MATERNAL AND PATERNAL OCCUPATION AND CLEFT LIP AND CLEFT PALATE IN OFFSPRING

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ABSTRACT

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Oral clefting is defined as a fissure in the midline of the palate so that the two sides fail to fuse during embryonic development; in some cases, the fissure may extend through both the hard and soft palates into the nasal cavity. Several studies have found an association between maternal and paternal occupations and risk of oral clefts in offspring. This study explored whether an association existed between maternal and paternal occupation and oral clefts in offspring among 563 births with oral clefts and 1386 births without any congenital malformations. The study population was Texas children born in 2000. The following maternal occupations: dental assistants, hairdresser, leather shoe repairer, nurse, retail sales worker, and surgical technologist; and the

following paternal occupation: automobile mechanic, farmer, leather shoe repairer, and painter were studied for their possible association with oral clefts in offspring. These occupations were selected because previous studies have found an association between these occupations and oral clefts in offspring. Descriptive statistics (frequencies and crosstabs) and logistic regression were used to analyze the data in SPSS version 11.0.

No associations were found in the following occupations: maternal hairdresser (odds ratio 1.5, 95% CI 0.3, 6.2), maternal nurse (odds ratio 1.6, 95% CI 0.8, 3.3), paternal automobile mechanic (odds ratio 0.8, 95% CI 0.4, 1.6), and paternal painter (odds ratio 0.3, 95% CI 0.1, 1.4). Elevated odds ratios were found in the following occupations: maternal dental assistant (odds ratio 2.1, 95% CI 0.3, 15.2), paternal farmer (odds ratio 1.9, 95% CI 0.4, 8.7) and maternal retail sales workers (odds ratio 2.0, 95% CI 1.0, 4.1). For all of these occupations, the 95% confidence intervals for the odds ratios included 1.0 indicating no significant association between having those occupations and having a child with an oral cleft. Also, smoking was a statistically significant risk factor for oral clefts in offspring (odds ratio 2.5, 95% CI 1.8, 3.7, $p < 0.05$). Several occupational groups of interest had no case or control parents so these could not be studied. Those occupations included: maternal leather shoe repairer, maternal surgical technologist and paternal leather shoe repairer. In conclusion, this study did not find any statistically significant associations between maternal and paternal occupations and oral clefts in offspring. However, maternal smoking was a significant risk factor for oral clefts in this population.

CHAPTER 1

INTRODUCTION

The purpose of this study was to examine the association between maternal and paternal occupation as recorded on the birth and fetal death certificates and risk of cleft lip and cleft palate in Texas children born in 2000. Maternal occupations that were examined included those in healthcare (registered nurses, surgical technologists, and dental assistants); retail sales positions; leather shoe repairers; and hairdressers. Paternal occupations that were examined included agricultural workers (farmers), automotive mechanics, painters and leather industry workers (leather shoe repairer).

Definition and Classification of Oral Clefts

A cleft lip is a condition that creates an opening in the upper lip between the mouth and nose. The opening can range from a single notch in the lip (unilateral) to complete separation in one or both sides extending up and into the nose (bilateral). Often a cleft in the gum may occur in association with a cleft lip. The cleft may range from a small notch in the gum to a complete separation of the gum. A cleft palate occurs when the soft or hard palate of the mouth has not joined completely. A cleft palate can range from just an opening at the back of the soft palate to a nearly complete separation.

Oral clefting is defined as a fissure in the midline of the palate so that the two sides fail to fuse during embryonic development; in some cases, the fissure may extend

through both the hard and soft palates into the nasal cavity (Kalumuck, et.al, 2002). The lip structures are formed between the fourth and seventh weeks of intrauterine life, while clefting of the palate generally occurs between the seventh and twelfth weeks of gestation (Stark, 1968). Embryologists have suggested using the terms "primary palate" for the lip and "secondary palate" for the hard and soft palates because of the chronology of the developing structures in the embryo (Stark, 1968).

About 80 percent of cases of cleft lip are unilateral; of these, 70 percent occur on the left side and 20 percent are bilateral (Kalumuck, et.al, 2002). A cleft lip is unilateral if the cleft only occurs on the right or left side of the lip. A cleft lip is bilateral if the cleft occurs on both the left and right side of the lip. Clefts of the primary palate may be complete or incomplete, and they may be unilateral, bilateral or median (Watson, et.al, 2001). Oral clefting is described by degrees. The first degree is incomplete, which is a small cleft in the uvula (Kalumuck, et.al, 2002). The second degree is also incomplete, through the soft palate into the hard palate or it may be a horseshoe type in which there is a bilateral cleft proceeding almost to the front of the mouth (Kalumuck, et.al, 2002). A third degree bilateral cleft extends through both palates but bilaterally through the gums, resulting in a separate area of the alveolus where the teeth will erupt and show up in a very small segment (Kalumuck, et.al, 2002). In addition to the lip, gum, and palate deviations, abnormalities of the nose may also occur (Kalumuck, et.al, 2002).

CHAPTER II

LITERATURE REVIEW OF ORAL CLEFTS

Treatment of Oral Clefting

The treatment of oral clefting is multifaceted. Cleft lip surgery usually occurs when the baby is at least seven pounds, while surgery to the soft or hard palate typically occurs when the child is at least nine months of age (Kalumuck, et.al, 2002). The major purpose of surgery is to achieve a functional palate (Kalumuck, et.al, 2002). Successful repair greatly improves speech, appearance, the physiology of the oral and nasal cavity, breathing, and the function of the palate (Kalumuck, et. al, 2002).

Incidence and Sequelae

Problems begin at birth for the child born with oral clefting. The most immediate problem is feeding. The baby cannot build up enough suction to nurse efficiently (Kalumuck, et.al, 2002). Babies with oral clefting are more susceptible to colds than children born with normal palates (Kalumuck, et.al, 2002). Ear infections and hearing loss, which may become permanent, also occur (Kalumuck, et.al, 2002). Some of these children have extra or missing teeth (Kalumuck, et.al, 2002). Teeth that are present may be malformed. Dental problems include injury to the teeth during development, fusion of teeth to form one large tooth, teeth lacking enamel, and too little calcium in the dental

enamel (Kalumuck, et.al, 2002). Another possible problem is maxillary arch collapse, which can be remedied with orthodontic treatment (Kalumuck, et.al, 2002).

Cleft palate and lip are congenital defects. Cleft lip is more common in boys (65 percent), and cleft palate is common in girls (61.1 percent) (Holdsworth, 1970). Orofacial clefts are the most common of all facial malformations, occurring in all major racial and ethnic groups (Ross, et. al, 1972). Cleft lip or palate occurs in approximately 1/1000 live births among Caucasians, 1/550 births among Asians, and about 1/1800 births among African Americans (Blakeley, 2000). In the majority of cases, the cleft will be the only defect, but clefts of the lip and palate may also be found in association with other congenital anomalies, and may occur as part of a well defined syndrome (Watson, et. al, 2001). The incidence appears to be slowly rising for both cleft lip and cleft palate (Stark, 1968; Watson, et. al, 2001). In Denmark, the incidence of these defects rose from 1.45/1000 live births in 1943 to 1.89/1000 live births in 1981 (Watson, et. al, 2001). Additionally, the incidence of oral clefts among Asians have been extensively studied (Ross, 1972). A study of the Japanese population indicated that the incidence of cleft lip with or without cleft palate is very high at 2.13/1000 (Ross, et. al, 1972). This increase in incidence may, however, be due to better reporting. The incidence of facial clefting is higher in those races with a broad face and broad cranial base (Longacre, 1970). The risk to subsequent siblings after a child with unilateral cleft palate is about 2.5 percent, but nearly 6 percent with bilateral cleft lip and palate (Longacre, 1970). Oral clefts have both an environmental and genetic component. The defect may skip generations (Ross, 1972).

Risk Factors

Cleft palate may be inherited, probably as a result of the interaction of several genes (Kalumuck, et.al, 2002; Watson, et.al, 2001). In addition, environmental factors may influence the embryonic development during the first trimester, such as maternal exposure to drugs, alcohol, or smoking (Kalumuck, et.al, 2002; Watson, et.al, 2001). Several drugs have been implicated in animal studies including tumor-inhibiting drugs and alkylating agents such as chlorambucil, triethylamine melamine, and thio-TEPA (Stark, 1968). Currently, only phenytoin has been found to be a teratogen for these defects in humans (Watson, et. al, 2001). Other risk factors include deficiencies of vitamins or minerals in the mother's diet; radiation from x-rays; diabetes; and infectious diseases such as German measles (Kalumuck, et.al, 2002; Ross, et. al, 1972). Folic acid may have a protective effect (Watson, et. al, 2001).

Maternal age, substance abuse, and smoking have been found to be risk factors. According to Meskin (1971) the older the age of the mother, the greater the risk of an oral cleft (no odds ratio or confidence intervals given). The study population in this article was children identified with an oral cleft from their birth certificate. When substance abuse was researched, the incidence of oral clefts was 10 times greater when the mother was a substance abuser than that among nonusers in the general population (no confidence intervals given) (Thomas, 1995). Women in this study reported using heroin, methadone, alcohol, cocaine, amphetamines, and tegretol (Thomas, 1995). The author suggested that no single drug alone will cause an oral cleft, but rather several drugs acting together. The study population included all live births from 1986 in the Drug Use in Pregnancy service in Westmead Hospital in Western Sydney. Some studies found an

increase in oral clefting with increased periconceptional smoking by the mother (Lieff, et.al, 1990; Lorente, et.al, 2000; Khoury, et.al, 1989). A dose response was found between maternal smokers relative to nonsmokers and risk for offspring with cleft lip and palate: odds ratio of 1.09 (95% C. I. 0.6, 1.9) for light (1-14 cigarettes/day) smokers; odds ratio of 1.84 (95% C. I. 1.2, 2.9) for moderate (15 – 24 cigarettes/day) smokers; and odds ratio of 1.85 (95% C. I. 1.0, 3.5) for heavy (24 + cigarettes per day) smokers (Lieff, et.al, 1990). The study population consisted of liveborn or still born infants from the Slone Epidemiology Unit Birth Defects Study initiated in 1976 at Boston University (Leiff, et. al, 1990). In Lieff's (1990) study, confounding variables considered included infant sex; mother's and father's age, and education; history of maternal convulsive disorder; ectopic pregnancy; miscarriage; therapeutic abortion or stillbirth; and family history of oral clefts among first degree relatives. One of the limitations of this study was the exclusion of non-white subjects. Khoury, et. al (1989) examined the relationship between maternal cigarette smoking and the risk of oral clefts in offspring with 1968 - 1980 data from the Metropolitan Atlanta Congenital Defects Program. For mothers who smoked fourteen or less cigarettes per day, the odds ratio relative to nonsmokers was 1.56 (95% C. I. 1.02, 2.38); for fifteen to twenty-four cigarettes, the odds ratio was 1.55 (95% C. I. 1.00, 2.40), and for greater than twenty-four cigarettes, the odds ratio was 1.87 (95% C. I. 0.95, 3.65) (Khoury, et. al, 1989). One study found a nonlinear relationship between the number of cigarettes smoked during the periconceptional period and oral clefting of the newborn (Werler, et. al, 1990). For mothers who smoked one to fourteen cigarettes per day, the odds ratio relative to nonsmokers was 1.2 for offspring with cleft lips (95% C. I. 0.9, 1.6) (Werler, et. al, 1990). For cleft lip with or without cleft palate,

there was a 1.4 fold increased relative risk (95% C. I. 1.0, 2.1) for mothers who smoked between fifteen and twenty-four cigarettes per day (Werler, et. al, 1990). For mothers who smoked more than twenty-five cigarettes per day, the odds ratio was 0.7 (95% C. I. 0.3, 1.6) (Werler, et. al, 1990). The Werler, et. al (1990) study was part of the Slone Epidemiology Unit Birth Defects Study during the years of 1983 through 1987.

Occupational Exposures

Several studies have looked at parental occupational exposures as possible risk factors for oral clefts. Mothers who worked in occupations involving exposure to electromagnetic fields of 50 Hz were more likely to have a baby with an oral cleft than those mothers in the general population who were not exposed to electromagnetic fields (Blaasaas, et.al, 2002). In the Blaasaas study (2002), mothers who were exposed to four to twenty-four hours of 50 Hz electromagnetic fields had an odds ratio of 1.07 for oral cleft in offspring (95% C. I. 0.86, 1.34), and those exposed to greater than twenty-four hours had an odds ratio of 1.73 (95% C. I. 1.00, 2.99). This study population came from the Medical Birth Registry of Norway.

Other studies found a positive relationship between maternal occupational exposure in the leather industry and oral clefts in offspring (Bionchi, et. al, 1997; Garcia, et.al, 1998; Laumon, et.al, 1996). Bionchi, et. al (1997) found a positive association between oral clefts and mothers involved in leather and shoe manufacturing (odds ratio 3.9, 95% C. I. 1.5, 9.8). Cases and control women came from EUROCAT (a European Registration of Congenital Anomalies) between 1982 and 1989 (Bianchi, et. al, 1997). Garcia, et. al (1998) also found an increase of the risk for oral clefts in mothers involved in the leather and shoe manufacturing industry during pregnancy (adjusted odds ratio

6.18, 95% C. I. 1.48, 25.69). Cases and controls were selected from births from January 1993 through December 1994 in eight public hospitals serving the main intensive agricultural zones in Comunidad Valencia, Spain. Cases were identified from hospital discharge records, while controls were obtained from births occurring in the same hospitals and matched on date of birth with a ratio of one to one (Garcia, et. al, 1998). The most important risk factor identified in the leather industry was exposure to organic solvents (Laumon, et.al, 1996). In a study by Lauman et.al (1996), solvents were divided into nine groups that included halogenated aromatics, other aromatics, halogenated aliphatics, other aliphatics, alcohols, glycols, ketones, aldehydes, and esters. Only mothers exposed to halogenated aliphatic solvents and ketones were found to have significant odds ratios for offspring with oral clefts. Women who were exposed to halogenated aliphatic solvents had an odds ratio of 4.40 (95% C. I. 1.41, 16.15) for bearing offspring with oral clefts, and women exposed to ketones had an odds ratio of 2.19 (95% C. I. 0.46, 11.32) (Lauman, et. al, 1996). The cases and controls were infants born between 1985 and 1989 in the Rhone-Alpes region of France.

Other industries that have been found to be associated with oral clefts (and exposure to organic solvents) are maternal and paternal work in manufacturing, painting, dry cleaning, health care, agriculture, and plumbing (Holmberg, et.al, 1979; McMartin, et.al, 1998; Olshan, et.al, 1991). Holmberg, et. al (1979) found the highest number of oral clefts among women working in nursing and as nursing home-aids (no odds ratio or confidence intervals given). Paternal occupations associated with oral clefts included agricultural work, machine tending, and plumbing (no odds ratios or confidence intervals

given). The study population came from the Finnish Register of Congenital Malformations (Holmberg, et. al, 1979).

A meta-analysis of both cohort and case-control studies indicated a significant relationship between organic solvent exposure in the first trimester and oral clefts in offspring. The summary odds ratio for the cohort studies was 1.73 (95% C. I. 0.74, 4.08), and the summary odds ratio for the case-control studies was 1.62 (95% C. I. 1.12, 2.35) (McMartin, et. al, 1998). Organic solvent exposures included aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons, aliphatic alcohols, glycols and glycol ethers (McMartin, et. al, 1998). Olshan, et. al (1991), found positive associations between paternal occupations and oral clefts for the following occupations: painters (odds ratio 3.36, 95% C. I. 1.19, 9.46) and vehicle mechanics (odds ratio 2.12, 95% C. I. 1.13, 3.99) (Olshan, et. al, 1991). Cases were identified from the British Columbia Health Surveillance Registry. Cordier, et. al (1997) found maternal occupational exposure to glycol ethers associated with oral clefts in offspring (odds ratio 1.44, 95% C. I. 1.10, 1.90). The cases and controls came from six EUROCAT registries between 1989 and 1992 (Cordier, et. al, 1997). The group of cleft lip (with or without cleft palate) showed a pattern of increasing odds ratios with an increasing glycol ether exposure index (Cordier, et. al, 1997). Glycol ethers are a family of approximately forty chemicals, derivatives of ethylene glycol and propylene glycol; they can be found in a wide range of domestic and industrial products, including paints, varnishes, inks, cosmetics, cleaning agents (in particular, window cleaners), and products for mechanics or metallurgy (Cordier, et. al, 1997). Khattak et al. (1999) found maternal exposure to organic solvents in medical laboratory work associated with oral clefts (odds ratio of 13.0, 95% C. I. 1.8, 99.5). The

organic solvents included aliphatic and aromatic hydrocarbons, phenols, trichloroethylene, xylene, vinyl chloride, and acetone (Khattak, et. al, 1999).

Healthcare workers might also be at an increased risk of having babies with oral clefts (Cordier, et.al, 1992; Farkas, et.al, 1969; Khattak, et.al, 1999; Kurppa, 1983; Matte, et.al, 1993; Wennborg, et.al, 2000). Occupations found associated with these defects include laboratory workers, operation room personnel, cleaning personnel, and nurses (Khattak, et.al, 1999; Kurppa, et.al, 1983; Matte, et.al, 1993; Wennborg, et.al, 2000). Healthcare workers are exposed to anesthetic gases, antineoplastic agents, sterilants, and disinfectants (Ahlborg, et.al, 1995; Cordier, et.al, 1992; Holmberg, et.al, 1982; Matte, et.al, 1993). Cordier, et. al (1992) studied exposure of anesthetic gases, antineoplastic drugs, disinfectants and maternal health occupations. The case-control study was conducted between 1984 and 1987 in two areas of France (Paris and Marseille) and included fifteen maternity hospitals (Cordier, et. al, 1992). Solvents were the main exposure of interest and hospital work was the main occupational group studied (Cordier, et. al, 1992). Women exposed to solvents had an odds ratio of 6.8 for oral clefts in offspring (95% C. I. 0.7, 128.3) and women exposed to disinfectants had an odds ratio of 3.4 (95% C. I. 0.4, 50.4) (Cordier, et. al, 1992).

In a Czechoslovakian study, researchers found that fathers who worked in healthcare occupations had a higher number of offspring with oral clefts (no odds ratio given) (Farkas, et al, 1969). The study population came from Clinics of the Plastic Surgery of Charles University in Prague (Farkas, et. al, 1969). Healthcare occupations included those in which radiation was part of the work environment.

A Finnish study looked at maternal healthcare workers and the incidence of oral clefts (Kurppa, et. al, 1983). An increased malformation rate was reported for hospital personnel exposed to hexachlorophene (no odds ratio given) (Kurppa, et. al, 1983). Additionally hand washing agents were implicated in maternal exposure and oral clefting. The hand washing agents included chlorhexidine, hexachlorophene, and iodine containing agents (Kurppa, et. al, 1983). Matte, et. al (1993) studied the relation between healthcare occupations and oral clefting. They found an increased risk of oral clefting in female nurses (odds ratio 1.42, 95% C. I. 1.06, 1.88) (Matte, et. al, 1993). The study population came from the Metropolitan Atlanta Congenital Defects Program between 1968 and 1980 (Matte, et. al, 1993). Wennborg, et. al (2000) studied possible effects of laboratory work on the reproductive outcomes of female laboratory personnel in Sweden from 1990 to 1994 (no odds ratio given). The cohort came from women born in 1945 or later from records of the Swedish Employee Salaries and Pension Board (Wennborg, et. al, 2000). Exposure to various agents included chemicals (non-specific), radioactive isotopes, cell techniques, viruses, and bacteria. The malformations included were those defined as type II malformations in the Medical Birth Register, which includes malformations with a high degree of diagnostic and Register stability (Wennborg, et. al, 2000). No association was found between mothers working in a laboratory and adverse reproductive outcomes. Holmberg, et. al, (1982) studied maternal organic solvent exposure and incidence of oral clefting. Maternal occupations in healthcare included exposure to volatile anesthetics under operating room conditions (Holmberg, et. al, 1982). The cases and controls came from the Finnish Register of Congenital Malformations (Holmberg, et. al, 1982). The researchers also examined the organic

solvents that laboratory assistants were exposed to (Holmberg, et. al, 1982). Those organic solvents included petroleum ether and benzene (Holmberg, et. al, 1982). No odds ratios were given in the study.

Lorente, et. al (2000) found maternal occupations in hairdressing (odds ratio 5.1, 95% C. I. 1.0, 26.0) and housekeeping (odds ratio 2.8, 95% C.I. 1.1, 7.2) to be associated with oral clefts in offspring. Exposures to the following chemicals were likely in these occupations: lead compounds (odds ratio 4.0, 95% C. I. 1.3, 12.2), biocides (odds ratio 2.5, 95% C. I. 1.0, 6.0), and aliphatic acids (odds ratio 6.0, 95% C. I. 1.5, 22.8) (Lorente, et. al, 2000). The data for analysis came from EUROCAT (a European Registration of Congenital Anomalies) between 1989 and 1992.

Occupations with prolonged standing have been found to be a risk factor for oral clefts (Kersemaeker, et.al, 1997; Lin, et.al, 1998). Occupations with prolonged standing include retail sales positions, healthcare workers, cashiers, machine operators, production inspectors, and hairdressers (Kersemaeker, et.al, 1997; Lin, et.al, 1998).

Agricultural workers have been found to be at increased risk of having offspring with oral clefts (Garcia, et.al, 1998; Garcia, et.al, 1999; Kristensen, et.al, 1997; Nurminen, 1995; Nurminen, et.al, 1995; Schnitzer, et.al, 1995; Shaw, et.al, 1999). The most likely paternal exposure is from pesticides, and according to Garcia, et. al (1998) the most likely pesticides to cause oral clefts in offspring are pyridil derivatives (odds ratio 2.77, 95% C. I. 1.19, 6.44). Cases and controls in the Garcia et. al (1998) study came from eight hospitals of Communidad Valencia, Spain between 1993 and 1994. In another case control study by the same authors, they found a statistically significant association for maternal involvement in agricultural work (adjusted odds ratio 3.16, 95%

C. I. 1.11, 9.01); however, the data did not show an increased risk for paternal involvement in agricultural work or pesticide application. The analysis of maternal handling of pesticides was limited by small numbers.

A meta-analysis by Nurminen (1995) found that maternal agricultural exposure to pesticides resulted in increased oral clefting (no odds ratio given). These data came from the Finnish Register of Congenital Malformations of births between 1967 and 1977 (Nurminen, 1995). In another Finnish study, maternal agricultural occupations were associated with an increased risk of oral clefting (adjusted odds ratio 1.4, 95% C. I. 0.9, 2.0) (Nurminen, et. al, 1995). The source of the data was also the Finnish Register of Congenital Malformations (Nurminen, et. al, 1995). The data were collected between June 1976 and December 1982. Most of the agriculture work was done by women who were manual laborers. Chemical exposure was from the following chemicals: insecticides containing pyrethrins and piperonyl butoxide or dimethoate, and a fungicide containing quintozene.

A positive association was found between paternal agricultural work and oral clefts in an Atlanta, Georgia study (odds ratio 3.3, 95% C. I. 0.9, 11.9) (Schnitzer, 1995). In this case-control study, the data were obtained from the Metropolitan Atlanta Congenital Defects Program of births between 1968 and 1980. The study classified paternal occupation according to the job held during the time from six months before until one month after the estimated date of conception. A limitation of the study was that the author used paternal occupation as a surrogate for work place exposure. In a California case control study of births between 1987 and 1989, a positive association was found between agricultural work and the incidence of oral clefting (Shaw, et. al, 1999).

The maternal odds ratio for agricultural work exposure was 2.2 (95% C. I. 0.7, 6.8) and the paternal odds ratio was 1.7 (95% C. I. 0.9, 3.4) (Shaw, et. al, 1999). In a study of Norwegian farmers between 1967 and 1991, moderately negative associations were found for paternal pesticide exposure (odds ratio 0.75, 95% C. I. 0.55, 1.01) (Kristensen, et. al, 1997). The cases and controls were obtained from the Medical Birth Registry of Norway (Kristensen, et. al, 1997).

CHAPTER III

METHODS

Study Design Definitions

This study used existing data provided by the Texas Birth Defects Registry (TBDR) of children who were born in 2000 to Texas residents and who were diagnosed as having oral clefts. The Texas Department of Health and the Texas State University Institutional Review Boards have approved the study "Residential Proximity to Environmental Hazards and Congenital Malformations in Offspring" of which this thesis is part of. The maternal and paternal occupations and industries were coded using the Standard Occupational Classification (SOC) and the North American Industry Classification System (NAICS), U.S., 2002 (Executive Office of the President Office of Management and Budget, 2000; Executive Office of the President Office of Management and Budget, 2002). The following variables were obtained from the vital records: sex of child, maternal age, maternal education, maternal race/ethnicity, maternal smoking, maternal and paternal occupation; and maternal and paternal industry. For comparison to case births, a random sample of control births without congenital malformations were used that was selected from the computerized birth certificate file maintained by the Texas Bureau of Vital Statistics. These control births were frequency matched to the case births by Public Health Region of maternal residence for births in 2000. The same

covariates collected for the cases were available on the control birth records. The independent variables were sex of child, maternal age, maternal education, maternal race/ethnicity, maternal smoking and maternal and paternal occupation. The dependent variable was whether or not the child was born with a cleft lip or palate. In the data analysis, each maternal and paternal group of interest was compared relative to those case and control parents without that particular occupation.

Study Design

The study design is a population-based, case-control study in which case and control mothers and fathers were compared with respect to various occupations and risk for oral clefts in offspring.

Study Population

The study population was drawn from the Texas Birth Defects Registry (oral cleft cases) and the Texas Department of Health Bureau of Vital Statistics (controls). A total of 563 births with oral clefts and 1386 control births were available for the study. Fifty-nine cases were lost because of fetal deaths whose records contained no information on parental occupation. The continuous study variables that were used included maternal age and education. The nominal variables included maternal race/ethnicity; sex of the child; maternal smoking; maternal and paternal occupation and industry; and case/control status. Maternal age in years was categorized as <20, 20-24, 25-29, and >= 30. Maternal education in years was categorized as <7, 7-11, >= 12. Race/ethnicity was classified as White (non-Hispanic), Black (non-Hispanic), Hispanic and Other. The following occupations and their Standard Occupational Classification Codes (SOC codes) were examined:

Maternal Occupations	SOC code	Paternal Occupations	SOC code
surgical technologists	292055	farmers	119012
registered nurses	291111	automotive mechanics	493023
dental assistants	319091	painters	519120
hairdressers	395012	leather shoe repairers	516041
retail sales workers	413000		
leather shoe repairers	516041		

Data Collection

Data collected for this study included demographic and occupational information from the Texas Birth Defects Registry and livebirth records. A database with maternal and paternal demographic data was created in SPSS version 11.0. The case mother and father were defined as parents who had offspring with an oral cleft. The control mother and father were defined as parents who had offspring without a congenital anomaly during the study period. Occupations and industries for each case and control mother and father were coded using Standard Occupational Classification (SOC) and North American Industry Classification System (NAICS), respectively (Executive Office of the President Office of Management and Budget, 2002; Executive Office of the President Office of Management and Budget, 2000).

Data Analysis

Using SPSS 11.0, unadjusted odds ratios and 95% confidence intervals were computed for the various occupational groups with the use of Crosstabs in SPSS 11.0. Logistic regression (SPSS 11.0) was used to calculate the adjusted odds ratios for oral clefts associated with various maternal and paternal occupations of interest while

controlling for maternal age, education, and smoking. In the data analysis, each maternal and paternal occupational group of interest was compared relative to those case and control parents without that particular occupation.

Benefits of Study

Much research has already been done on maternal and paternal occupation and incidence of cleft lip and cleft palate. However, much of the previous studies have been conducted among non-Hispanic populations. The results of this study will add to the knowledge base already established. Specifically, knowledge will be added to the Texas based population in the year 2000, in which a substantial proportion of births (45 %) were Hispanic.

CHAPTER IV

RESULTS

Descriptive Statistics

For this study, a total of 563 cases of oral clefts and 1386 comparison births were available for analysis. Case and control women were similar with respect to age. Approximately 23% of the case women and 22% of the control women were less than 20 years of age; 22% of the case and 23% of the control women were 20 through 24 years of age; 26% of the case and control women were 25 through 29 years of age; and 29% of the case and control women were 30 years or older. Table 1 shows the characteristics of the case and control women by age and other attributes.

Cases and control women were also similar with respect to years of education. Approximately 8% of case and control women had less than seven years of education; 25% of the case and control women had between seven and eleven years of education; and 66% of the case mothers and 67% of the control women had greater than twelve years of education.

Four race/ethnicity groups were studied: white, non-Hispanic; Black, non-Hispanic; Hispanic; and other. Approximately, 48% of cases and controls were Hispanic;

41% of cases and 40% of controls were white, non-Hispanic; 8% of cases and 10% controls were Black; and 10.7% of cases and 2.9% of controls were other.

The sex of offspring of case and control women was similar. Case women had 59% male births and 41% female births. Control women had 51% male births and 49% female births.

Maternal smoking status differed between cases and controls. Approximately, 11% of case women smoked compared to 5% of control women. The overall odds ratio for oral clefts associated with maternal smoking in this study was 2.5 (95% C. I. 1.8, 3.7). Descriptive statistics are summarized in Table 1.

TABLE 1
Characteristics of Case-Women with Oral Cleft Births and Control-Women, Texas, 2000

	Case Women		Control Women	
Characteristics	***n***	***%***	***n***	***%***
Maternal Age (yr)				
<20	130	23 1	305	22.0
20-24	125	22.2	318	22.9
25-29	146	25.9	364	26.3
>=30	162	28.8	399	28.8
Education				
<7	46	8.2	114	8.2
7-11	142	25.2	348	25.1
>=12	375	66.6	924	66.7
Race/Ethnicity				
White (non-Hispanic)	230	40.9	546	39.4
Black (non-Hispanic)	40	7 1	144	10.4
Hispanic	269	47.8	658	47.5
Other	24	4.3	38	2.7
Smoking*				
Yes	60	10 7	62	4.5
No	503	89.3	1346	97.1
Sex of Birth				
Male	331	58.8	713	51.4
Female	232	41.2	673	48 6

* Eleven case and twenty-three control women were missing information on smoking

Logistic Regression Models

Because the case and control women were very similar with respect to age and education, occupational groups were only adjusted for maternal race/ethnicity and smoking. Analyses of paternal occupation were only adjusted for maternal race/ethnicity. There were six maternal occupation logistic regression models and four paternal models. The maternal occupation predictor variables included dental assistant, hairdresser, leather shoe repairer, nurse, retail sales worker and surgical technologist. The paternal occupation predictor variables included automobile mechanic, farmer, leather shoe repairer and painter. Maternal occupation group predictor variables are summarized in Table 2. Paternal occupation group predictor variables are summarized in Table 4. Logistic regression maternal models are summarized in Table 3, and paternal logistic regression models are summarized in Table 5.

There were two case and control mothers each who were dental assistants. The adjusted odds ratio for oral clefts associated with the maternal occupation as dental assistant was 2.1 (95% CI 0.3, 15.2) and the Wald statistic was 0.5 ($p > 0.05$). Three case mothers and five control mothers were hairdressers. The adjusted odds ratio was 1.5 (95% CI 0.3, 6.2) and the Wald statistic was 0.3 ($p > 0.05$). Thirteen case mothers and twenty-two control mothers were classified as nurses. The adjusted odds ratio was 1.6 (95% CI 0.8, 3.3). The Wald statistic was 1.9 ($p > 0.05$). Fourteen case women and 18 control women were classified as retail sales workers. The adjusted odds ratio associated with maternal occupational group was 2.0 (95% CI 0.8, 3.3) and the Wald statistic was 3.6 ($p > 0.05$). There were 60 case women and 62 control women classified as smokers. The adjusted odds ratio was 2.5 (95% CI 1.8, 3.7) and the Wald statistic was 24.5 ($p <$

0.001). No logistic models were done for maternal leather shoe repairers and surgical technologists because there were no cases or controls documented as having those occupations.

TABLE 2
Maternal Occupation and Risk of Oral Clefts in Offspring, Texas, 2000

Maternal Occupational Group	Case Women		Control Women		Unadjusted Odds Ratio (95% C.I.)
	n	%	*n*	%	
Dental Assistant	2	0.4	2	0.1	2.5 (0.3, 17 6)
Hairdresser	3	0.5	5	0.4	1.5 (0.4, 6.2)
Leather Shoe Repairer	0	0.0	0	0.0	n/a
Nurse	13	2 3	22	1 6	1.5 (0.7, 2.9)
Retail Sales Worker	14	2.5	18	1.3	1.9 (1.0, 3.9)
Surgical Technologist	0	0.0	0	0.0	n/a

Table 3
Maternal Occupation and Oral Clefts in Offspring Multivariate Analysis, Texas, 2000

Model #	Predictor Variable	Beta	S.E. (Beta)	Odds* Ratio	95% CI	Wald Statistic	p-value
1	Dental Assistant	0.7	1.0	2.1	0 3, 15.2	0.5	0 5
2	Hairdresser	0.4	0.7	1.5	0.3, 6 2	0.3	0.6
3	Leather Shoe Repairer	n/a	n/a	n/a	n/a	n/a	n/a
4	Nurse	0.5	0.4	1.6	0.8, 3.3	1.9	0.2
5	Retail Sales Worker	0.7	0.4	2.0	1.0, 4.1	3 6	0.1
6	Surgical Technologist	n/a	n/a	n/a	n/a	n/a	n/a
7	Smoking	0.9	0.2	2.5	1.8, 3.7	24.5	0.0

*Adjusted for race/ethnicity and smoking

Among paternal occupations examined, no case or control fathers were classified as leather shoe repairers. Therefore, no logistic models were created for this occupational group. The paternal occupational category of mechanics had the greatest number of cases

and controls (13 cases and 38 controls). The adjusted odds ratio was 0.8 (95% CI 0.4, 1.6), and the Wald statistic was 0.3 ($p > 0.05$). Three case fathers and four control fathers were classified as farmers. The adjusted odds ratio was elevated at 1.9 (95% CI 0.4, 8.7). The Wald statistic was 0.7 ($p > 0.05$). Only 2 case fathers, but 16 control fathers were classified as painters. The adjusted odds ratio was protective at 0.3 (95% CI 0.1, 1.4); the Wald statistic was 2.4 ($p > 0.05$).

TABLE 4
Paternal Occupation and Risk of Oral Clefts in Offspring, Texas, 2000

Paternal Occupational Group	Case Fathers		Control Fathers		Unadjusted Odds Ratio (95% C.I.)
	n	%	*n*	%	
Automobile Mechanic	13	2.3	38	2.7	0.8 (0.4, 1 6)
Farmer	3	0.5	4	0.3	1.9 (0.4, 8.3)
Leather Shoe Repairer	0	0.0	0	0.0	n/a
Painter	2	0.4	16	1.2	0.3 (0.1, 1.3)

Table 5
Paternal Occupation and Oral Clefts in Offspring Multivariate Analysis, Texas, 2000

Model #	Predictor Variable	Beta	S.E. (Beta)	Odds* Ratio	95% CI	Wald Statistic	p-value
1	Automobile Mechanic	-0.2	0.3	0 8	0.4, 1.6	0.3	0 6
2	Farmer	0.7	0.8	1 9	0.4, 8.7	0.7	0.4
3	Leather Shoe Repairer	n/a	n/a	n/a	n/a	n/a	n/a
4	Painter	-1.2	0.8	0.3	0.1, 1 4	2.4	0.1

*Adjusted for maternal race/ethnicity

CHAPTER V

DISCUSSION AND CONCLUSION

Strengths and Limitations

One of the major strengths is that the investigator used a population-based case control study design in studying relatively rare birth defects, oral clefts. Another strength is that the study population was drawn from the Texas Birth Defects Registry (oral cleft cases) and the Texas Department of Health Bureau of Vital Statistics (controls), in which data on birth defects as well as maternal and paternal demographic information are available. Uniform occupation and industry coding was accomplished because Standard Occupational Classification (SOC) and the North American Industry Classification System (NAICS) were used. These two coding schemes are standards of occupation and industry classification in North America.

Despite these strengths, the study has limitations. One of the main limitations is small sample size. There were 563 total cases and 1386 total controls sampled in the database. This small sample size yielded very small numbers of exposed mothers and fathers in the occupations of interest, ranging from no "exposed" cases and controls (maternal leather shoe repairer, maternal surgical technologist and paternal leather shoe repairer) to 13 cases and 38 controls (paternal automobile mechanic).

Another study limitation is that not all maternal and paternal cases and controls could be coded using the standard classification system. For example, only 55.42% of paternal cases and 67.03% of paternal controls could be coded. Among women who were not classified as homemakers, 104 case women's occupations and 174 control women's occupations could not be coded. There were a total of 271 case women and 705 control women classified as homemakers. The housewives could not be coded because according to the Standard Occupational Classification coding scheme, they do not earn a reportable wage.

Findings and Relation to Previous Work

Healthcare and dental workers are routinely exposed to anesthetic gas (Khattak, et al., 1999; Farkas, et al., 1969; Matte, et al., 1993; Ahlborg, et al., 1995). In previous studies, this exposure has been found to be a risk factor in oral clefts in offspring. This study contradicts the work of Matte, et al., 1993, in that they found female dental workers did not show an increased risk of oral clefts in offspring (odds ratio 1.4, 95% CI 0.7, 2.6), while this study found that dental assistants had an increased risk of oral clefts in offspring (adjusted odds ratio 2.1, 95% CI 0.3, 15.2). Kurppa, et al. (1983) supports this study in that they found a strong association between dental assistant occupations and oral clefts.

Lin, et al. (1998) found no association (odds ratio 1.4, 95% CI 1.0, 2.0) between oral clefts in offspring and mothers being employed as retail sales workers. This study, however, found that maternal retail sales workers had an elevated risk of oral clefts in offspring (adjusted odds ratio 2.0, 95% CI 1.0, 4.1).

Hairdressers constitute a major occupational group of female workers who are exposed to chemicals during child bearing years (Kersemaeker, et al., 1997). Kersemaeker, et al. (1997) found an odds ratio of 1.6 (95% CI 0.3, 8.4) and this study had a similar adjusted odds ratio of 1.5 (95% CI 0.3, 6.2).

An important women-dominated occupational group with potential chemical exposure to chemicals is the healthcare profession, including nurses (Khattak, et al., 1999). Khattak, et al. (1999) found a strongly positive association between being a healthcare worker and oral clefts in offspring (odds ratio 13.0, 95% CI 1.8, 99.5). In this study, however, mothers who were classified as working in nursing were 1.6 times more likely to have offspring with oral clefts (95% CI 0.8, 3.3).

In previous studies, maternal smoking has been found to be a risk factor for oral clefting in offspring (Lieff et al., 1999; Lorente et al., 2000; Khourey, et al., 1989). Lieff et al. (1999) found a positive dose response between light smokers (odds ratio 1.1, 95% CI 0.6, 1.9), moderate smokers (odds ratio 1.8, 95% CI 1.2, 2.9) and heavy smokers (odds ratio 1.85, 95% CI 1.0, 3.5) and risk for oral clefts in offspring relative to nonsmokers. Lorente, et al. (2000) found a slightly elevated odds ratio of 1.79 (95% CI 1.1, 3.0) between maternal smoking and oral clefts in offspring. Khourey, et al. (1989) found slightly elevated odds ratios for light smokers (odds ratio 1.6, 95% CI 1.0, 2.4), moderate smokers (odds ratio 1.6, 95% CI 1.0, 2.4), and heavy smokers (odds ratio 1.87, 95% CI 1.0, 3.7). These studies support this study in that the odds ratio was 2.5 (95% CI 1.8, 3.7) for smokers relative to nonsmokers for having a baby with an oral cleft.

Farm workers constitute a large paternal occupational group that are exposed to pesticides (Garcia, et al., 1998; Garcia, et al., 1999; Kristensen et al., 1997; Schnitzer et

al., 1995). Garcia, et al. (1999) found that fathers employed in agriculture work were 1.5 (95% CI 0.9, 2.4) times more likely to have an offspring with an oral cleft, while Schnitzer, et al. (1995) found fathers at 3.3 times the risk of having an oral cleft offspring (95% CI 0.9, 11.9). This study supports the work of Garcia, et al. (1999) (odds ratio 1.49, 95% CI 0.94, 2.35), and Schnitzer et al. (1995) (odds ratio 3.3, 95% CI 0.9, 11.9) in that this study found a slightly elevated odds ratio of 1.9 (95% CI 0.4, 8.7) for oral clefts associated with the paternal occupational group of farming. This study contradicts the work of Kristensen et al. (1997) (adjusted odds ratio 0.94, 95% CI 0.74, 1.20) in which no association was seen between farming and oral clefts.

Automobile mechanics are often exposed to organic solvents through lubricants, greases, and oils. Olshan, et al. (1991) found automobile mechanics were 2.12 times more likely to have offspring with an oral cleft (odds ratio 0.8, 95% CI 1.13, 3.99). This contradicts the work of this study in that automobile mechanics were less likely (odds ratio 0.8, 95% CI 0.4, 1.6) to have offspring with an oral cleft.

Painters are also often exposed to organic solvents primarily through paint thinners. This study found that paternal painters were 0.3 times more likely to have an oral cleft in their offspring (95% CI 0.1, 1.4). This study contradicts the work of Olshan, et al. (1991) in which painters were 3.4 times more likely to have offspring with oral clefts.

Conclusion

In conclusion, this study adds important information about the association between maternal and paternal occupations and risk of oral clefts in offspring. An especially important association was found among maternal dental assistants, maternal

retail sales workers and maternal smokers. Perhaps, in the future, more attention will be taken in selecting an occupation, knowing the risk of congenital malformations may be a consequence. Also, appropriate engineering and safety controls need to be put in place at worksites to protect workers from potential reproductive toxicants. Women would do well to also refrain from smoking during pregnancy since smoking appears to be a significant risk factor for oral clefts.

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