Utility of Family History Reports of Major Birth Defects as a Public Health Strategy

Paul A. Romitti, PhD

Department of Epidemiology, University of Iowa, Iowa City, Iowa

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ABSTRACT

A major birth defect is an abnormality that can affect the structure or function of an organ. In the United States, major birth defects are the leading cause of infant mortality and contribute substantially to childhood disability and morbidity. Globally, these conditions lead to the death of millions of infants and children annually. Patients with 1 or more affected family members may be at increased risk for having a child with a major birth defect; thus, accurate knowledge of these conditions among family members of their patients gives the clinician the ability to provide improved risk assessment and reproductive planning. Such knowledge can also serve as motivation for patients to adhere to healthy behaviors such as folic acid use or smoking cessation. To evaluate the utility of collecting family history reports of major birth defects as a public health strategy, 6 key criteria were examined by reviewing the relevant published literature. Overall, the review showed that major birth defects satisfied several of the criteria. Additional research is needed, however, regarding the awareness of parent reports of the occurrence of these conditions among relatives and how knowledge of birth defect diagnoses and related risk factors are transmitted among relatives. Such research needs to encompass not only immediate family members but also other first-degree and second-degree relatives. In summary, routine collection of family history reports of birth defects in pediatric practice holds promise as a public health strategy to reduce the burden of morbidity, mortality, and disability associated with major birth defects.
A positive family history of disease has often been ascribed to an underlying genetic susceptibility. In recent years, our understanding of specific genetic predispositions to the risk of disease has been enhanced through information provided by the Human Genome Project and related endeavors such as the International Haplotyping Mapping Project. To date, gene discovery using such information has accounted for a small proportion of the total burden of a particular disease (eg, BRCA1 mutations for breast cancer prevention). Less well understood is the contribution of a positive family history as a predictor of common chronic diseases that encompass both genetic and partial genetic origins (ie, multifactorial conditions).

For the pediatric patient, birth defects exemplify such multifactorial conditions. Birth defects can be grouped into 2 broad categories: major and minor defects. A major defect is an abnormality of an organ structure or function that results in physical disability, mental disability, or death, whereas a minor defect does not produce significant health consequences. Both major and minor defects can occur as isolated entities, affecting 1 organ system, or as multiple defects, affecting 1 or several organ systems. Alone, minor defects are not considered to have significant health consequences, although their presentation with 1 or more major defects can provide clues to an underlying genetic or teratogenic etiology. Conservatively, estimates suggest that a causal gene or teratogen accounts for <30% of defects that occur. For the remainder, the most likely explanation is a confluence of genetic and teratogenic exposures and, to a lesser degree, factors such as intrauterine constraint and amniotic bands that can lead to deformations and disruptions, respectively, of otherwise normally developed structures.

As with many common chronic diseases, multiple etiologies for major birth defects present challenges in disentangling risk associated with a reported family history of these conditions. Approaches to inferring risk of common chronic diseases on the basis of family history information have been attempted through calculation of quantitative family history scores or classification of risk into qualitative categories. Most recently, Yoon et al proposed development of a public health–oriented family history tool to identify risks for common chronic diseases. To be most effective across diverse populations, they recommended that the tool be simple, easily applied, and inexpensive and that a disease to be included in such a tool (1) contributes to a substantial public health burden, (2) has a well-defined case definition, (3) generates awareness among relatives, (4) is accurately reported by family members, (5) has family history as an established risk factor, and (6) has established and effective interventions for prevention.

To date, the work by Yoon et al has encompassed evaluation of family history information for several common chronic diseases. This article uses the framework established by Yoon et al to evaluate the utility of collecting family history reports of major birth defects as a pediatric public health strategy. Specifically, it attempts to summarize the relevant published literature to assess each criterion for inclusion.

Substantial Public Health Burden

In the United States, major birth defects, including structural defects and chromosome anomalies, are estimated to affect 3% of all live births. Major birth defects continue to be the leading cause of infant mortality in the United States and costs for care and treatment of children with major birth defects annually totals millions of dollars. Canfield et al used pooled data from 11 states with active case finding to calculate national birth prevalence estimates for 18 selected defects. Rates calculated ranged from 0.82 per 10 000 live births for transverse arteriosis to 13.65 per 10 000 live births for Down syndrome, and these estimates varied according to race and ethnicity. Compared with the rates for children of non-Hispanic white mothers, rates were significantly higher for tetralogy of Fallot, lower-limb–reduction defects, and trisomy 18 among children of non-Hispanic black mothers and significantly higher for anencephalus, spina bifida, encephalocele, gastrochisis, and Down syndrome among children of Hispanic mothers.

Major birth defects also represent a global public health burden. A recent report by the March of Dimes showed that, worldwide, an estimated 6% of births or 7.9 million children are born annually with a major birth defect of genetic or partially genetic origin. Among the most common disorders identified were congenital heart defects, neural tube defects, thalassemia, sickle cell disease, Down syndrome, and glucose-6-phosphate dehydrogenase deficiency. The report also cited that, annually, hundreds of thousands more children are born with defects resulting from in utero exposure to teratogenic agents, such as alcohol or infectious disease, and that at least 3.3 million children <5 years old die as a result of major birth defects. The highest totals of occurrence (94%) and deaths (95%) that resulted from major birth defects were found in middle- and low-income countries.

Well-Defined Case Definition

Detailed clinical descriptions or definitions are available for individual major birth defects. For example, a cleft lip (CL) can be defined as an incomplete closure of the lip that is often accompanied by a maxillary alveolar defect (gum), cleft palate (CP), or both. The maxillary alveolar defect can be a complete cleft that is continuous with the CP, or it can be limited to a notch on the gum. The CL can show unilateral, bilateral, or median presentation and can be further specified as a complete CL, in which the defect extends through the entirety of the lip and the
nasal floor and is often associated with a more-severe nasal deformation, or an incomplete CL, in which the defect does not extend into the nasal floor. In clinical practice, major birth defects are usually documented by using the World Health Organization’s International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Birth defect monitoring systems, such as the Metropolitan Atlanta Congenital Defects Program, use an expanded version of the ICD-9-CM that is based on the British Paediatric Association (BPA) Classification of Diseases. These modified BPA codes retain the original ICD-9-CM code for a particular defect and expand the code to include reference to location. For example, a unilateral complete CL could be further specified as a right, unilateral complete CL.

AWARENESS OF BIRTH DEFECTS AMONG RELATIVES

Although well-defined case definitions exist for major birth defects, the awareness of a diagnosis among relatives or even self-awareness of a diagnosis is variable. Romitti evaluated family history reports of birth defects provided by telephone interview from a sample of mothers (case mothers, n = 28; control mothers, n = 29) who participated in a population-based study of orofacial clefts in Iowa. Responses for specific birth defects reported by these mothers were reviewed by a board-certified clinical geneticist and classified as definite; possible, but more information needed; or excluded (ie, not a birth defect). Of the 84 defects reported for relatives, 38 (45.2%) were classified as definite, 6 (7.1%) were classified as possible, and 40 (47.6%) were excluded. Examples of excluded defects were single-gene conditions that manifested later in childhood such as cystic fibrosis and multifactorial traits such as asthma. Using this sample, Romitti requested permission from mothers to contact first- and second-degree relatives to obtain self-reports of birth defects. Overall, 345 (66%) case and 380 (69%) control adult relatives provided self-reports and reports for 299 offspring. These reports recorded 147 birth defects among relatives, and review by a clinical geneticist classified 68 (47.0%) as definite and 27 (15.1%) as possible; the remaining 52 (37.9%) reports were excluded.

More recently, family history reports provided by telephone interview from case (n = 9331) and control (n = 3390) mothers who participated in the National Birth Defects Prevention Study were evaluated (R. Fisk Green, PhD, R. S. Olney, MD, J. Reelhuis, PhD, L. D. Botto, MD, P.A.R., National Birth Defects Prevention Study, unpublished data, 2007). Maternal reports of birth defects were classified initially according to the type of condition (eg, birth defect, genetic disorder, or developmental disability), and reports coded as birth defects or genetic disorders were subsequently assigned a level of detail (high, medium, or low) that corresponded to the terminology used by the mothers. For example, a maternal report that provided the specific medical terminology to describe the defect (eg, ventricular septal defect) was coded as having a high level of detail; a report that provided a positional or conformational description (eg, hole in heart) was coded as having a medium level of detail; and a report that provided a nonspecific description or mentioned only the organ group (eg, heart defect) was coded as having a low level of detail. Using this coding system, they found that mothers most often tended to provide a high level of detail for defects that were phenotypically evident (eg, neural tube defects and orofacial clefts), whereas a medium or low level of detail tended to be reported for defects that were less phenotypically evident (eg, heart defects) (R. Fisk Green, PhD, R. S. Olney, MD, J. Reelhuis, PhD, L. D. Botto, MD, P.A.R., National Birth Defects Prevention Study, unpublished data, 2007). Fisk Green et al also noted that reports were influenced by case status and maternal demographic factors; mothers who were non-Hispanic white, aged ≥25 years, had more than a high school education, and had an annual income greater than $20 000 were more likely to provide reports of affected relatives.

ACCURATE REPORTING OF BIRTH DEFECTS AMONG RELATIVES

Four published studies were identified that have examined the accuracy of reporting of birth defects among relatives: 3 that examined maternal reports for offspring only and 1 that examined maternal reports for offspring and first- and second-degree relatives. Axelsson and Rylander compared questionnaire reports of birth defects among offspring provided by 745 mothers with information recorded in the Swedish Register of Congenital Malformations. They found that mothers failed to identify 10 of the 38 children recorded in the register as having a defect and also listed 24 defects that were not ascertained by the register. Although not reported by the authors, sensitivity and specificity estimates computed by using these data would have been 74% and 97%, respectively. In a similar comparison of maternal interview reports from the Atlanta Births Defects Case-Control Study and records from the Metropolitan Atlanta Congenital Defects Program, Rasmussen et al found that 3024 of 4929 case mothers reported that their child had a major birth defect (yes/no for presence of a defect), for a sensitivity estimate of 61%; 67 of 3029 control mothers gave responses that indicated that their child had a major birth defect, which produced a specificity estimate of 98%. The authors also reported that maternal age of ≥25 years, college education, and non-Hispanic white race were independently associated with the sensitivity of interview responses. More recently, Chessa et al used a modified Leuven knowledge questionnaire to survey parents of patients with congenital heart defects at a university pediatric cardiology department in Italy. The investigators surveyed parents in 148
families and found that 91% of them were able to correctly name the heart defect diagnosed for their children, and 55% were able to indicate on a diagram where the heart defect was located, but only 10% correctly identified their risk of having another child with congenital heart disease.20

Using the relative self-reports described previously as a gold standard, Romitti et al21 evaluated maternal interview reports of family history information. For all relatives combined, sensitivity for presence (yes/no) of a birth defect was 31% for case mothers and 9% for control mothers; specificity was 98% and 97%, respectively. Mothers who correctly identified a relative who recorded a birth defect also often showed agreement for the specific defect group. In addition, the authors found that the sensitivity of interview responses was higher when the child was first in the birth order and mothers were <30 years old and participated in family genealogy.21

Taken together, these studies showed that the sensitivity of maternal reports for presence of a defect was high for offspring but considerably lower for other first-degree and second-degree relatives. For all relatives, the accuracy of reports varied according to the type of defect.

FAMILY HISTORY AS AN ESTABLISHED RISK FACTOR
For several major defects, an affected parent has an increased risk of delivering a child with the same malformation compared with an unaffected parent. Also, parents with 1 or more affected children have a higher risk of having a subsequent affected pregnancy. Using isolated CL plus CP as an example, unaffected parents with no family history of CL plus CP have a risk of ~0.1% for delivering a child with CL plus CP. If 1 of these parents is affected with CL plus CP, the risk increases to 2% to 5%. In addition, parents who have 1 affected pregnancy have a 3% to 7% risk for recurrence in a subsequent pregnancy (sibling), and those with 2 affected pregnancies have an 8% to 14% risk. It is important to note that these estimates might vary depending on characteristics of the underlying population (eg, race or ethnicity) and location of the defect (eg, bilateral versus unilateral). In addition, recurrence risk for CL plus CP with an underlying genetic origin might be as high as 25% for unaffected parents.22

Several researchers have also investigated the risk of major birth defects associated with a reported family history of a defect in combination with other factors. Although a detailed review of these studies is beyond the scope of this discussion, use of selected examples highlights their commonalities. Hwang et al23 examined the risk of clefting associated with a family history of birth defects, maternal smoking, and variants in the transforming growth factor α gene (TGFA) among case and control children delivered in Maryland from 1984 through 1992. They found a significantly higher frequency of family history of birth defects among case children compared with control children. In addition, they reported a significantly increased risk of CP associated with the potential interaction between mothers who smoked during pregnancy and infants who carried the rarer C2 allele at the TGFA Taq1 site (odds ratio [OR]: 8.69; 95% confidence interval [CI]: 1.57–47.8).23 Findings from this study were replicated in an investigation in California24 but not in investigations in Iowa25 or Denmark.26 In these latter studies, however, a family history of clefting was found more frequently among case than among control children.

Using data from the Atlanta Birth Defects Case-Control Study, Honein et al27 examined the association of family history of clubfoot and maternal smoking on the occurrence of clubfoot in offspring. They found elevated risk estimates for the independent effects of family history of clubfoot (OR: 6.52; CI: 2.95–14.41) and smoking (OR: 1.34; 95%; CI: 1.04–1.72) and for the joint effects of each exposure (OR: 20.30; CI: 7.90–52.17).27 An investigation of similar risk factors in Washington State tended to support the findings of an elevated risk of clubfoot associated with maternal smoking and an increased occurrence of clubfoot among relatives of case children compared with relatives of control children.28

In the studies mentioned previously, reports of birth defects among relatives were provided by the mother through an interview or self-administered questionnaire, and birth defect reports for relatives tended to be higher among mothers of case children than mothers of control children. Selected environmental agents also affected the risk estimates reported, which supports the suspected multifactorial inheritance for these defects. The magnitude of risk observed could reflect a true difference in occurrence of defects between case and control relatives, true differences in exposure to deleterious environmental agents, reporting bias between case and control mothers, or, most likely, some combination of these explanations.

EFFECTIVE INTERVENTIONS FOR PREVENTION
The myriad risk factors for major birth defects present numerous approaches for reducing the occurrence of these conditions. Among the approaches are avoidance of selected medications during pregnancy,29 vaccinations against infectious disease,30 and cessation of cigarette smoking31 and alcohol consumption32 to reduce risk. Perhaps one of the biggest success stories in birth defects prevention has been the identification of the benefits of folic acid. Randomized clinical trials have demonstrated the benefits of periconceptional supplementation of folic acid and a reduced risk of neural tube defects,33,34 which prompted public health recommendations for daily folic acid supplementation for reproductive-aged women and, since 1998, folic acid fortification of grain products in the United States. Evaluation of population prev-
lence for neural tube defects after fortification has shown a decline in rates in the United States. In addition, a recent review of US birth certificates also showed a decrease in the prevalence rates for orofacial clefts after folic acid fortification.

Prevention programs have been developed to reduce the recurrence of neural tube defects by targeting families with an affected child. Collection of family history reports among these families provides an opportunity to target additional relatives who might benefit from directed interventions to reduce the occurrence of these defects. To date, limited published information exists about the utility of such an approach. Byrne et al examined folic acid knowledge and use among aunts of children with neural tube defects in Ireland to identify the success of prevention approaches in high-risk families. They found 57.9% of pregnancies reported by aunts to have been supplemented before pregnancy and 89.5% of pregnancies to have been supplemented during pregnancy. Byrne also examined the effect of distributing a folic acid–intervention pack to the aunts and female first cousins of children who were affected with neural tube defects. Although 73% of the aunts and cousins had knowledge of the benefits of folic acid, only 8.8% used folic acid before the intervention; the rate of use increased to 19% after intervention.

CONCLUSIONS

Major birth defects satisfy many of the criteria outlined by Yoon et al for use of family history reports as a public health strategy. These defects represent a substantial public health burden both in the United States and worldwide. There also exist well-defined case definitions for major birth defects, including systematic criteria for diagnosis of recognizable patterns of defects that may have an underlying genetic or teratogenic etiology. In addition, family history is a risk factor for birth defects, although the magnitude of risks observed could also reflect differences in exposure to deleterious environmental agents, reporting bias, or a combination of these factors. Last, effective interventions exist for reduction of major birth defects, including folic acid supplementation and fortification, which may be especially important in families with a family history of folate-sensitive birth defects.

Less clear and less well studied, however, are the awareness of major birth defects among relatives and the accuracy of reporting these defects. Additional research is needed regarding the awareness of these conditions among relatives, including self-awareness, and the accuracy of parent reports for these conditions among relatives. In particular, research to date has largely focused on defects that occurred among offspring and needs to be extended to other relatives. Also, such research needs to encompass all pregnancy outcomes for an individual, because major birth defects contribute to miscarriage, intrauterine death, and stillbirth. For example, the occurrence of CL, CP, or both, is thought to be 3 times higher among pregnancies that end in miscarriage or stillbirth compared with live births. In addition, future research should target how knowledge of birth defect diagnosis and shared risk is transmitted among immediate family members and more distant relatives.

To improve awareness of birth defects among relatives, classification schemes developed for surveillance projects might be useful. For their work with the Anti-retroviral Pregnancy Registry, Scheuerle and Tilson condensed and rearranged the BPA code list to create a classification scheme that combined defects with common general diagnoses and some degree of common pathogenesis to classify affected pregnancies among mothers who took antiretroviral medications during pregnancy. As an example, they reduced the numerous available codes for CL plus CP to CL of any type without CP, CL of any type with CP, and CP alone. A related approach was developed by the Iowa Registry for Congenital and Inherited Disorders (IRCID) to notify birth parents of an affected live-born child that their child has been identified by the IRCID. This notification is made by mail and includes a letter describing the IRCID and the defect diagnosis(es) of the child. So that parents recognize the terms used to describe a defect, the letter includes both the medical term (BPA definition) and a lay term for the defect that was developed by a group of clinical geneticists, genetic counselors, and IRCID staff.

To improve the accuracy of reporting of birth defects among relatives, attention should be paid to the mode of information request and the types of items used. Cole et al designed a mailed, self-administered family history questionnaire for patients who were attending a medical genetics clinic to replace collection of pedigree information at the time of the clinic visit. Comparing family history information collected in the clinic setting with that collected by the self-administered questionnaire, Cole et al found that the questionnaire provided patients with the opportunity to consult with other family members, increased their awareness regarding reasons for their clinic visit, reduced clinic time, and increased standardization of family history data collection. Romitti et al concurred with Cole et al on the use of a self-administered questionnaire and recommended that attention be given to the type of birth defect items used. The authors found that less-specific items (eg, born with an eye defect) tended to encourage the recording of defects (eg, farsighted) that were neither classified as definite nor possible birth defects and produced reports of unspecified defects (eg, limb defects) in excess of expected prevalence rates. As such, Romitti et al recommended that family history questionnaires for investigations of birth defects contain only specific, closed-ended items.

In summary, accurate knowledge of family history of
birth defects is important for making informed decisions regarding clinical care, risk assessment, and reproductive planning. Before implementing a routine family history tool for birth defects in the pediatric visit, further research is needed in how best to collect and evaluate the accuracy of birth defect reports and how knowledge of birth defect diagnosis and related risk factors is transmitted among relatives. As recommended by Yoon et al., improved understanding of these factors will allow for evaluation of the analytic and clinical validity of the tool developed, as well as the clinical utility of such knowledge in reducing the public health burden of birth defects.

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REFERENCES

17. Romitti PA. Evaluation of Family History Information Provided by Maternal Telephone Interview [PhD thesis]. Iowa City, IA: University of Iowa; 1994
33. MRC Vitamin Study Research Group. Prevention of neural


44. Diehn TN, Romitti PA. Using birth defects surveillance data to address the priorities of public health and individual families [abstract]. *Frontiers Fetal Health*. 2002:4:22

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