

ORIGINAL ARTICLES

Priorities for Future Public Health Research in Orofacial Clefts

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The National Center on Birth Defects and Developmental Disabilities at the Centers for Disease Control and Prevention conducted a workshop in January 2006, entitled "Prioritizing a Research Agenda for Orofacial Clefts." The goals of the meeting were to review existing research on orofacial clefts (OFCs), identify gaps in knowledge that need additional public health research, and develop a prioritized research agenda that can help guide future public health research. Experts in the field of epidemiology, public health, genetics, psychology, speech pathology, dentistry, and health economics participated to create the research agenda. Research gaps identified by the participants for additional public health research included: the roles of maternal nutrition, obesity, and diabetes in the etiology of OFCs; psychosocial outcomes for children with OFCs; the quality of life for families and children with OFCs; and the health care costs of OFCs. To create the research agenda, the participants prioritized the research gaps by public health importance, feasibility, and outcomes of interest. This report summarizes the workshop.

KEY WORDS: *orofacial clefts, public health, research priorities*

In January 2006, the National Center on Birth Defects and Developmental Disabilities at the Centers for Disease Control and Prevention conducted a workshop entitled "Prioritizing a Research Agenda for Orofacial Clefts." Forty-five experts in the fields of epidemiology, public health, genetics, psychology, speech pathology, dentistry, health economics, and others participated in this workshop to review the state of knowledge on orofacial clefts (OFCs), identify knowledge gaps that need additional public health research, and create a prioritized public health research agenda based on these gaps.

To set the stage for the workshop, experts were invited to make presentations on the current state of knowledge in various OFC research areas, and identify critical gaps in existing knowledge. After the presentations, participants were divided into two breakout groups. The groups were asked to identify

gaps in two major areas of public health research: (1) genetic and environmental risk factors and gene-environment interactions in the causation of OFCs, and translation of these findings into primary prevention of OFCs, and (2) longer term outcomes such as psychological concerns, communication difficulties, health care costs, and effect on the family. Each group used the research gaps they identified to define up to 10 public health questions, prioritized by public health importance and feasibility. Afterwards, the entire group reconvened to discuss the identified gaps and create a prioritized research agenda comprised of issues related to both primary and secondary prevention. This agenda could be of value in guiding future research in the area of OFCs.

CURRENT STATE OF KNOWLEDGE

OFCs affect approximately 6,800 births in the United States each year (Centers for Disease Control and Prevention, 2006). Although some genetic and environmental risk factors for OFCs have been identified, many nonsyndromic clefts are not linked to any of these factors (Wyszynski and Beaty, 1996; Hayes, 2002). In addition, there is a paucity of information available on the long-term consequences for children born with OFCs. The presentations of and gaps identified by the speakers formed the basis for the entire workshop and the priorities developed from the meeting. Key issues raised in the presentations are summarized below.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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Risk Factors and Gene-Environment Interactions

Drs. Peter Mossey (Dundee University Dental School, Dundee, Scotland) and Ronald Munger (Utah State University, Logan, UT) summarized the current state of knowledge on genetic and environmental risk factors and gene-environment interactions, respectively, in the etiology of OFCs. Maternal tobacco smoking has been identified as a risk factor for OFCs, with a recent meta-analysis showing a 20%–30% increase in the risk for OFCs depending on the type of cleft (Little et al., 2004). Several studies have shown an association between prenatal alcohol exposure and OFCs, as well as potential gene-environment interactions with alcohol and certain genes (Munger et al., 1996; Romitti et al., 1999; Lorente et al., 2000; Chevrier et al., 2005). Maternal diabetes and obesity have also been linked to an increased risk of OFCs (Moore et al., 2000; Aberg et al., 2001; Cedergren and Kallen, 2005). In addition, strong evidence suggests an association between OFCs and nutritional factors, including vitamin A, riboflavin, folic acid, pantothenic acid, vitamin B₁₂, vitamin B₆, and zinc (Yoneda and Pratt, 1982; Wyszynski and Beaty, 1996; Munger, 2002; Krapels et al., 2004; Tamura et al., 2005). Less consistent associations have been found when looking at OFCs and anti-convulsant medications, seizure disorders, caffeine, corticosteroids, or benzodiazepines (Safra and Oakley, 1975; Rosenberg et al., 1982, 1983; Kelly et al., 1984; Abrishamchian et al., 1994; Czeizel and Rockenbauer, 1997; Carmichael and Shaw, 1999; Browne, 2006).

Using a candidate gene approach and genome wide linkage studies in families with multiple cases, associations have been identified between OFCs and a number of genes, including *MTHFR*, *TGFA*, *MSX1*, *PVRL1*, *GSTT1*, and *TGFB3* (Wong and Hagg, 2004). In some OFC cases, mutations have been identified in one of the following genes: *IRF6*, *SATB2*, *MSX1*, *ACOD4*, *PVRL1*, and *TBX22* (Wong and Hagg, 2004). For some populations, mutations in *IRF6* might be contributing to OFCs in as many as 12% of the cases (Zuccheri et al., 2004; Lidral and Moreno, 2005). Identification of genes that predispose individuals to the occurrence of OFCs would make possible the identification of those at risk, enhance our understanding of pathogenesis, and facilitate the study of gene-environment interactions, which could be translated into prevention strategies for these malformations.

Psychosocial

Drs. Kathleen Kapp-Simon (Northwestern University Feinberg School of Medicine, Westchester, IL) and Hillary Broder (University of Medicine and Dentistry of New Jersey, Newark, NJ) summarized the current state of knowledge on psychosocial issues for families of and children with OFCs, and Dr. Lynn Richman (University of Iowa, Iowa City, IA) reviewed the neurobehavioral deficits and neuroimaging findings in children with OFCs. The stress associated with having a child with an OFC has been well documented. Mothers often report feelings of resentment, hurt, and disappointment after discovering

their child has an OFC (Carreto, 1981; Speltz et al., 1990). Later on, family members often experience additional stress as they face difficulties with feeding, multiple surgeries, speech therapy, and dental care. The children themselves are likely to have lower self-concept scores compared with children with no physical defects (Broder and Strauss, 1989). They are also at risk for learning disabilities, grade retention, low school achievement (Broder et al., 1998), and dyslexia related to fluency and naming speed (Richman and Ryan, 2003). It is important for parents and teachers to be aware that 30%–40% of children with clefts are at risk for early reading problems (Richman et al., 2005). As they grow older, adolescents with clefts can show social inhibition (Kapp-Simon and McGuire, 1997) and those with low social competence report loneliness and social anxiety (Pope and Ward, 1997).

Health professionals working with children with OFCs have noted a modest decrease in the health-related quality of life among children with clefts (Wehby et al., 2006). Compared with children with no chronic conditions, children with visible facial differences have lower quality of life scores (Topolski et al., 2005). However, their quality of life is comparable with that of children with other chronic disorders, except in the area of family relationships, where children with facial differences tend to score slightly better (Topolski et al., 2005). Similarly, health-related quality of life scores, reported oral symptoms, or measures of emotional well-being have shown few differences between children with orofacial conditions and children with dental caries (Locker et al., 2005). The same study found that children with OFCs had no evidence of social inhibition or withdrawal, even though they had more reported problems with social well-being, and that children with OFCs rated their oral health better than that of children with dental caries (Locker et al., 2005).

Neuroimaging studies have found significant differences among individuals with OFCs when compared with healthy individuals. One study found that male individuals with cleft lip and palate (CLP) had a significantly smaller temporal lobe, occipital lobe, and cerebellar size, as well as a significantly larger frontal lobe (Nopoulos et al., 2000). Other studies have found that the structural abnormalities in the brain are related to behavioral differences. In one study, men with CLP were more likely to have a midline brain anomaly and lower IQ scores than controls (Nopoulos et al., 2001). In another study, men with OFCs were found to have reductions in the volume and area of their orbitofrontal cortex, which was significantly associated with a decline in their social functioning scores (Nopoulos et al., 2005).

Long-Term Outcomes and Public Health

Dr. Camilla Bille (University of Southern Denmark, Odense, Denmark) summarized the studies of longer term health outcomes for children with OFCs. An investigation of causes of mortality in individuals with OFCs found an increase in total mortality (all causes combined), as well as an increased risk of cancer, cardiovascular events, and a significantly increased

risk of suicide (Christensen et al., 2004). Another study found no association between OFCs and overall risk for cancer. It did, however, find an increased risk of breast cancer for people with OFCs compared with those without OFCs, which the authors attributed, in part, to other factors such as delayed motherhood and nulliparity among women with OFCs. This study also showed an increase in lung cancers among men with cleft lip and palate and of brain cancer among women with cleft palate alone, but these findings could be related to multiple comparisons (Bille et al., 2005).

Dr. Katherine Lyon Daniel (Centers for Disease Control and Prevention, Atlanta, GA) discussed the social marketing approach, and how that might be used in the prevention of OFCs associated with identified risk factors such as maternal smoking. Social marketing uses commercial marketing concepts and techniques to facilitate behavioral and social changes. Some relevant features of social marketing are: (1) identifying a product, concept, or service based on needs (such as programs aimed at prenatal smoking cessation); (2) assessing the price of the product (measured in time, money, or opportunity costs) and ensuring that it is acceptable to the target audiences; (3) promoting the product to appeal to both the target audience and the providers of the product; and (4) placing or distributing the product to achieve acceptance of the product (Prue and Daniel, 2006).

Economic Impact

Dr. Norman Waitzman (University of Utah, Salt Lake City, UT) presented some of the challenges of calculating the economic burden of having a child with an OFC, and Dr. John Tilford (University of Arkansas for Medical Sciences, Little Rock, AR) discussed some strategies to assess the impact on caregivers and, in particular, the time costs associated with caring for a child with an OFC. Drs. Waitzman and Tilford emphasized the importance of cost analyses to: (1) calculate the benefit of primary prevention, (2) prioritize resources for research, (3) identify costly secondary conditions among affected children, and (4) evaluate treatment strategies. The lifetime costs for a child with a cleft lip or palate based on patterns of care and utilization for a 1988 cohort updated to 1992 dollars was estimated to be \$101,000 (Centers for Disease Control and Prevention, 1995). This estimate does not incorporate the cost to the family, which can include out-of-pocket expenses for medical treatments, educational assessments, transportation, lodging, and child care (Berk and Marazita, 2002), reduction in income and employment opportunities (Berk and Marazita, 2002), and reduction in leisure time (Tilford et al., 2001). In addition to the direct economic impact, the health state of parents or other caregivers can be affected by their caregiving duties. Both costs and the effect on caregivers are likely to vary dramatically depending on the severity of the child's OFC. Unfortunately, more recent estimates of both the direct and indirect costs for OFC treatment have not been published. Presumably, costs have increased substantially in parallel with overall rising health care costs (Strunk et al., 2002;

Bodenheimer, 2005). There have also been numerous changes in the medical management of OFCs since 1988 that likely have affected costs.

Dr. Ronald Strauss (University of North Carolina at Chapel Hill, Chapel Hill, NC) presented data showing that children with OFCs have limited access to oral health care. This disparity in dental health care is also found among children of lower socioeconomic status without OFCs, who are more likely to suffer from dental caries, be in greater need of dental treatment, and have worse dental health than children of higher socioeconomic status (Irigoyen et al., 1999; Gillcrist et al., 2001). Children with special health care needs often report having trouble finding dentists who are willing to treat them; in this population, poor oral health and cleft palate were also identified as barriers to accessing dental care (Al Agili et al., 2004).

PRIORITIES FOR FUTURE PUBLIC HEALTH RESEARCH ON OFCS

Workshop participants from the two breakout groups combined identified 18 priority topics for further research. After brief presentations from each breakout group of the priorities identified by the group, each participant selected five top priorities (in order) from the combined priorities of the two breakout sessions. The top five selections from each participant were combined to create the complete prioritized list. The topics are listed below in order of priority beginning with the research area that received the most support from the participants.

1. Phenotype Characterization to Define More Etiologically Homogeneous Categories of OFCs

Better characterization of phenotypes of OFCs can be accomplished using neuroimaging, family history questionnaires, and physical examinations. Improved phenotype characterization should enhance our ability to understand the etiology of OFCs by enabling us to group affected infants into more etiologically homogeneous categories. Using homogeneous categories will improve the likelihood of identifying risk factors and might also be helpful in predicting outcomes. Due to the importance of including diverse populations in initiatives to improve phenotype characterization, international collaborations were suggested.

2. Effects of Nutrition and Nutritional Supplements on the Risk of OFCs

Although numerous studies have identified nutritional factors as potentially important in the causation of OFCs, the role of maternal nutrition and specific nutrients contributing to the etiology of OFCs is still undefined. In addition to understanding the role of maternal nutrition, it is important to determine if these factors are affected or modified by the maternal or fetal genotypes, or both. Because accurate measurement of nutritional exposures is difficult, the use of biomarkers, in addi-

tion to self-reported intake, could improve our ability to study the role of nutrition in the causation of OFCs. Also, it is important to consider that other environmental exposures, such as smoking and compounds that interfere with the metabolism of folic acid (folic acid antagonists) or other nutrients, might modify the effect of nutritional factors.

3. Early Screening Measures to Identify Learning Outcomes in Children with OFCs

Screening instruments are available for reading problems (including dyslexia) that can affect children with OFCs. However, better information is needed to determine if early screening measures using existing instruments to assess (1) auditory discrimination, (2) sound blending, (3) short-term automatic memory, and (4) rapid naming are predictive of oral reading and comprehension outcomes by school age for children with OFCs. There is also a need to assess the timing of interventions and surgeries to determine if earlier interventions optimize speech and hearing outcomes, and whether these improved speech and hearing outcomes predict better educational achievement.

4. Quality of Life for Children with OFCs

To enhance the quality of life for children with OFCs, it is essential to have an improved understanding of the most influential factors for these children and their families. When measuring quality of life, the following factors should be considered: (1) access to an interdisciplinary team of specialists, (2) educational outcome, (3) psychological outcome, (4) timing and type of surgery, (5) reading interventions, (6) adherence to parameters of care, (7) family out-of-pocket costs, and (8) effect on caregivers. Because the needs of children with OFCs are unique, instruments to measure quality of life that are specific to children with OFCs are needed, even though this limits comparability of quality of life assessments across disorders. Although measuring quality of life can be difficult, universal instruments and data collection forms across centers for OFC treatment could make the task easier. In addition, a better understanding of how individual components (e.g., speech and facial appearance) correspond to overall measures of quality of life could help to identify ways to improve the quality of life for individuals with OFCs. To get a more comprehensive picture, it is important to separately assess the perceptions of quality of life for parents, children, and health care providers.

5. Social Marketing Campaign Targeting Smoking and OFCs

Because maternal smoking has been consistently identified as a risk factor for OFCs, interventions such as awareness and social marketing campaigns focused on positive behavior change are needed to reduce smoking during pregnancy. These could be combined with other smoking and pregnancy messages that are currently being used. Using such an approach

would require defining the goal, identifying and segmenting the audience(s) and their needs and desires; identifying, analyzing, and addressing competition to the smoking cessation message; conducting market research to design, test, and evaluate a positive exchange; and delivering the smoking cessation program and message to maximize benefit. The addition of OFC risk-related information to existing educational efforts to reduce smoking during pregnancy could reach women who have not been receptive to current messages and could, therefore, have maternal and infant health benefits beyond the prevention of OFCs.

6. Long-Term Outcomes for Individuals with OFCs

In view of the limited number of studies that have looked at the long-term outcomes for individuals with OFCs, more research is needed to evaluate the risk of chronic disease, oral health, and mortality in this population, in addition to quality of life issues that are mentioned in the fourth research priority. These outcomes might be related to genetic factors predisposing the individual to both an OFC and another adverse health outcome. Alternatively, the longer term outcomes might be the result of medical or social consequences, or both, of having an OFC or its treatment. An improved understanding of long-term outcomes could allow us to better direct treatment and develop prevention strategies for individuals at risk.

7. Effect of Timing of OFC Diagnosis

The effects that timing of diagnosis and early identification of a cleft (prenatal versus postnatal) have on the child's outcome have received very little attention. Better information is needed on how early diagnosis can affect parental stress, economic costs, family coping, health care decision-making, and infant outcomes such as feeding, weight gain, and neonatal care. It is also important to identify the indication for the prenatal diagnosis, whether it was complemented by counseling, and what kind of information was provided to the family following the diagnosis.

8. Obesity, Maternal Diabetes, and Insulin Resistance in the Etiology of OFCs

The roles of maternal diabetes, insulin resistance, and obesity in the etiology of OFCs are not well understood. We need to improve our understanding of how body mass index, adiposity, glucose tolerance, and patterns of weight gain and loss affect the occurrence of OFCs. In addition, it is important to consider whether fetal or maternal genetic background, or both, as well as exogenous exposures such as smoking and folic acid antagonists might modify the role of maternal diabetes and obesity.

9. Using "Parameters of Care" in Treatment of OFCs

There is a need to better understand the quality of medical care that children with OFCs are receiving and how it impacts

outcomes. This includes the identification of children who are receiving timely and appropriate care, consistent with established guidelines entitled “Parameters for Evaluation and Treatment of Patients with Cleft Lip/Palate or Other Craniofacial Anomalies” (American Cleft Palate–Craniofacial Association, 1993). Studies are most needed to elucidate how children who are receiving care consistent with the established guidelines differ from those who are not, in terms of demographic factors and long-term outcomes. It is also important to assess frequency and timing of services, access to required specialists, volume of care at the center used for treatment, and treatment management by multidisciplinary teams versus individual treatment providers. Further, as medical treatment and care change, assessing trends over time might be helpful.

10. Ethnicity and Population Differences in OFCs

The differences in the prevalence of OFCs among various ethnic and racial groups noted by numerous investigators (Erickson, 1976; Croen et al., 1998; Forrester and Merz, 2004) need to be further defined in order to help better understand the etiology of OFCs. Studies should account for confounding factors such as socioeconomic status, maternal smoking, nutrition, alcohol use, genotype, and family migration patterns. Population-based surveillance with high sensitivity for case ascertainment will be needed to address these issues. International collaboration in this effort might be helpful in characterizing these differences within a diverse population.

11. Effects of Maternal Medication Use in the Etiology of OFCs

Although several studies have identified specific medications as potentially significant in the causation of OFCs (Hill et al., 1988; Hayes, 2002), the role of many more, including over-the-counter medications and common prescription medications, is still not clear. Medications of particular interest for further research are: antidepressants, antiepileptic medications, folate antagonists, corticosteroids, and other commonly used prescription and over-the-counter medications. These investigations should consider the role of fetal or parental genetic background, or both, as well as concurrent environmental exposures such as maternal smoking.

12. Mental Health in Adolescents with OFCs

Outcomes in adolescents with OFCs have not been sufficiently studied. In particular, we need an improved understanding of their mental health and whether anxiety disorders, depression, and other affective disorders are increased in adolescents with OFCs compared with adolescents in the general population. In addition, data are needed to assess differences in high-risk behaviors in adolescents with OFCs compared with those of adolescents not affected by a major birth defect. To get a clearer picture of mental health outcomes in this pop-

ulation, objective measures are needed to assess these disorders.

13. Costs Associated with OFCs

More comprehensive data are needed on the financial costs associated with OFCs for both the family with an affected child and society. In addition to calculating direct medical, dental, and therapeutic costs, indirect costs such as those related to special education, caregiving, indirect productivity, and private tutoring, as well as other out-of-pocket costs also need to be factored into the overall cost estimates. Furthermore, consideration should be given to the severity and type of OFC, which can directly affect costs.

14. Maternal Infection and OFCs

There is a need to better understand the possible role of maternal infections in the etiology of OFCs. Other environmental exposures such as smoking and folate antagonists, as well as fetal or maternal genetic background, or both, need to be considered when assessing the role of maternal infections.

15. Maternal Alcohol Consumption and OFCs

Several studies have looked at the effects of maternal alcohol consumption during pregnancy; however, more research is needed to further our understanding of the role that prenatal alcohol exposure plays in the etiology of OFCs. Concurrent exogenous exposures, such as maternal smoking and folate antagonist use, need to be examined as well as fetal or maternal genetic background, or both.

16. Effect of Payor Status on Outcomes in Children with OFCs

Very little is known on whether there is a difference in outcomes for children with OFCs based on payor status (private versus Medicaid). Studies should identify potential differences in the access to and quality and cost of care by the type of provider, purchaser, or payor. In addition, it will be important to learn if payor status leads to disparities in access to specialized care (i.e., multidisciplinary cleft team), utilization of services, timeliness of service provision, patient satisfaction, and parental stress.

17. Dyslexia Intervention for Children with OFCs

Children with OFCs are at increased risk for dyslexia related to fluency and naming speed. For this reason, they might respond well to specific interventions that are typically used to treat dyslexia; however, few studies have investigated the effectiveness of these interventions (e.g., auditory retraining, interventions for improving phonological awareness and processing, language comprehension, and vocabulary building) among children with OFCs. Multiple tests can be used to ac-

curately measure the effect of these interventions, including: objective reading tests, standardized measures of phonological processing, behavior outcomes, and social competence.

18. Air Pollution in the Etiology of OFCs

At least one study has shown that women exposed to high levels of ozone and carbon monoxide during pregnancy are more likely than other women to give birth to children with OFCs (Ritz et al., 2002). This, coupled with several reports from the United States and other countries showing an association between air pollutants and low birth weight, premature birth, stillbirth, and infant death (Sram et al., 2005), warrants further research on this potential association.

CONCLUSION

The goal of this priority-setting process, which focuses on identified gaps in our knowledge of OFCs, is to begin addressing significant public health research questions in topics underpinning their causation, pathogenesis, and effect. Collaborative, interdisciplinary efforts already initiated in certain areas need to be strengthened and expanded to achieve these goals. The primary public health goals from these priorities are: (1) to increase our capacity to prevent OFCs, and (2) to improve the quality of life and other long-term outcomes for children and families affected by OFCs.

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