



Ethics in Public Health Research

Fostering International Collaboration in Birth Defects Research and Prevention: A Perspective From the International Clearinghouse for Birth Defects Surveillance and Research

Lorenzo D. Botto, MD, Elisabeth Robert-Gnansia, MD, Csaba Siffel, MD, John Harris, MD, Barry Borman, PhD, and Pierpaolo Mastroiacovo, MD

The International Clearinghouse for Birth Surveillance and Research, formerly known as International Clearinghouse of Birth Defects Monitoring Systems, consists of 40 registries worldwide that collaborate in monitoring 40 types of birth defects. Clearinghouse activities include the sharing and joint monitoring of birth defect data, epidemiologic and public health research, and capacity building, with the goal of reducing disease and promoting healthy birth outcomes through primary prevention.

We discuss 3 of these activities: the collaborative assessment of the potential teratogenicity of first-trimester use of medications (the MADRE project), an example of the intersection of surveillance and research; the international databases of people with orofacial clefts, an example of the evolution from surveillance to outcome research; and the study of genetic polymorphisms, an example of collaboration in public health genetics. (*Am J Public Health*. 2006;96:XXX-XXX. doi:10.2105/AJPH.2004.057760)

THE INTERNATIONAL

Clearinghouse for Birth Defects Surveillance and Research (known until 2005 as the International Clearinghouse for Birth Defects Monitoring Systems) was founded in 1974 after the thalidomide tragedy of the 1960s. The Clearinghouse now includes 40 registries from developed and developing countries that jointly monitor 40 birth defects. In addition to monitoring, activities include public health research and capacity building to reduce disease and promote healthy outcomes through primary prevention. Specifically, the Clearinghouse monitors for teratogenicity of medications, an example of the intersection of surveillance and research; manages an international database of people with orofacial clefts, to promote outcome research; and has completed an international study of genetic polymorphisms of folate genes, to promote international public health genetic research.

Such international collaboration advances crucial public health goals related to healthy pregnancy and child survival. Sustained recognition and sup-

port of collaborating programs from governmental and international organizations is critically important to further these goals in developed and developing countries.

30 YEARS OF INTERNATIONAL COLLABORATION

The Clearinghouse began as a response to the threat of unrecognized teratogens. When they met in 1974 in Helsinki, Finland, in the aftermath of the thalidomide epidemic, representatives of birth defect registries from the Americas and Europe agreed to share and jointly monitor birth defect data in a regular and timely manner to help prevent such tragedies in the future.¹ To do so, they established the Clearinghouse with seed monies from the March of Dimes.

Since then, the Clearinghouse has evolved in size and scope. Forty registries (up from 10 in 1974) now collaborate to monitor 40 types of birth defects (up from 22 in 1974) among 3.5 million yearly births.² The Clearinghouse has also developed a

head office and coordinating center, the International Center on Birth Defects (ICBD), with seed monies from nongovernmental and governmental organizations (mainly from Norway, Italy, the European Commission, and the United States) and has established official relations with several like-minded international bodies including other birth defect networks and the World Health Organization.

As a result, the Clearinghouse has been able not only to continue the joint exchange and monitoring of birth defect data but also to conduct epidemiologic and public health research as well as help new countries develop and improve surveillance systems (Table 1). These 3 focus areas—surveillance, research, and capacity building—share the goal of reducing disease and promoting healthy outcomes through primary prevention. Therefore, they represent the natural evolution of the original mission of the Clearinghouse.

We selected 3 ongoing Clearinghouse activities, 1 in each of these 3 areas, as examples of creative and crosscutting efforts that



TABLE 1—Examples of International Collaboration in the International Clearinghouse for Birth Defects Surveillance and Research

| Area | Current Examples | Expanded Activities |
|--|--|---|
| Surveillance | Rapid and yearly assessment of 40 major birth defects. Monitoring of multiple congenital anomalies, teratogen-associated phenotypes, chromosomal anomalies, and associations with first-trimester exposure to medications | Include other outcomes (e.g., developmental disabilities); actively promote the use of data for public health action |
| Public health research and information dissemination | Birth defect occurrence in relation to folic acid policies and activities; increasing rates of gastroschisis and associated factors; international impact of birth defects; aspects of human genome epidemiology; database on typical orofacial clefts | Promote etiologic studies, disease registries, research involving non-Clearinghouse members, enrollment of areas of the world for which few data are currently available; develop information and educational tools on Web site |
| Program development | Increasing collaboration with other networks in Europe and the United States and with international organizations; ongoing advisory and technical support for developing programs | Develop guidelines and tools for birth defect surveillance and research for developed and developing countries, with emphasis on data sharing and regional activities |

Source. Information from <http://www.icbd.org>.

leverage existing systems to develop new data with limited additional resources: the ongoing collaborative assessment of the potential teratogenicity of first-trimester use of medications (the maternal drug exposure [MADRE] project), as an example of the intersection of surveillance and research; the development of international databases of people with orofacial clefts, as an example of the ongoing evolution from surveillance to outcome research and evaluation; and the international study of genetic polymorphisms in folate genes, as an example of the opportunities for international collaboration in public health genetics.

Other current surveillance activities are not discussed here but

can be found in the annual reports of the Clearinghouse, which are publicly available in printed form and electronically (visit <http://www.icbd.org>).

SEARCHING INTERNATIONAL REGISTRIES FOR UNSUSPECTED TERATOGENS

Maternal use of medication has accounted for clusters of birth defects in the past, such as those related to thalidomide³ and, more recently, retinoic acid.⁴ Moreover, the safety during pregnancy of many medications has not been conclusively established. Because women frequently use medications during

the first months of pregnancy,⁵ often before the pregnancy is recognized, even small teratogenic risks can result in many infants being affected. Registries of congenital malformations can provide crucial data to identify teratogenic effects of medications.

The analytic approach depends on the design of the registry, which in the Clearinghouse typically falls into 1 of 3 main types. In the first, the registry is built on the medical registration of all births, as occurs in the Nordic countries in Europe. The Swedish Medical Birth Registry, for example, contains prospectively collected information on drug use as reported by the pregnant woman at her first visit to the antenatal care system,⁶ and

this information has been used for evaluation of pregnancy outcome after exposure to drugs.^{7,8} The second type of registry is designed as an ongoing case-control study. Each case is matched with a control, which is often defined as the next nonmalformed birth of the same sex as the case. The third type, exemplified by most registries, includes cases but no controls and relies on the completion of special notification forms that list the malformations and medications used during the first trimester.

The first 2 types of registries lend themselves naturally to the study of associations between malformations and maternal use of medication; the third type of registry, which enrolls only cases, may also be helpful in this regard. The Clearinghouse has thus implemented the MADRE project as a collaborative study among several registries of the third type, the main features of which are summarized in Table 2.⁹

In MADRE, medications are cross-tabulated against malformations and a 2-by-2 table is constructed for each combination of medication and malformation. An infant is defined as a case infant if it has the malformation in question and as a control infant otherwise. An infant is defined as exposed if the mother used the drug in question during the first trimester and as unexposed otherwise. If exposures and malformations are unrelated, drug types and malformation types should be randomly distributed, and deviations from this distribution will show up as increased odds



TABLE 2—International Screening for Drug Teratogenicity: The MADRE (Maternal Drug Exposure) Project of the International Clearinghouse for Birth Defects Surveillance and Research

| Goal | Screen for potential teratogenicity of medications |
|---|---|
| Approach | Case-only study of cases of birth defects following reported exposure to maternal medication use during first trimester of pregnancy; all cases are malformed and all cases were exposed to some medication; analysis is through a modified case-affected control approach, stratified by registry |
| Current data | More than 15 000 cases of birth defects from 12 registries |
| Selected findings (antiseizure medications) | Confirmed classical associations: phenobarbital with oral clefts and heart defects; valproic acid with spina bifida, hypospadias, and heart defects; and carbamazepine and heart defects Testing associations suggested in literature: evaluated and confirmed the reported association between valproic acid and craniosynostosis |
| Evolution | Refine classification according to pathogenetic mechanisms; assess specific risks for multiple congenital anomalies; focus on selected major defects (heart defect subtypes, gastroschisis); increase registry participation |

ratios. Such deviations can be used to screen for associations that deserve further study.

This approach has limitations and strengths. By design, the approach lends itself to identifying differential effects of medications on malformations, so that drugs that increase risk equally for all birth defects will be missed. Classification of medications and malformations is also crucial. In MADRE, malformations are coded according to the *International Classification of Diseases, Ninth Revision* system adapted by the British Pediatric Association,¹⁰ and medications are coded according to the Anatomical Therapeutic Chemical system.¹¹ These systems have limitations that are being circumvented by further lumping and splitting of categories. International variability in the use of medications and in the occurrence of malformations is also a concern. In MADRE, all analyses are stratified by registry and evaluated for heterogeneity.

The main strength of MADRE is that it uses available data as an adjunct tool to screen for teratogens at low cost. Associations thus identified should be further assessed in other data sets. The international setting and the large sample size obtainable from collaborating registries also lead to improved statistical power and provide, to some extent, internal indicators of consistency. For example, an association is increasingly unlikely to be because of chance if it occurs simultaneously in different registries. Finally, because all cases are affected, differential recall of medication use is less of a concern than in a case-unaffected control setting.

The MADRE project now includes more than 15 000 cases. The analyses have detected several associations, both known (e.g., valproic acid and spina bifida) and new. New associations are considered as hypotheses to be tested on further samples, as was the case for the association

between corticosteroids and orofacial clefts. The first suggestion for such an association was reported in 1994,⁹ and 3 epidemiological studies since have confirmed a weak association^{12–14}; the association was confirmed in 2003 by the MADRE data.¹⁵ The MADRE database also is used to test associations as they appear in the literature. For example, we confirmed the suggested association between valproic acid and craniosynostosis (mainly trigonocephaly)¹⁶ but could not replicate the reported association between trimethoprim and malformations such as neural tube and cardiac defects.¹⁷

DEVELOPING INTERNATIONAL DATABASES: THE CASE OF OROFACIAL CLEFTS

Developing international databases of people with congenital malformations is crucial as one basis among many for elaborating and disseminating facts and

events that can then lead to improving health and preventing unnecessary suffering. On this premise and using craniofacial malformations as a model, the National Institute of Dental and Craniofacial Research and the Human Genetics Program at the World Health Organization, in September 2002, promoted the development of the International Database of Craniofacial Anomalies (IDCFA) and assigned its coordination to the ICBDB, the head office of the Clearinghouse (Table 3).

The international database properly is a set of databases that vary in topic and aims. At present, the efforts of IDCFA focus on developing the “International Perinatal Databases of Typical Orofacial Clefts” (IPDTC). As of July 2004, 56 registries had joined the data collecting effort, representing 36 countries: 21 in Europe; 12 in North, Central, and South America and the Caribbean; and Japan, South Africa, and the United Arab Emirates. Currently, data are available from more than 3.5 million births, and registries are expected to update their submissions yearly.

Although participation requires additional effort on their part, contributing programs, though at times strained for resources, can benefit in many ways. First, they benefit from increased visibility, nationally and internationally, as their data are used in this international collaboration and acknowledged. Moreover, program representatives who fulfill journal authorship guidelines are also recognized in



TABLE 3—International Database of Craniofacial Anomalies of the International Clearinghouse for Birth Defects Surveillance and Research

| | |
|-------------------|--|
| Goal | Long-term goal: assess the range of issues pertaining to people with craniofacial anomalies, including etiology, phenotype, impact, health and social outcomes, quality of health care services First step: build an ongoing international registry of people with typical orofacial clefts (perinatal database) |
| Support | World Health Organization (Human Genetics Program), National Institute of Dental and Craniofacial Research of the US National Institutes of Health |
| Approach | Stepwise approach, ongoing data collection from birth defect registries using standard case definitions, clinical classification (isolated, multiple congenital anomalies, syndromes), and centralized review |
| Current data | 5100 cases of typical orofacial clefts from 56 registries in the Americas, Europe, Middle East, South Africa, and Japan, ascertained among 3.5 million births (birth years 2001-2003) |
| Selected findings | Birth prevalence varies internationally, with high rates in Japan, Utah, Mexico, and low rates in Spain and Italy. Rates of cleft lip/palate (but not cleft palate alone) increase significantly with increasing latitude in Europe. The higher the rate of clefts, the higher the proportion of severe forms (cleft lip and palate), consistent with multifactorial model. Other available findings in perinatal database include distribution by clinical phenotype, gender, birth outcomes, birthweight and length of gestation, twinning, and maternal age |
| Evolution | Expand contributing area; evaluate syndromic and multimalformed infants; initiate prospective monitoring; enroll surgical and other treatment centers |

the authorship. Second, contributors have access to the entire data set for specific studies, as detailed in the study protocol. Contributors also benefit from the data review and cleaning as well as from the epidemiological expertise of the International Center on Birth Defects staff. Finally, contributors have control over the use of their data, as they have to approve publications and can choose not to be part of specific studies.

As of July 2004, information has been collected for 5432 cases of typical orofacial clefts identified among 3 529 582 births (Table 3). The overall rate of oral clefts is 15.4 per 10 000 births (including terminated pregnancies). The rates vary internationally, and the variation is driven mainly by the rates of cleft lip with or without cleft palate (CL±P). From the data of the 26 registries in Europe, it ap-

pears that rates of CL±P correlate directly with latitude ($r=0.61$; $P<.01$), with higher rates in the north and lower rates in the south. This correlation is not present for cleft palate.

In areas with high overall rates of orofacial clefts, cases of cleft lip and palate, the more severe form of primary palate defects, tend to represent a higher proportion of all cases than they do in areas with lower overall rates of orofacial clefts. This is consistent with the multifactorial model, which predicts that the more common the defect in a population the higher the proportion of severe forms of that defect. Other information that is currently available from the IPDTC includes the distribution of rates by clinical presentation of the child (isolated, multimalformed, syndrome), maternal age, gender, defect phenotype (e.g., bilateral vs

unilateral cleft lip), twinning status, pregnancy outcome (e.g., termination of pregnancy), birthweights, and length of gestation. (For more information, visit <http://www.who.int/genomics/anomalies/idcfa/en> and <http://www.icbd.org>.)

A further purpose of the international database is to stimulate the creation of specific databases of craniofacial anomalies. An International Database on Moebius Syndrome (Italy, United States, Brazil) was developed recently (for information, visit <http://www.icbd.org>), and plans are being formulated for the International Surgical Departments Database of Craniofacial Anomalies, which will collect information from surgical departments in defined areas (country, region, city). More generally, a goal of IDCFA is to assemble multiple databases, each with its own methods and aims, so that they

can collectively help answer a range of questions relevant to people with craniofacial anomalies, their families, and their health care providers.

PUBLIC HEALTH GENETIC RESEARCH: INTERNATIONAL OPPORTUNITIES

International collaboration in genetics provides a range of opportunities for improving public health research and prevention. For example, such collaboration can provide the fundamental molecular epidemiology of genes of public health importance, which is the basis for the study of gene–disease associations.¹⁸ International collaboration also helps researchers assess such associations across a wider and therefore more informative range of genotype frequencies and environmental exposures than would be feasible in any particular country. At the same time, collaboration provides quick access to larger study populations, with resulting improvement in the statistical power of the study.

Equity is a further consideration. In its 2002 report on genomics and world health,¹⁹ the World Health Organization underscored the potential for genome technology to exacerbate global health inequities if it is used only in selected “First World” countries. Organizations such as the International Clearinghouse for Birth Defects Surveillance and Research can help support international research by reaching populations in developed and underdeveloped



TABLE 4—International Collaboration in Genetics Within the International Clearinghouse for Birth Defects Surveillance and Research

| | |
|-------------------|---|
| Goal | Assess international variation of genotypes of public health importance and their relation to adverse birth outcomes; promote genomic capacity, particularly in developing world |
| Approach | Coordinate registries in developing and conducting anonymous systematic surveys of unaffected newborns; coordinate interlaboratory quality control |
| Current data | More than 7000 samples from 16 regions, collected systematically; information on the 677C→T allele of 5,10 methylenetetrahydrofolate reductase |
| Selected findings | Geographic variation of 677C→T allele, with high rates of homozygosity in China (particularly in the north), Mexico, and southern Italy; also ethnic variation, with high rates among Hispanics and low rates among people of African origin or ancestry; no gender variation |
| Evolution | Evaluate expanding survey to other genotypes (e.g., other folate genes) and other areas (e.g., in Asia and Africa); enroll affected infants for association studies |

countries; facilitating reciprocal access to skills, expertise, and technology; and supporting full participation of programs with low technology in high-level international collaborations.

One such successful collaboration within the framework of the Clearinghouse was supported in part by the Centers for Disease Control and Prevention's National Center on Birth Defects and Developmental Disabilities and the Italian Ministry for Research. This collaboration evaluated the 677C→T allele of 5,10 methylenetetrahydrofolate reductase, a folate-related gene, in well-defined populations from 14 areas in the Americas, Europe, Australia, and China.²⁰ As summarized in Table 4, the study identified significant geographic and ethnic variation in this specific genotype, which has been associated with an increased risk for neural tube defects.²¹ For example, a high frequency of homozygosity (20% or more of the population) for the variant allele was found in Mexico, northern China, and

southern Italy. Ethnic variability was also remarkable, with a high frequency of homozygosity (18%) among Hispanic Americans, intermediate frequency (11%) among non-Hispanic White Americans, and low frequency (<3%) among African Americans in a population-based sample in the Atlanta area.²⁰

From a practical perspective, this collaboration experienced the full range of capacities among partners. Some registries (e.g., China, Atlanta) could have entirely supported a local study, from sample collection to genetic testing and report writing, but chose to collaborate and thus, gain inclusion in a larger, stronger, and more meaningful study. Other programs (e.g., Israel, Mexico) had many of the capabilities but little funding, but, with some financial support (mainly for reagents), were able to provide more data and the participation of populations of interest. Many other programs were able to collect but not analyze samples and through this collaboration were able to partic-

ipate in novel genetic studies and generate locally relevant data. Finally, some programs participated in the discussions but not in the study and thus were able to develop some knowledge in areas such as study design, sample collection and storing, quality control, and data analysis.

Ultimately, this successful collaboration provides the basis for further public health research on other genotypes of public health importance in the context of a partnership of developed and developing countries.

OTHER MONITORING AND RESEARCH ACTIVITIES

In addition to the activities summarized in this report, the Clearinghouse conducts other ongoing and systematic epidemiological assessments of birth defects (Table 1). These include ongoing collaborative monitoring of selected conditions, performed both as rapid assessments (every 3 months) and as annual evaluations. Conditions such as Down syndrome and multiple congeni-

tal anomalies are monitored separately by ad hoc methods (e.g., using maternal age-specific analysis for Down syndrome). The annual data are used in public health research such as an assessment of birth defect rates in relation to folic acid recommendations and a retrospective case-control study on gastroschisis. After updating and further review, annual data have been used to create the World Atlas of Birth Defects, now in its second edition, to provide information on the prevalence and burden of congenital malformations worldwide.²² Updated information on these and other resources can be found in the annual reports of the Clearinghouse (visit <http://www.icbd.org>). In these and other activities, the Clearinghouse increasingly collaborates with other organizations, such as the European Surveillance of Congenital Anomalies and the National Birth Defects Prevention Network in the United States.

STRATEGIC DIRECTION

In 2004, on the occasion of the organization's 30th anniversary, under the chairmanship of one of the authors (B.B.), the ICBDMs initiated a strategic planning process in order to critically examine current activities and to redirect its efforts going forward. The strategic planning team consisted of a selective group of committed program directors with diverse opinions. As is the case with any strategic planning process, the lessons learned from past activities—both



strengths and weaknesses—will be used to inform future directions.

Lessons Learned, 1974 to 2004

First, monitoring congenital anomalies and publishing the demographics of who is at risk among large populations throughout the world has been an important first step. However, going forward, surveillance of birth defects needs to become the critical activity for Clearinghouse members. The team defined “monitoring” as an activity for which the primary task is counting accurately. “Surveillance,” on the other hand, begins with counting but involves systematic public health action as follow-up. This action might be etiologic research, advocacy, educating policymakers, or assessing the effectiveness of interventions such as folic acid fortification.

Second, conducting etiologic research, although an activity of some individual Clearinghouse members, has been underemphasized by the Clearinghouse as an organization. Since congenital anomalies are common—approximately 1 in 33 live births—and causes are mostly unknown, the only way to develop effective prevention strategies is to increase understanding about why congenital anomalies occur.

Third, between 1974 and 2004, the Clearinghouse had as a membership criterion that programs must monitor structural congenital anomalies. Many organizations that were effectively monitoring other common children’s disabilities with high mor-

bidity, such as prematurity or cerebral palsy, have not been part of the Clearinghouse.

Fourth, quarterly statistical surveillance and investigation of clusters of congenital anomalies, although useful services to communities, have not in 30 years of Clearinghouse operation resulted in the discovery of even one cause of any structural congenital anomaly anywhere in the world.

Strategic Direction of the Clearinghouse, 2004 Going Forward

The Clearinghouse has provided an invaluable international forum in which epidemiological data on structural congenital anomalies have been compiled, exchanged, and published. These activities will continue. However, the strategic planning team recommended the following changes for the future, subject to member ratification:

1. Surveillance rather than monitoring will be emphasized.
2. Non-Clearinghouse researchers will be invited to collaborate with Clearinghouse members to use the diverse population-based data, the core strength of Clearinghouse programs, to test important research hypotheses.
3. Surveillance programs that include children’s disabilities other than structural congenital anomalies will be invited to join the Clearinghouse.
4. There will be less emphasis on quarterly statistical monitoring and more emphasis on constant communication among Clearinghouse members.
5. The name of the organization will be changed to the International Clearinghouse for Birth Defects Surveillance and Research to reflect the strategic direction. (This has been ratified and implemented.)

FINAL CONSIDERATIONS

As international priorities change and technical capacity increases, the range of activities for organizations such as the Clearinghouse appear not so much to change but rather to expand. Surveillance remains a priority and is now increasingly geared toward providing timely information for action. Primary prevention of some birth defects, which was limited 30 years ago, is today feasible with folic acid and other interventions and requires promotion and evaluation. Etiologic research, through new tools (e.g., molecular genetics), can find unique avenues for progress through registry-based international collaboration. Developing countries, where most births now occur, must be supported in their concerns relating to birth defects and genetic diseases. In a time of information explosion and Internet-based communication, international networks can help provide multilingual content and a supranational conduit for disseminating crucial information on birth defects’ impact, health outcomes, and prevention.

Yet such remarkable possibilities can be made real only through a conscious investment in international collaboration. Such effort over 30 years has

produced remarkable results but has been based on limited funding and much in-kind work by partner programs. This is a testament to the activity of many but hardly a policy for sustainable development.

Crucial support has come from several institutions, both governmental (e.g., the US Centers for Disease Control and Prevention, the National Institutes of Health, the Norwegian and Italian governments, the European Commission) and nongovernmental (e.g., the March of Dimes). What is needed, as we move forward in the years ahead, is a concerted and sustainable effort by the international community, through national and international agencies, to support and sustain the international activities that it considers important and thus realize the possibilities of birth defect surveillance, research, and primary prevention for the world as a whole. ■

About the Authors

At the time of the study, Lorenzo D. Botto and Csaba Siffel were with the Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities, in Atlanta, Georgia; Elisabeth Robert-Gnansia was with the Institut Européen des Génomutations in Lyon, France; John Harris was with the California Birth Defects Monitoring Program in Berkeley, California; Barry Borman was with Public Health Intelligence in Wellington, New Zealand; and Pierpaolo Mastroiacovo was with the International Centre on Birth Defects, Rome, Italy, the head office of the International Clearinghouse for Birth Defects Surveillance and Research.

Requests for reprints should be sent to Lorenzo D. Botto, MD, Division of Medical Genetics, Department of Pediatrics, University of Utah, 2C412 SOM, 50 N Medical Dr, Salt Lake City, UT 84132 (e-mail: lorenzo.botto@hsc.utah.edu).



This article was accepted February 1, 2005.

Contributors

All authors helped to originate ideas, develop the framework, and write and review drafts of the article.

Acknowledgments

We acknowledge the support of the Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities (cooperative agreement No. U50/CCU207141), and of the World Health Organization, Human Genetics Program.

We thank the following Clearinghouse members, who, in addition to some of the authors (B.B., P.M., E.R.-G., J.H.), were involved in the strategic planning team: Eduardo Castilla, Hermien de Walle, David Erickson, Miriam Gatt, Lorentz Irgens, and Brian Lowry. Finally, we acknowledge the researchers and programs participating in the activities described in this article, including the many contributors to the International Perinatal Databases of Typical Orofacial Clefts, the MADRE study, and the international folate genetics study. (Contributors are listed in more detail at <http://www.icbd.org>)

Human Participant Protection

No protocol approval was needed for this review.

References

1. *Congenital Malformations Worldwide: A Report From the International Clearinghouse for Birth Defects Monitoring Systems*. New York, NY: Elsevier Science Publishers; 1991.
2. International Clearinghouse for Birth Defects Monitoring Systems. *Annual Report 2003*. Rome, Italy: International Centre for Birth Defects; 2003.
3. Lenz W. A short history of thalidomide embryopathy. *Teratology*. 1988; 38(3):203–215.
4. Lammer EJ, Chen DT, Hoar RM, et al. Retinoic acid embryopathy. *N Engl J Med*. 1985;313(14):837–841.
5. Headley J, Northstone K, Simmons H, Golding J, and the ALSPAC Study Team. Medication use during pregnancy: data from the Avon Longitudinal Study of Parents and Children. *Eur J Clin Pharmacol*. 2004;60(5):355–361.
6. National Board of Health and Welfare Centre for Epidemiology. Research Report: the Swedish Medical Birth Registry—a summary of content and quality. Available at: <http://www.sos.se/epc/english/Medical%20Birth%20Registry.htm>. Accessed November 3, 2005.
7. Källén B, Mottet I. Delivery outcome after the use of meclozine in early pregnancy. *Eur J Epidemiol*. 2003;(18): 665–669.
8. Källén B, Olausson PO. Monitoring of maternal drug use and infant congenital malformations. Does lorazepam cause hypospadias? *Int J Risk Safety Med*. 2001;14:115–119.
9. Robert E, Vollset SE, Botto L, et al. Malformation surveillance and maternal drug exposure: the MADRE project. *Risk Safety Med*. 1994;6:75–118.
10. *Classification of Diseases*. London, England: British Paediatric Association; 1987.
11. WHO Collaborating Center for Drug Statistics Methodology, Nordic Council on Medicines. *ATC Classification*. Oslo, Norway: Norwegian Institute of Public Health; 2005. Also available at: <http://www.whocc.no/atcddd>. Accessed November 3, 2005.
12. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. *Am J Med Genet*. 1999;86(3):242–244.
13. Edwards MJ, Agho K, Attia J, et al. Case-control study of cleft lip or palate after maternal use of topical corticosteroids during pregnancy. *Am J Med Genet*. 2003;120A(4):459–463.
14. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology*. 2000;62(6):385–392.
15. Pradat P, Robert-Gnansia E, Di Tanna GL, Rosano A, Lisi A, Mastroiacovo P. First trimester exposure to corticosteroids and oral clefts. *Birth Defects Res A Clin Mol Teratol*. 2003;67(12): 968–970.
16. Lajeunie E, Barcik U, Thorne JA, Ghouzzi VE, Bourgeois M, Renier D. Craniosynostosis and fetal exposure to sodium valproate. *J Neurosurg*. 2001; 95(5):778–782.
17. Hernández-Díaz S, Werler MM, Mitchell AA. Teratogen update: trimethoprim teratogenicity. *Birth Defects Res A Clin Mol Teratol*. 2004; 70(S10):276.
18. Khoury MJ, Little J. Human genome epidemiologic reviews: the beginning of something HuGE. *Am J Epidemiol*. 2000;151(1):2–3.
19. World Health Organization. Genomics and world health: report of the Advisory Committee on Health Research. 2002. Available at: <http://www3.who.int/whosis/genomics/pdf/genomics%5Freport.pdf>. Accessed November 3, 2005.
20. Wilcken B, Bamforth F, Li Z, et al. Geographical and ethnic variation of the 677C→T allele of 5,10 methylenetetrahydrofolate reductase (MTHFR): findings from over 7000 newborns from 16 areas world wide. *J Med Genet*. 2003; 40(8):619–625.
21. Botto LD, Yang Q. 5,10-Methylenetetrahydrofolate reductase gene variants and congenital anomalies: a HuGE review. *Am J Epidemiol*. 2000;151(9): 862–877.
22. International Clearinghouse for Birth Defects Monitoring Systems. *World Atlas of Birth Defects*. 2nd ed. Geneva, Switzerland: World Health Organization; 2003.