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Human Teratogens Update 2011: Can We Ensure Safety during Pregnancy?

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Abstract

Anniversaries of the identification of three human teratogens (i.e., rubella virus in 1941, thalidomide in 1961, and diethylstilbestrol in 1971) occurred in 2011. These experiences highlight the critical role that scientists with an interest in teratology play in the identification of teratogenic exposures as the basis for developing strategies for prevention of those exposures and the adverse outcomes associated with them. However, an equally important responsibility for teratologists is to evaluate whether medications and vaccines are safe for use during pregnancy so informed decisions about disease treatment and prevention during pregnancy can be made. Several recent studies have examined the safety of medications during pregnancy, including antiviral medications used to treat herpes simplex and zoster, proton pump inhibitors used to treat gastroesophageal reflux, and newer-generation antiepileptic medications used to treat seizures and other conditions. Despite the large numbers of pregnant women included in these studies and the relatively reassuring results, the question of whether these medications are teratogens remains. In addition, certain vaccines are recommended during pregnancy to prevent infections in mothers and infants, but clinical trials to test these vaccines typically exclude pregnant women; thus, evaluation of their safety depends on observational studies. For pregnant women to receive optimal care, we need to define the data needed to determine whether a medication or vaccine is "safe" for use during pregnancy. In the absence of adequate, well-controlled data, it will often be necessary to weigh the benefits of medications or vaccines with potential risks to the embryo or fetus.

INTRODUCTION

The year 2011 brought some key anniversaries for scientists with an interest in teratology. Seventy years ago, in 1941, Norman Gregg, an Australian ophthalmologist, identified rubella as a human teratogen after noting a characteristic form of congenital cataracts in 78 infants, 68 of whom had been born to mothers with rubella during pregnancy (Gregg, 1941). Development of a vaccine against rubella and a vaccination program subsequently resulted in elimination (defined as absence of ongoing transmission in a geographic area) of rubella and congenital rubella syndrome from the United States (Centers for Disease Control and Prevention, 2005; Reef and Cochi, 2006). Fifty years ago, data suggesting that thalidomide

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exposure during pregnancy causes birth defects first became available. In November of 1961, Lenz presented data on 52 infants born to mothers taking thalidomide during pregnancy at a meeting of the German Society for Pediatric Medicine, and he later received 115 additional reports of similarly affected infants from physicians in Germany, Belgium, Sweden, and England (Lenz, 1962). In December of 1961, McBride published a letter in *Lancet*, noting severe abnormalities among offspring born to mothers on thalidomide during pregnancy, and asked whether other physicians had seen abnormalities among infants whose mothers had taken this medication during pregnancy (McBride, 1961) In a letter to *Lancet* published in early 1962, Lenz reported the specificity of the findings (e.g., an unusual type of limb defects, hemangiomata, absent auricles) in the cases he had collected (Lenz, 1962). Identification of thalidomide as a teratogen and the resulting decrease in sales of the medication resulted in an abrupt decrease in the number of the cases with the characteristic limb defects (Običan and Scialli, 2011). Forty years ago, in 1971, Herbst et al. reported a new association between maternal diethylstilbestrol use during pregnancy and occurrence of adenocarcinoma of the vagina in their daughters 15 to 20 years later in the *New England Journal of Medicine*. The authors compared clinical histories from eight patients who presented to New England Hospitals with this rare tumor in their teens and early 20s to those from matched controls, and found that seven of eight mothers of the case patients had been treated with diethylstilbestrol during pregnancy, compared to none in the control group (Herbst et al., 1971). These findings raised the specter of effects of teratogens occurring many years after the prenatal exposure (Goodman et al., 2011).

Identification of new human teratogens is a key role for members of the Teratology Society and readers of the *Birth Defects Research* journals because recognition of teratogenicity can lead to prevention of birth defects caused by these agents (Običan and Scialli, 2011). However, determining whether an agent is a teratogen is not as straightforward as one might think. Even some “classic” teratogens such as rubella virus and thalidomide were not immediately accepted by the medical community as causes of birth defects (Swan, 1944; Warkany, 1988).

An equally important responsibility for researchers and clinicians in teratology is to assess the safety of medications and vaccines used during pregnancy. Recent data suggest that medications are commonly used during pregnancy. In one study, about half of the pregnant women in the United States were taking one or more prescription medications in 2008 (Mitchell et al., 2011). However, limited data are available on the safety of medications used during pregnancy: a recent review of prescription medications approved by the U.S. Food and Drug Administration (FDA) from 2000 to 2010 showed that the teratogenic risk was undetermined in 97.7% (Adam et al., 2011). In addition, certain vaccines (e.g., against influenza and tetanus, diphtheria, and pertussis) are recommended for use during pregnancy to protect the mother and/or infant from disease (CDC, 2011a; CDC, 2011b). For women to receive optimal care during pregnancy, we need to better define what data are needed to determine whether a medication or vaccine is “safe” for use during pregnancy. In addition, in the absence of adequate, well-controlled data, it is important to determine how best to weigh the benefits of medications or vaccines with potential, but often unknown, risks to the embryo or fetus. Another essential concern is to understand how we can communicate these

complicated issues to health care providers and pregnant women faced with decisions about these exposures during pregnancy (Conover and Polifka, 2011).

Several articles published in the past year have brought these issues to the forefront. For example, Pasternak and Hviid (2010a) examined the use of acyclovir, valacyclovir, and famciclovir, antiviral medications used to treat herpes simplex and herpes zoster, during the first trimester of pregnancy. Using a large nationwide cohort study for births in Denmark between January 1996 and September 2008, they compared outcomes of 1804 pregnancies exposed to one of these three antiviral medications to outcomes of unexposed pregnancies. Forty infants (2.2%) of babies born to mothers taking one of these medications had a major birth defect, compared to 2.4% of babies born to unexposed mothers (adjusted prevalence odds ratio [POR] of 0.89; 95% confidence interval [CI] 0.65–1.22). However, despite the large size of this study, with 1561 women exposed to acyclovir, the most commonly used of these medications, an accompanying editorial by Drs. James Mills and Tonia Carter (2010) noted that these data are not adequate to rule out this medication as a potential teratogen: “From a public health perspective, this study provides fairly strong reassurance that acyclovir is not a major cause of birth defects. However, this study leaves a key question unanswered – is acyclovir a teratogen?” The authors note that teratogens typically increase the risk for certain birth defects, rather than an increase in all birth defects (Mills and Carter, 2010). Thus, this study, despite its large size, had insufficient power to provide reassurance about the safety of these medications.

Proton-pump inhibitors (PPIs) are medications that are frequently used to treat gastroesophageal reflux, a common symptom among pregnant women. However, data on the use of PPIs during pregnancy are limited. An article by Pasternak and Hviid (2010a), using the same nationwide cohort study from Denmark, examined the use of these medications during pregnancy, with 3651 pregnancies exposed to any PPI and 1800 exposed to omeprazole. Neither exposure to any PPI or to omeprazole was associated with birth defects (adjusted POR, 1.10; 95% CI 0.91–1.34 for any PPI; adjusted POR, 1.05; 95% CI, 0.79–1.40 for omeprazole; Pasternak and Hviid, 2010b). But again, despite these relatively reassuring data with large numbers of exposed pregnancies, an accompanying editorial by Dr. Allen Mitchell noted that these data were insufficient to ensure safety: “The report on proton-pump inhibitors…is therefore both timely and important…however, these data provide only a broad –and incomplete – overview” (Mitchell, 2010).

Molaard-Nielson and Hviid, using the same Danish dataset and study design, evaluated the risk associated with use of certain antiepileptic medications during pregnancy (Mølgaard-Nielsen and Hviid, 2011). Treatment of epilepsy is challenging because several antiepileptic medications (e.g., phenytoin, valproic acid, and carbamazepine) have been associated with an increased risk for birth defects. In addition to treating epilepsy, antiepileptic medications are increasingly used to treat other conditions, such as migraines and bipolar disorders. Several newer-generation antiepileptic medications have become available, but the safety of these medications during pregnancy is unknown. The Danish authors focused their analysis on these newer-generation medications, including lamotrigine, oxcarbazepine, topiramate, gabapentin, and levetiracetam. Based on study of 1532 pregnancies exposed to these medications, maternal exposure during pregnancy was not associated with an increased risk

for birth defects (adjusted POR, 0.99; 95% CI, 0.72–1.36). Likewise, no increased risk was observed for the more frequently used of these medications, lamotrigine (1019 exposed women; adjusted POR, 1.18; 95% CI, 0.83–1.68) and oxcarbazepine (393 exposed women; adjusted POR, 0.86; 95% CI, 0.46–1.59). The numbers of women exposed to the other medications were small, ranging from 108 for topiramate to 58 for levetiracetam, making inferences regarding the safety of these medications difficult. Similar to the limitations noted for the previous two studies by this group, the numbers of cases exposed, even to the more frequently used medications, were insufficient to examine the risk for specific defects. As an example, among the 1532 pregnancies exposed to these newer-generation antiepileptic medications, only two infants were born with orofacial clefts. The authors appropriately noted these limitations and commented that while topiramate, gabapentin, and levetiracetam did not seem to be major teratogens, their study was unable to exclude minor to moderate increases in the risk for birth defects.

Of note, the article by Mølgaard-Nielsen and Hviid (2011), published in the May 18, 2011, issue of the *Journal of the American Medical Association*, did not include mention of the decision posted online in March of 2011 by the FDA to make a labeling change for topiramate from Pregnancy Category C (meaning that animal studies suggest a potential fetal risk or are lacking and that there are no adequate, well-controlled human studies available to assess safety) to Pregnancy Category D (meaning that there is positive evidence of human fetal risk, but that the benefits of use may exceed the risks for some women; Food and Drug Administration, 2011). The FDA cited data presented in June 2010 at the Teratology Society meetings (Hernandez-Diaz et al., 2010) from the North American Antiepileptic Drug Pregnancy Registry that suggested that women taking topiramate during pregnancy were significantly more likely to have an infant with a cleft, compared to women in the general population; two topiramate-exposed infants (0.69%) had an isolated cleft lip, compared to an expected prevalence of isolated cleft lip in the general population of around 0.07%. Similarly, the UK Epilepsy and Pregnancy Register reported a 16-fold increased risk for orofacial clefts associated with topiramate exposure during pregnancy, compared to the background rate in the population (Hunt et al., 2008).

Concerns about topiramate have also been raised because of its inclusion in combination with phentermine as a potential therapy for obesity. This combination treatment, called Qnexa, was studied in clinical trials and submitted to the FDA for approval. In those trials, this combination was reportedly well tolerated and was associated with significant weight loss, making it a promising new treatment for obesity. Given the increasing prevalence of obesity in the United States, with more than one third of U.S. women ages 20 to 39 years categorized as obese in 2007 to 2008 (Flegal et al., 2010) and the many adverse outcomes (including adverse pregnancy outcomes) associated with obesity (Scialli, 2006), a safe and effective treatment for obesity would be of great interest to women of childbearing age. However, in October 2010, the FDA did not approve the initial application for Qnexa, in part because of concerns for an increased risk for oral clefts when used during pregnancy. Their review included the epidemiologic data on topiramate exposure during pregnancy already cited, in addition to supportive animal data and information from the FDA's review of the Adverse Events Reporting System database, which showed 64 infants with birth

defects whose mothers were exposed to topiramate, including 11 infants with cleft lip and/or cleft palate (Roberts, 2010). Additional data on the effects of topiramate during pregnancy are clearly needed to provide more information on its use as an isolated treatment or used in combination with phentermine as a treatment for obesity.

Another event that has recently increased awareness of the need for more data on the safety of medications and vaccines during pregnancy is the 2009 H1N1 pandemic, and this experience highlights the need to weigh the benefits of medications and vaccines with the potential risks. Based on information available from previous pandemics and from seasonal influenza, pregnant women were anticipated to be at increased risk for influenzaassociated complications (Rasmussen et al., 2008). Thus, pre-pandemic recommendations were developed that in a pandemic, pregnant women should receive prompt empiric treatment with an antiviral medication (the specific medication to be used was to be based on antiviral sensitivity patterns; Rasmussen et al., 2009). It was expected that the benefits of antiviral treatment would outweigh the potential, but unknown, risks to the embryo or fetus associated with antiviral medication use. Before the pandemic began, data on the use of antiviral medications during pregnancy were very limited. For example, data on oseltamivir use during pregnancy were limited to 61 reports of oseltamivir-exposed pregnancies during the post-marketing period, and data on zanamivir were even more limited – only three zanamivir-exposed pregnancies were reported during the clinical trials for this medication (Rasmussen et al., 2009). In addition, because influenza vaccine protects not only the pregnant mother from influenza, but also her infant, who is not eligible to receive an influenza vaccine until 6 months of age (Zaman et al., 2008), it was recommended that pregnant women be a priority group to receive a pandemic vaccine, once it became available. However, it was recognized that although observational data regarding use of seasonal influenza vaccine during pregnancy have been reassuring (Tamma et al., 2009), well-controlled studies with sufficient power to assess the risks of individual birth defects were not available. In addition, given the increased risk for adverse outcomes associated with hyperthermia during pregnancy (Moretti et al., 2005), it was recommended that pregnant women with fever receive antipyretic treatment, and after review of the available antipyretic medications, acetaminophen was deemed to be the best option (Rasmussen et al., 2009). However, even for a commonly used medication like acetaminophen, data that would ensure safety were not available. Thus, public health recommendations were made based on weighing the benefits of treatment or prophylaxis against the potential risks to the embryo or fetus.

Data on effects of the 2009 H1N1 pandemic on pregnant women have become available in the two years since the pandemic. These data suggest that pregnant women are more than four times as likely to be hospitalized, compared to the general population (Jamieson et al., 2009). In addition, pregnant women made up a disproportionate number of deaths; even though pregnant women make up about 1% of the general population, 5% of deaths in the early wave of the pandemic were among pregnant women (Jamieson et al., 2009). Deaths occurred in all three trimesters, and occurred even in women for whom the only risk factor for severe illness was pregnancy. Finally, pregnant women who received antiviral medications within the first two days after symptom onset were much less likely to be admitted to an intensive care unit or to die (Siston et al., 2010). Since the pandemic,

additional data have become available on the safety of influenza medications (Tanaka et al., 2009; Greer et al., 2010) and of seasonal and monovalent 2009 H1N1 vaccine (Moro et al., 2011a; Moro et al., 2011b), and all have been reassuring. Based on these data, it seems likely that the risks associated with antiviral medications or with influenza vaccine are outweighed by the benefits of early treatment or of prevention of influenza for pregnant women. However, further data are needed so that risks can be appropriately assessed.

The experience with the 2009 H1N1 pandemic also underscores the difficulty with communicating issues regarding benefits and potential risks of medications to health care providers and pregnant women. Despite clear public health recommendations for empiric treatment of pregnant women with suspected influenza with oseltamivir, treatment was often delayed, and as noted previously, delay in antiviral treatment was associated with severe outcomes (intensive care unit admission or death; Siston et al., 2010). One reason that likely contributed to treatment delays is the reluctance by pregnant women to take medications during pregnancy that are perceived as possibly harmful to the embryo or fetus (Lynch et al., 2011). Despite reassuring data about the safety of influenza vaccine during pregnancy and information on the severity of influenza among pregnant women, about 10% of obstetrician-gynecologists surveyed did not recommend seasonal influenza vaccination in the first trimester of pregnancy because of concerns about its safety (Kissin et al., 2011). Educational efforts for pregnant women and their health care providers about the benefits and potential risks of exposures during pregnancy need to use communication strategies shown to be effective (Conover and Polifka, 2011).

The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) is a study aimed at improving understanding of the effects of antiviral medications and influenza vaccines during pregnancy (Schatz et al., 2011). VAMPSS uses two complementary study designs: a prospective cohort identified through the Organization of Teratology Information Specialists Research Center at the University of California San Diego and a case-control study conducted through the Slone Epidemiology Center at Boston University. The prospective cohort arm of the study will compare pregnancy outcomes of women who have received an influenza vaccine or antiviral medication to women who were not exposed. A wide variety of outcomes can be analyzed, including spontaneous abortion, fetal death, preterm birth, small for gestational age, preeclampsia, and presence of a malformation. The case-control study design focuses on specific major malformations identified through hospitals and birth defects surveillance systems. Mothers of babies with (cases) and without (controls) malformations are interviewed within six months of delivery about exposures to influenza vaccine (seasonal and 2009 H1N1) and antiviral medications, as well as about potential confounding factors. The use of both cohort and case-control study designs is advantageous, given that each study design has its strengths and limitations and no one methodology is sufficient to determine if an exposure is safe during pregnancy.

VAMPSS investigators have addressed the issue of the difficulty in assessing safety in their study by setting up “safety thresholds” that specify when data will be reviewed by an independent advisory committee. An odds ratio of ≤1.0 with an upper 95% confidence bound of ≤4.0 may be defined by the committee as “no evidence of risk”, whereas, an odds

ratio of ≤1.0 with an upper 95% confidence bound of ≤2.0 may be defined as “evidence of relative safety” (Schatz et al., 2011).

Acetaminophen was also widely used during the pandemic to treat fever, and since the pandemic, additional data have become available regarding risks to the embryo or fetus after use of acetaminophen during pregnancy. In 2010, Feldkamp et al. reported data from the National Birth Defects Prevention Study that showed no increased risks with maternal acetaminophen exposure for each of over 50 birth defects (Feldkamp et al., 2010). Before the pandemic, some studies had shown an association between maternal acetaminophen use and asthma in childhood (Shaheen et al., 2002; Koniman et al., 2007; Persky et al., 2008; Rebordosa et al., 2008; Garcia-Marcos et al., 2009), although not all studies had identified an association (Kang et al., 2009). Two additional studies became available after the pandemic, but these have failed to quell the controversy over this issue. A study by Perzanowski et al. (2010) supported an association; maternal acetaminophen use was associated with current wheezing (risk ratio, 1.71; 95% CI, 1.20–2.42), with risk increasing as the number of days of acetaminophen use increased (Perzanowski et al., 2010). In contrast, a study by Bakkeheim et al. (2011) showed no association between prenatal acetaminophen use and asthma at age 10 years (Bakkeheim et al., 2011). In a recent review Scialli et al. concluded that data to support a causal association are currently inconclusive (Scialli et al., 2010).

Similar to the way the 2009 H1N1 pandemic raised questions about the safety of influenza medications and vaccines during pregnancy, the recent outbreak of pertussis in the United States has also raised the issue of safety of vaccination with the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine during pregnancy. Pertussis (also known as whooping cough) is a respiratory illness caused by the bacteria *Bordetella pertussis*. Pertussis is transmitted easily between persons by coughing or sneezing while in close contact. In 2010, the state of California reported the highest number of cases of pertussis (9120) with onset in 2010 in 63 years and the highest rate (23.3 cases per 100,000) in 52 years. During 2010, nearly 10% of cases required hospitalization (55% were <3 months of age and 72% were <6 months of age), and there were 10 deaths, 9 in infants <2 months of age (California Department of Public Health, 2011).

Vaccination can reduce the risk for pertussis illness; however, infants <2 months of age account for the majority of pertussis cases, hospitalizations, and deaths, but are too young to be vaccinated (CDC, 2011b). Beginning in 2005, the Advisory Committee on Immunization Practices (ACIP), which provides advice and guidance to the CDC regarding vaccine-preventable diseases, recommended “cocooning” (vaccination of mothers and other family members of newborn infants) as a strategy to protect infants from pertussis. However, this strategy has been challenging to implement on a large scale (Healy et al., 2009; Healy et al., 2011). Given that transplacental maternal antibodies might protect infants from vaccine-preventable disease, the ACIP recently considered Tdap vaccination during pregnancy as an option.

ACIP deliberations regarding Tdap vaccination during pregnancy addressed several issues including evidence related to the safety of Tdap vaccine during pregnancy, to the protection

of infants from pertussis from transplacental maternal antibodies, and to the possibility of interference with the infant's immune response to their primary vaccination with diphtheria toxoid, tetanus toxoid, and acellular pertussis (DTaP) vaccination. For all of these issues, definitive data were lacking. Because prelicensure studies of Tdap vaccine had excluded pregnant women, available information on the safety of Tdap during pregnancy was limited to unpublished data from the Vaccine Adverse Event Reporting System and pharmaceutical company-sponsored pregnancy registries along with a few small published studies (Talbot et al., 2010; CDC, 2011b; Gall et al., 2011). However, the ACIP found the available data on safety to be reassuring. In addition, tetanus and diphtheria toxoid vaccines have been used widely during pregnancy throughout the world for the prevention of neonatal tetanus, and studies suggest that these vaccines are not teratogenic (Silveira et al., 1995; Czeizel and Rockenbauer, 1999). Although maternal vaccination with Tdap vaccine during pregnancy has not yet been shown to protect infants from pertussis, infants born to mothers who received Tdap vaccine before or during pregnancy have higher levels of anti-pertussis antibodies in cord blood, compared to infants born to unvaccinated mothers, suggesting that the infant will be protected (Gall et al., 2011; Leuridan et al., 2011). Whether maternal vaccination could blunt the infant's immune response to vaccination against pertussis is also unknown; however, data suggest that blunting would not persist, given that maternal pertussis antibody levels decline quickly after birth, with a half-life of approximately six weeks (Van Savage et al., 1990; Healy et al., 2004; Van Rie et al., 2005; Hardy-Fairbanks et al., 2010). Based on a review of these data on the risks and benefits of Tdap vaccination during pregnancy, ACIP recommended that health care providers administer Tdap vaccine during pregnancy, preferably during the third or late second (after 20 weeks gestation) trimester (CDC, 2011b).

In conclusion, determining whether a medication or vaccine is "safe" for use during pregnancy is challenging. The mean time for a medication approved by the FDA since 1980 and initially classified as having an undetermined risk by the Teratogen Information System to be assigned a more precise risk is 27 years (Adam et al., 2011). This lack of adequate information leaves pregnant women and their health care providers without the evidence base needed to guide decisions about treatment and prevention during pregnancy (Chambers et al., 2008). To remedy this predicament, more research is needed to understand causes of birth defects and other adverse outcomes. Understanding the basic mechanisms of teratogenesis is also essential. Careful consideration needs to be made as to when it is appropriate to include pregnant women in clinical trials (Chervenak and McCullough, 2011). Given that different study designs have strengths and limitations in identifying risks of exposures during pregnancy, complementary study designs (e.g., cohort and case-control studies) should be used to assess potential risks of exposures during pregnancy. Studies may benefit from criteria set in advance to define "safety", similar to those defined by VAMPSS (Schatz et al., 2011). However, in the meantime, pregnant women, their health care providers, and public health professionals will need to continue to balance the benefits of medication or vaccine with the potential, but unknown, risks. More research is needed on how to communicate this complicated information of risks and benefits and the uncertainty of our current knowledge to pregnant women and their partners.

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