilepsy: a retrospective study of 151 pregnancies. *Acta Neurol Scand* 1998;97(3):164-70.
65. Holmes LB, Harvey EA, Coull BA, Huntington KB, Khoshbin S, Haye Ryan LM. The teratogenicity of anticonvulsant drugs. *N Engl J Med* 2001; 344(15):1132-8.
66. Lindhout D, Schmidt D. In-utero exposure to valproate and neural tube defects. *Lancet* 1986;1:1392-3.
67. Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med* 1991;324(10):674-7.
68. Kaneko S, Otani K, Kondo T, Fukushima Y, Kan R, Takeda A, et al. Teratogenicity of antiepileptic drugs and drug specific malformations. *Jpn J Psychiatry Neurol* 1993;47(2):306-8.
69. Lindhout D, Hoppener RJ, Meinardi H. Teratogenicity of antiepileptic drug combinations with special emphasis on epoxidation (of carbamazepine). *Epilepsia* 1984;25(1):77-83.
70. Kaneko S, Battino D, Andermann E, Wada K, Kan R, Takeda A, et al. Congenital malformations due to antiepileptic drugs. *Epilepsy Res* 1999;33:145-58.
71. Lindhout D, Meinardi H, Meijer WA, Nau H. Antiepileptic drugs and teratogenesis in two consecutive cohorts: changes in prescription policy paralleled by changes in pattern of malformations. *Neurology* 1992;42(Suppl 5):94-100.
72. Zahn C. Neurologic care of pregnant women with epilepsy. *Epilepsia* 1998;39(Suppl 8):S26-31.
73. Van Dyke DC, Hodge SE, Heide F, Hill LR. Family studies in fetal phenytoin exposure. *J Pediatr* 1988;113:301-6.
74. Finnell RH. Teratology: general considerations and principles. *J Allergy Clin Immunol* 1999;103(2):S337-42.
75. Buehler BA, Delimont D, van Waes M, Finnell RH. Prenatal prediction of risk of the fetal hydantoin syndrome. *N Engl J Med* 1990;322:1567-72.
76. Dean JCS, Moore SJ, Osborne A, Howe J, Turnpenny PD. Fetal anticonvulsant syndrome and mutation in the maternal MTHFR gene. *Clin Genet* 1999;56:216-20.
77. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: management issues for women with epilepsy (summary statement). *Epilepsia* 1998;39(11):1226-31.
78. Yerby MS. Contraception, pregnancy and lactation in women with epilepsy. *Bailliere's Clin Neurol* 1996;5(4):887-908.
79. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. *N Engl J Med* 1998;338(16): 1128-37.
80. Shepard TH. *Catalog of teratogenic agents*. 10th ed. Baltimore: Johns Hopkins University Press; 2001.
81. Scialli AR. Identifying teratogens: the tyranny of lists. *Reprod Toxicol* 1997;11(4):555-9.
82. Sadee W. Pharmacogenomics. *West J Med* 1999;171(5/6):328-32.
83. Roses AD. Pharmacogenetics and the practice of medicine. *Nature* 2000; 405(6788):857-65.
84. Wolfe CR, Smith G, Smith RL. Pharmacogenetics. *BMJ* 2000;320(7240): 987-90.
85. Khoury MJ. Genetic susceptibility to birth defects in humans: from gene discovery to public health action. *Teratology* 2000;61:17-20.
86. Van Dyke DC, Ellingrod VL, Berg MJ, Niebyl JR, Sherbondy AL, Trembath DG. Pharmacogenetic screening for susceptibility to fetal malformations in women. *Ann Pharmacother* 2000;34:639-45.

Additional resources

Canadian teratology information services

- IMAGE: Info-Medicaments en Allaitement et Grossesse
  (514) 345-2333
  Geographic region: province of Quebec
  Accepts calls from: health care professionals only (members of the public should call Motherisk)
- Motherisk program
  (416) 813-6780
  Geographic region: province of Ontario
  Accepts calls from: the public and health care professionals

Clinical teratology resources

Briggs GG, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. 6th ed. Baltimore: Lippincott Williams & Wilkins Publishers; 2002.

Drugs and pregnancy. 2nd ed. Gilstrap LC III, Little BB, editors. New York: Chapman & Hall; 1998

Friedman JM, Polifka JE. *Teratogenic effects of drugs: a resource for clinicians*. 2nd ed. Baltimore: Johns Hopkins University Press; 2000.

Maternal-fetal toxicology: a clinician's guide. 2nd ed. Koren G, editor. New York: Marcel Dekker, Inc.; 1994.

Schardein JL. *Chemically induced birth defects*. 3rd ed. New York: Marcel Dekker; 2000.

Scialli AR, Lione A, Boyle Padgett GK. *Reproductive effects of chemical, physical, and biologic agents–REPROTOX*. Baltimore: Johns Hopkins University Press; 1995.

Shepard TH. *Catalog of teratogenic agents*. 10th ed. Baltimore: Johns Hopkins University Press; 2001.

Web site resources

- Agency for Toxic Substances and Disease Registry (ATSDR): http://www.atsdr.cdc.gov
- Clinical Teratology Web site: http://depts.washington.edu/~terisweb/
- NIEHS Center for the Evaluation of Risks to Human Reproduction (CERHR): http://cerhr.niehs.nih.gov
- Organization of Teratology Information Services (OTIS): http://www.otispregnancy.org/
- Teratology Society: http://teratology.org/
- US EPA Chemicals in the Environment: OPPT Chemical Fact Sheets: http://www.epa.gov/opptintr/chemfact/

Correspondence to: *Dr. Janine E. Polifka, TERIS, Box 357920, University of Washington, Seattle WA 98195-7920, USA; fax 604 875-3490; polifka@u.washington.edu*