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Emerging Issues in Teratology: An Introduction

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Teratology is the study of congenital anomalies and their causes, and interest in teratology has been longstanding, with Egyptian wall paintings depicting children with birth defects over 5,000 years ago [Barrow, 1971]. By definition, teratogenic factors include both non-genetic and genetic factors that increase the risk for birth defects [Fraser, 2010]; however, traditionally, the term “teratogenic” has been used to refer to non-genetic factors that cause birth defects. The study of human teratogenic exposures is a relatively new one, emerging in the past 70 years. Before maternal rubella infection during pregnancy was identified as a cause of birth defects and developmental disabilities in 1941 by an ophthalmologist, Norman Gregg, birth defects were generally believed to be inherited [Gregg, 1991; Webster, 1998]. The uterus was thought to serve as a barrier, protecting the infant from the effects of external factors [Fraser, 2010]. But recognition of maternal rubella syndrome and subsequently, of thalidomide as a cause of birth defects in 1961 by McBride and Lenz [McBride, 1961; Lenz and Knapp, 1962], increased awareness of the effects that non-genetic factors could have on the development of the embryo or fetus.

Much more is now known about teratogenic factors. Understanding these teratogenic exposures is important to geneticists and genetic counselors for several reasons. First, teratogenic conditions need to be included in the differential diagnosis for children and adults presenting to genetics clinic. Clinicians need to ask about potential exposures during pregnancy, be aware of those exposures recognized as causing adverse outcomes, and finally, think beyond what is known, to consider whether an exposure could be the cause of the abnormalities observed in a particular patient. In the past, key observations by astute clinicians have often been critical to the recognition that a particular exposure could be related to an adverse outcome [Carey et al., 2009]. Another reason that geneticists and genetic counselors need to know about teratogenic exposures is that genetic clinicians often serve as a source of information about these exposures. Clinicians who see women during pregnancy are often asked about the safety of a particular medication, and families who have had a child with a birth defect or developmental disability often also ask about whether a particular exposure during their pregnancy might have caused the defects in their child. Finally, identification of non-genetic factors that increase the risk for adverse outcomes can lead to the development of strategies for primary prevention, such as those developed for the prevention of fetal alcohol syndrome, following identification of alcohol as a teratogen [Rasmussen et al., 2009].

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Recent years have brought incredible advances in the world of genetics, with cytogenetic microarray analysis [Lu et al., 2008] and exome sequencing [Biesecker, 2010] as two recent examples. These advances have improved the information available to physicians, patients, and families about causes of birth defects. Significant improvements in the understanding of teratogenic exposures have also occurred in recent years. The goal of this special issue is to provide readers of *Seminars in Medical Genetics* with an update of these advances. We have selected topics that we believe are timely and have been fortunate to recruit authors who are experts and leaders within their field.

The first article in this issue is a review of teratogenic exposures by Običan and Scialli. These authors review recognized teratogenic exposures and how these exposures were determined to be related to birth defects. Their review provides a historical context to the special issue and presents an overview of our current knowledge in this area. While the authors emphasize that clinicians involved in counseling regarding potential teratogenic exposures need to have access to updated sources of information, clinicians need to be aware of exposures that are recognized as teratogenic and the outcomes associated with them.

The next article by Friedman continues on this theme. The article entitled “How can we be sure an exposure really is teratogenic in humans?” raises a critical issue: that in order for us to recognize an exposure as teratogenic, pregnant women need to have been exposed and to have had an adverse outcome. Friedman notes that the goal of clinical teratology is to recognize that an agent causes adverse outcomes as quickly as possible and reviews the different methodologies that are used to assess teratogenicity.

The next article assesses our current state of knowledge (and lack of knowledge) regarding the teratogenic effects of maternal prescription medication use during human pregnancy. In this article, Adam et al. find that the risk in human pregnancy for 172 drug treatments approved by the U.S. Food and Drug Administration between 2000 and 2010 is currently undetermined for 97.7%. In addition, the authors estimate that it takes almost 27 years, on average, for a medication initially classified as having an “undetermined” risk to be given a more specific risk classification. The authors call for a more active approach to post-marketing surveillance of medications during pregnancy.

The next section of the special issue summarizes the methods used to determine whether a particular exposure is teratogenic. The first article by Daston describes laboratory models that are used to assess the teratogenic potential of various exposures. Regulatory requirements for evaluating developmental toxicity of chemicals and medications focus on animal models, typically including both a rodent and non-rodent species. The issues of concordance between different animal species and between results of animal studies and the human experience are discussed in the article. New laboratory methods for assessment of developmental toxicity, including in vitro studies and computational approaches, are also discussed.

The topic of the article by Jones and Carey is the importance of dysmorphology in the identification of previously unrecognized human teratogenic exposures. The authors note that astute clinicians have played a key role in the identification of most exposures that are

teratogenic in humans by recognizing the association between a particular novel phenotype in the child and a rare exposure that the mother had during pregnancy. The limitations of the "astute clinician" approach and the need for confirmation of these findings by other studies are also discussed.

The article by Chambers discusses the use of Teratology Information Services to assess teratogenicity. The primary role of these services is to furnish pregnant women and their health care providers with information on the fetal effects of medications and other exposures during pregnancy. However, these services have also been used to ascertain pregnant women with specific pregnancy exposures and unexposed control women for research studies. Chambers discusses the strengths and limitations of these studies and introduces new strategies that have been developed to address some of the limitations of this approach.

Given that birth defects are a rare outcome, one of the most common approaches used to identify teratogenic exposures is the case–control study. Werler et al. review the case–control design and discuss several examples of the use of case–control studies in teratology research. This article highlights several epidemiologic issues that clinicians must consider when interpreting data from a case–control study. The authors also discuss two specific case– control studies of birth defects, the National Birth Defects Prevention Study and the Slone Epidemiology Center Birth Defects Study, which provide much of the information that has recently become available on associations between pregnancy exposures and birth defects.

The article by Howard et al. provides a summary of the approach taken by the U.S. Food and Drug Administration to watch for teratogenic signals among FDA-approved medications. The article provides examples of how clinical and epidemiological data are used to develop pregnancy labeling for medications. The article also discusses FDA's authority to require postmarketing studies when a concern for safety (e.g., potential teratogenicity) has been raised. Finally, the article discusses FDA's plans for changes to pregnancy labeling of medications that will include elimination of the current letter categories (A, B, C, D, and X) and their replacement with narrative summaries that include a section on clinical considerations that will assist clinicians to weigh the risks and benefits of treating a particular pregnant woman with the medication. The Proposed Pregnancy and Lactation Labeling Rule is currently undergoing clearance at the FDA.

Most birth defects are believed to result from a combination of genetic and non-genetic factors. Teratogenic birth defects also have a genetic component, as evidenced by the fact that some women exposed to even potent teratogens have normal pregnancy outcomes and the risk of recurrence in subsequent pregnancies if the exposure continues is much greater than the risk of occurrence in the first pregnancy [Burd and Martsolf, 1989; Malm et al., 2002]. In the article by Wlodarczyk et al., the data supporting the role of genetic factors (maternal and fetal) in the susceptibility to birth defects due to teratogens are presented. Included in this article is information on gene-environment interactions involving factors that influence the risk for birth defects, including folic acid, cigarette smoking, alcohol, maternal hyperglycemia secondary to diabetes, and anti-epileptic medications.

The available data on the safety and risks of exposures during pregnancy are complex, and communicating these complicated issues to pregnant women is challenging, especially when continued exposure may be necessary for the health of the mother and her ability to continue the pregnancy. In the article “The art and science of teratogen risk communication,” Conover and Polifka discuss key issues in communicating these issues that are often based on limited and sometimes conflicting data. These authors discuss limitations in health literacy and numeracy (the ability to understand numbers) that are common among the general public and can result in misinterpretation of the data presented. Several different strategies for improving the communication regarding pregnancy exposures are described.

When a pregnancy exposure is identified as teratogenic, it is imperative to minimize the number of pregnancies exposed. Programs that focus on prevention of some specific teratogenic exposures, such as thalidomide and isotretinoin, have been developed [Honein et al., 2007; Bwire et al., 2011]. However, ensuring that women are not exposed to known teratogens has often proved to be difficult, as evidenced by the fact that alcohol and isotretinoin exposures continue to occur, despite strong evidence for their teratogenicity [Honein et al., 2007; Rasmussen et al., 2009]. Evidence regarding risks and benefits need to be carefully considered by clinicians when the risk/benefit ratio is less clear, as with antiepileptic medications [Molgaard-Nielsen and Hviid, 2011]. Gilboa et al. perform a modeling exercise to show the potential public health impact of a program designed to minimize exposure to two antiepileptic medications (valproic acid and carbamazepine) that have been shown to increase the risk for certain birth defects. These data show that altering prescribing practices to avoid use of these medications could reduce the number of infants born with the birth defects spina bifida and cleft palate. This approach could also be used to estimate the impact of changing prescribing practices for other medications. These results emphasize the importance of research to identify teratogenic exposures, followed by development of successful programs to minimize exposure to known teratogens.

The final article in the special issue is a Commentary by Parisi et al. The commentary notes that the lack of knowledge regarding medications and pregnancy includes not only information on teratogenicity, but also pharmacodynamics, pharmacokinetics, and efficacy. Because of this limited knowledge, pregnant women are more likely to be untreated or undertreated for serious medical illnesses, putting themselves and their babies at risk. Their article calls for more research into these areas.

In summary, we are hopeful that geneticists and genetic counselors will find this issue useful, and that the articles included here will better equip readers to understand the advances in the rapidly evolving field of teratology. In addition, we hope that the articles included here will provide readers with a better understanding of what is known, what is not known, and how to fill the gaps between the two. Geneticists must continue to serve as “alert clinicians” who recognize novel teratogen-induced syndromes and as translational investigators who seek to understand the cause of birth defects in every affected child they see.

Biographies

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REFERENCES

Barrow MV. A brief history of teratology to the early 20th century. Teratology. 1971; 4:119–129.

Biesecker LG. Exome sequencing makes medical genomics a reality. Nat Genet. 2010; 42:13–14. [PubMed: 20037612]

Burd L, Martsolf JT. Fetal alcohol syndrome: Diagnosis and syndromal variability. Physiol Behav. 1989; 46:39–43. [PubMed: 2682697]

Bwire R, Freeman J, Houn F. Managing the teratogenic risk of thalidomide and lenalidomide: An industry perspective. Expert Opin Drug Saf. 2011; 10:3–8. [PubMed: 21121869]

Carey JC, Martinez L, Balken E, Leen-Mitchell M, Robertson J. Determination of human teratogenicity by the astute clinician method: Review of illustrative agents and a proposal of guidelines. Birth Defects Res A Clin Mol Teratol. 2009; 85:63–68. [PubMed: 19107954]

Fraser, FC. Foreward: What is teratology?. In: Hales, B.; Scialli, A.; Tassinari, MS., editors. Teratology primer: Teratology society. 2010. p. viii-ix.http://connection.teratology.org/p/cm/ld/fid=6.

Gregg NM. Congenital cataract following German measles in the mother. 1941. Aust N Z J Ophthalmol. 1991; 19:267–276. [PubMed: 1789963]

Honein MA, Lindstrom JA, Kweder SL. Can we ensure the safe use of known human teratogens? The iPLEDGE test case. Drug Saf. 2007; 30:5–15. [PubMed: 17194167]

Lenz W, Knapp K. Thalidomide embryopathy. Arch Environ Health. 1962; 5:100–105. [PubMed: 14464040]

Lu XY, Phung MT, Shaw CA, Pham K, Neil SE, Patel A, Sahoo T, Bacino CA, Stankiewicz P, Kang SH, Lalani S, Chinault AC, Lupski JR, Cheung SW, Beaudet AL. Genomic imbalances in neonates with birth defects: High detection rates by using chromosomal microarray analysis. Pediatrics. 2008; 122:1310–1318. [PubMed: 19047251]

Malm H, Kajantie E, Kivirikko S, Kääriäinen H, Peippo M, Somer M. Valproate embryopathy in three sets of siblings: Further proof of hereditary susceptibility. Neurology. 2002; 59:630–633. [PubMed: 12196666]

McBride WB. Thalidomide and congenital abnormalities. Lancet. 1961; 2:1358.

Mølgaard-Nielsen D, Hviid A. Newergeneration antiepileptic drugs and the risk of major birth defects. JAMA. 2011; 305:1996–2002. [PubMed: 21586715]

Rasmussen SA, Erickson JD, Reef SE, Ross DS. Teratology: From science to birth defects prevention. Birth Defects Res A Clin Mol Teratol. 2009; 85:82–92. [PubMed: 19067401]

Webster WS. Teratogen update: Congenital rubella. Teratology. 1998; 58:13–23. [PubMed: 9699240]